Witness Name: Dame June Munro Raine CBE
Statement No.: 2
Exhibits: JR/1 – 517
Dated: 11 September 2024

UK COVID-19 INQUIRY

MODULE 4

WITNESS STATEMENT OF DAME JUNE MUNRO RAINE CBE

I, **June Munro Raine**, will say as follows: -

1. I make this statement in response to a Rule 9 request dated 1 September 2023 to address matters of relevance to the role of the Medicines and Healthcare products Regulatory Agency (referred to as the "MHRA" or "Agency") in the Covid-19 pandemic insofar as it relates to matters relevant to Module 4 and where specific information has been requested.

2. On behalf of the MHRA, I would like to express my sincere condolences and sympathy to all those affected by the Covid-19 pandemic.

3. This statement covers the period relevant to Module 4, i.e. between 30 January 2020 and 28 June 2022 as stated in the Rule 9 request, although I will refer to certain events outside this period in order to answer some of the Inquiry's specific questions. Unless stated otherwise, matters in my statement will refer to England, Wales, Scotland and Northern Ireland as the MHRA is the regulator for the UK nations. In Northern Ireland, the competent authority for EU authorised products is the European Medicines Agency (EMA). Within this statement I will focus on vaccines and therapeutics.

4. The preparation of this witness statement has required the involvement of specialists and officials within the MHRA and my legal advisers. This statement is to the best of my knowledge and belief accurate and complete at the time of signing. Notwithstanding this, it is the case that the MHRA continues to prepare for its involvement in the Inquiry. As part of these preparations, it is possible that additional relevant material may be identified. In that

eventuality the additional material will be provided to the Inquiry and a supplementary statement will be made if required.

Structure of this statement

Background

5. I am the Chief Executive of the MHRA; I took up that role as interim in September 2019 and became permanent from 23 February 2021. In this role I am accountable to Health Ministers for ensuring that the MHRA takes all possible steps to ensure that medicines, medical devices and blood products for transfusion meet appropriate standards of safety, quality, effectiveness and performance, thereby protecting the interests of the public, and that the MHRA provides high standards of services to manufacturers, healthcare professionals, patients and the public.

6. I trained in Medicine at the University of Oxford, and in 1978 attained a Bachelor of Medicine and Surgery after undertaking an intercalated MSc in Pharmacology by research. After undertaking various junior hospital jobs and attaining Membership of the Royal College of Physicians, I trained in general practice, attaining Membership of the Royal College of General Practitioners in 1982.

7. In 1985 I joined the Medicines Division of the Department of Health as a Senior Medical Officer working on the Review of Medicines. In 1989 I became a Group Manager in the Medicines Control Agency, an Arms-Length Body of the then Department of Health, overseeing post-authorisation licensing activities. From 1992 to 2005 I was the Principal Assessor to the Medicines Commission.

8. In 1998 I was appointed Director of the Post-Licensing Division of the Medicines Control Agency which, in 2006, became the Vigilance and Risk Management of Medicines Division. In this role, I was responsible for the operation of the Yellow Card Scheme which, as I explain further below, is a mainstay of safety monitoring of medicines in the UK.

9. From 2005 I chaired a European working party on pharmacovigilance and in 2012, I was elected Chair of the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency. In this capacity, I was closely involved in the introduction of the new European Union pharmacovigilance legislation.

10. Since 2003 I have been a member and subsequently Co-Chair of the World Health Organisation Advisory Committee on Safety of Medicinal Products.

The role, functions and aims of the MHRA

11. The MHRA is an executive agency of the Department of Health and Social Care ("DHSC"). This means that it is legally indistinguishable from the Secretary of State. However, it is operationally independent. Under the *Carltona* principle[1], the MHRA acts and takes decisions on behalf of the Secretary of State. The MHRA was formed in 2003 following the merger of the Medicines Control Agency and the Medical Devices Agency. In 2013 the MHRA merged with the National Institute for Biological Standards and Control ("NIBSC"). The mission of the MHRA is to enhance and improve the health of millions of people in the UK every day through the effective regulation of medicines and medical devices, underpinned by science and research.

12. The MHRA is the United Kingdom's regulator of medicines, medical devices, and blood components for transfusion, responsible for ensuring their safety, quality, and effectiveness. Specifically, the MHRA's primary responsibilities are:
    a. Ensuring that medicines, medical devices and blood components for transfusion meet applicable standards of safety, quality and effectiveness;
    b. Ensuring that the supply chain for medicines, medical devices and blood components is safe and secure;
    c. Promoting international standardisation and harmonisation to assure the safety, quality and effectiveness of all medicines;
    d. Helping to educate the public and healthcare professionals about the risks and benefits of medicines, medical devices and blood components, leading to safer and more effective use;
    e. Supporting innovation and research and development that are beneficial to public health; and
    f. Influencing UK and international regulatory frameworks so that they are risk-proportionate and effective at protecting public health.

13. The MHRA is responsible for regulating medical products, including vaccines, medicines, and devices in the UK by ensuring that they work and are acceptably safe. In this context, 'acceptably safe' means that based on the assessment of the MHRA, the benefits, or expected benefits, associated with a particular product are considered to outweigh any risks

[1] The principle was recognised by the Court of Appeal in *Carltona Ltd v Commissioners of Works* [1943] 2 All ER 560.

associated with that product, at a population level. I address this more fully later in the statement.

14. There is more specific information on the prior and current strategic ambitions of the MHRA in the MHRA's Delivery Plan 2021-2023 [**JR/1 – INQ000283597**] with updates for Year 2 [**JR/2 – INQ000283552** and the 2023-2026 Corporate Plan [**JR/3 – INQ000283598**].

15. Part of the MHRA's safety monitoring role includes reviewing reports of suspected side effects through the Yellow Card Scheme. The MHRA operates the Yellow Card Scheme jointly with the Commission on Human Medicines ("CHM"). The CHM takes on an advisory role and the MHRA runs the operation of the scheme. I address the Yellow Card Scheme in greater detail later in the statement.

16. Further information in relation to the MHRA's functions is set out in the Framework Agreement between the (then) Department of Health and the MHRA dated March 2016 ("the Framework Agreement") [**JR/4 – INQ000283506**]. A new version was published in 2024 (see paragraph 36).

17. The MHRA's laboratories, formerly the single entity known as the NIBSC play a major role, nationally and internationally in assuring the quality of biological medicines through developing standards and reference materials, product control testing and carrying out applied research. The MHRA's laboratories are responsible for developing and producing over 90% of the biological international standards in use around the world and are designated the UK's Official Medicines Control Laboratory ("OMCL"), responsible for independent regulatory testing of biological medicines within the framework of the European Union. The MHRA's laboratories also host the UK Stem Cell Bank and are a key UK research centre in the field of pandemic flu. During the pandemic the MHRA's laboratories played an important role in assuring the quality of biological medicines through developing standards and reference materials, product control testing and carrying out applied research.

Structure and make-up of the MHRA

18. I am asked to provide information about the structure and make-up of the MHRA, and the roles and responsibilities of staff. In the financial years 2019-2020 and 2020-2021, the MHRA employed an average of 1,291 and 1,388 full-time equivalent staff.

19. At Annex A to this statement, I have included organograms which provide an overview of the centres and divisions which were key to the pandemic response prior to the organisation's transformation which became fully effective from 1 June 2022. The MHRA's transformation to a 'One Agency' operating model from the three previous centres (NIBSC, the regulator and the Clinical Practice Research Database (CPRD)) was prompted by the rapidly changing world of life sciences, the Independent Medicines and Medical Devices Safety Review (a review conducted by Baroness Cumberlege), the UK's exit from the EU, and the learnings from the MHRA's role in the Covid-19 pandemic. The 'One Agency' MHRA is the result of a transformation programme which involved Agency restructuring, designing and implementing a future operating model, replacing legacy technology, assessing the way forward for the Agency's site infrastructure and achieving financial sustainability. The 'One Agency' operating model aims to put patients at the centre, drive the right collaborative behaviours across the Agency and enable new ways of working, systems partnerships and a focus on innovation. The transformation aims to shift the previous separate centre and team structures to an integrated, efficient, end-to-end 'lifecycle' model with patients and the public at the centre of all its activities.

20. I am asked to identify the key decision makers within the MHRA in respect of the topics outlined in the Provisional Outline of Scope for Module 4. What I outline below is accurate as at the time of making this statement.

21. As outlined above, I have been the Chief Executive and Accounting Officer of the MHRA (SCS3) since September 2019 (interim until February 2021). I led the design, delivery, and continuity of the MHRA's response to Covid-19. I reported to the Permanent Secretary, Sir Chris Wormald.

22. In respect of Licensing:

a. Dr Siu Ping Lam: Director of Licensing (SCS2), reporting to me. Dr Siu Ping Lam led on the assessment and licensing of new medicinal products and oversaw regulation of clinical trials. Dr Siu Ping Lam left the MHRA in January 2022.
b. Dr Krishna Prasad: Deputy Director, Licensing (SCS1), reporting to Dr Lam and, from October 2021 to Dr Laura Squire. He was the principal assessor to the CHM and helped set up the Expert Working Groups for Covid-19 Vaccines and Therapeutics. Dr Prasad was the MHRA representative to the RAPID C-19 Oversight Group. Dr Prasad sadly passed away in April 2023.
c. Dr Julian Bonnerjea: Head of Biological Products (SCS1), reporting to Dr Krishna Prasad, led the team dealing with authorisation of Covid-19 vaccines. Dr Bonnerjea left the MHRA in November 2022 but has recently returned.
d. Dr Jasvinder Singh: Head of New Active Substances (SCS1), reporting to Dr Krishna Prasad. He led the team dealing with authorisation of Covid-19 therapeutics.
e. Keith McDonald: Deputy Director, Licensing (SCS1), reporting to Dr Siu Ping Lam. He led a licensing team of assessors, including assessment of Covid-19 products. Mr McDonald left the MHRA in March 2021.
f. Elizabeth Baker: Group Manager, Licensing (SCS1), reporting to Dr Lam and, from October 2021 to Dr Laura Squire. She led a licensing team of assessors, including assessment of Covid-19 products. She left the MHRA in October 2022 but has recently returned.

23. In respect of Vigilance:
    a. Dr Sarah Branch: Interim Director of Vigilance and Risk Management of Medicines (SCS2), reporting to me. Dr Branch oversaw the post-authorisation medicines safety monitoring functions of the MHRA including the Yellow Card scheme, signal detection and benefit risk assessment. Dr Branch chaired a number of internal Covid-19-focused groups, including the Covid SitRep and the Vaccine Adverse Events Incident Management Team during the AstraZeneca thrombosis with thrombocytopenia syndrome signal (both meetings discussed below). Dr Branch retired from the MHRA in June 2022.
    b. Mick Foy: During 2020 and 2021 he was Head of Pharmacovigilance Strategy (SCS1) reporting to Dr Branch. In this role Mr Foy was responsible for the running of the adverse drug reaction and adverse device incident systems, including the

Yellow Card scheme, and the associated signal detection function. He was Deputy Director for Patient Safety Monitoring (SCS1) from February 2022, reporting to Dr Alison Cave. Since September 2022, Mr Foy has been Director of Delivery, reporting to me.

c. Dr Phil Bryan: Expert Scientific Assessor (SCS1), reporting to Dr Sarah Branch. Dr Bryan was responsible for the MHRA strategies and methodologies for vaccine surveillance, including coordination with the DHSC, JCVI and cross-system interaction with the UK healthcare family. He was an expert assessor in vaccine pharmacovigilance including with respect to Covid-19 vaccines. Dr Bryan left the MHRA in April 2021.

d. Phil Tregunno: Deputy Director, Patient Safety Monitoring (SCS1), reporting to Mick Foy and, from September 2022 to Dr Alison Cave. Led the team monitoring Yellow Card reports and post-authorisation safety surveillance of Covid-19 vaccines and therapeutics. Prior to September 2022, Phil Tregunno worked as Head of Vigilance before being promoted to Deputy Director of Patient Safety and Monitoring.

24. In respect of Manufacture and Supply:

a. Dr Samantha Atkinson: Interim Chief Healthcare Quality & Access Officer (SCS2), reporting to me, and Chair of the MHRA's Covid-19 taskforce; previously Director of Inspection, Enforcement and Standards. Dr Atkinson oversaw the MHRA's inspections programme, enforcement of medicines legislation, setting medicines standards including through publishing the British Pharmacopoeia. Managed interactions with companies in relation to initial authorisations of Covid-19 vaccines. She transferred from the MHRA to DHSC in April 2022.

b. Tracy Moore: Expert Good Manufacturing Practice (GMP) Inspector (SCS1), reporting to David Reed, Unit Manager. She inspected vaccine manufacturers both on-site and remotely, providing oversight of manufacture and distribution. She left the MHRA in October 2021.

c. Ian White: Expert Good Manufacturing and Distribution Practice (GMDP) Inspector working in Standard and Compliance (SCS1) since July 2022. Previously Expert GMP Inspector in the Inspection, Enforcement & Standards Department (SCS1) since August 2021 and Senior GMDP Inspector in the Inspection, Enforcement & Standards Department (G6) since June 2020 reporting to Christine Gray,

Operations Manager. He inspected vaccine manufacturers both on-site and remotely, providing oversight of manufacture and distribution. Mr White left the MHRA in November 2022.

25. In respect of Biological Standards and Control:
    a. Dr Christian Schneider: Interim Chief Scientific Officer (SCS2) from October 2020, reporting to me; previously his role was as Director of the NIBSC, reporting to me. Chaired the Vaccines Deployment Oversight Group (discussed below). Dr Schneider was responsible for delivering the laboratory scientific functions of NIBSC including control testing, biological standardisation, research and development, scientific advice and managing the national and international portfolio of the Institute. Dr Schneider left the MHRA in July 2021.
    b. Dr Nicola Rose: Deputy Director, Research and Development (SCS1) since March 2022, reporting to Dr Marc Bailey. Dr Rose oversees research and development programmes related to biological medicines. Previously Head of Vaccines, NIBSC, from January to March 2022. In that role she was responsible for the independent batch testing of Covid-19 vaccines. Previously Head of Virology, NIBSC, from February 2020 to end 2021, reporting to Dr Christian Schneider and subsequently Dr Marc Bailey. In that role she was responsible for coordinating the control testing of vaccines and produced a number of biological reference materials to support Covid-19 vaccine and diagnostic test development and evaluation.

26. In respect of Clinical Trials:
    a. Martin O'Kane: Deputy Director, Clinical Investigations and Trials (SCS1), since April 2022, reporting to Dr Marc Bailey. Previously Unit Manager for Clinical Trials reporting to Julian Bonnerjea. Mr O'Kane led the team authorising clinical trials of Covid-19 vaccine and therapeutics candidates. He left the MHRA in January 2023.
    b. Dr Kirsty Wydenbach: Expert Medical Assessor (SCS1) who led the team that assessed applications for clinical trials in the UK. Dr Wydenbach left the MHRA in June 2022, however, she is now working as a contractor for the MHRA. Previously Deputy Manager of the Clinical Trials Unit from April 2016 to May 2020, where she reported to Martin O'Kane.

27. In respect of Policy: Rachel Arrundale: Deputy Director, Partnerships (SCS1) since May 2020, reporting to Jonathan Mogford, Director of Policy and from October 2021 to the Chief Partnerships Officer, Dr Glenn Wells. Rachel Arrundale was the MHRA's Covid-19 policy lead; she led development of the regulatory approach, and cross-government liaison.

28. In respect of Communications:
    a. Rachel Bosworth: Director of Communications and Engagement (SCS1), reporting to me. In leading the MHRA's communication and engagement response to the pandemic she provided strategic planning and advice, in liaison with the DHSC.
    b. Stephen Hallworth: Deputy Director of News and Media (G6). Oversaw and led internal and external engagement and communications to support the MHRA's work on Covid-19.

29. In respect of ensuring continuity of the Covid-19 response from mid-2021 onwards:
    a. Dr Alison Cave: Chief Safety Officer (SCS2) since July 2021, reporting to me. Dr Cave oversees the safety and surveillance benefit risk evaluation teams and the patient safety monitoring team, who monitor safety surveillance of Covid-19 vaccines, medicines, and devices. Dr Cave oversees the team undertaking enforcement of medicines legislation and the Clinical Practice Research Datalink, a database of anonymised medical records which is used in safety surveillance.
    b. Dr Laura Squire OBE: From July 2023, Dr Squire has moved to an interim position at the MHRA leading on the medical devices regulatory reform reporting to me; Prior to this, she was Chief Healthcare Quality and Access Officer (SCS2) from November 2021, managing the licensing teams that approve vaccines and therapeutics for Covid-19, the MHRA's inspections programme, and the team which sets medicines standards, including publication of the British Pharmacopoeia. Before transferring to the MHRA, Dr Squire was the Deputy Director within the DHSC, working on Covid-19 vaccine deployment policy.
    c. Dr Marc Bailey: Chief Science and Innovation Officer (SCS2) since September 2021, reporting to me; previously interim Director of NIBSC from December 2020. Dr Bailey was responsible for delivering the laboratory scientific activities across NIBSC including control testing, biological standardisation, research and development, scientific advice and managing the national and international portfolio of the Institute.

The MHRA's cooperation and working with the UK Government and the Devolved Administrations

30. The MHRA always guards its independence as the UK regulator for medicines and medical devices. As the Chief Executive of the MHRA, I am ultimately accountable for all decisions taken by the MHRA, and this remained the case throughout the pandemic response. I was supported by my Executive team, the MHRA Board and wider MHRA officials. While maintaining its regulatory independence, the MHRA co-operated with government departments, agencies and wider, and did so continuously throughout the pandemic.

31. The MHRA is an executive agency of the DHSC. Many of the MHRA's duties and powers are provided for by the Human Medicines Regulations 2012 which set out the responsibilities of the "Licensing Authority". The Licensing Authority is responsible for the grant, renewal, variation, suspension and revocation of licences, authorisations, certificates, and registrations of medicinal products. The role of Licensing Authority may be carried out by the Secretary of State for Health and Social Care (in the UK Government) and the (Northern Ireland) Minister for Health, Social Services and Public Safety. In practice, this responsibility is devolved to the MHRA which takes regulatory decisions and action on behalf of Ministers who do not routinely approve MHRA's action on, for example, authorising medicines or imposing conditions on their use.

32. The MHRA is a UK wide authority: the Human Medicines Regulations 2012 apply in the same way to England, Scotland and Wales, and the MHRA has the same responsibilities in relation to each country. The MHRA is also the regulator for Northern Ireland, but following 1 January 2021, when the UK left the European Union, there was a divergence in the regulatory schemes as between Great Britain and Northern Ireland, the latter remaining subject to European legislation for medicines and medical devices.

33. On a day-to-day basis, the MHRA is accountable to the (UK Government) Secretary of State for Health and Social Care and is sponsored by the DHSC. MHRA officials also meet regularly with other policy officials in the Scottish, Welsh and Northern Ireland Governments, and officials from the devolved administrations are invited to the MHRA Board meetings.

The UK Government

34. I am asked to identify the key Ministers and civil servants with whom the MHRA interacted in relation to the scope of Module 4. As to Ministers, these were:

    a. Matt Hancock MP: served as the Secretary of State for Health and Social Care from 9 July 2018 to 26 June 2021 and liaised with me on vaccine safety.

    b. Nadine Dorries: Parliamentary Under-Secretary of State and subsequently Minister of State at the DHSC from July 2019 to September 2021. Minister Dorries took a number of decisions as the 'Licensing Authority' during the Covid-19 pandemic.

    c. Lord Bethell: Parliamentary Under-Secretary of State at the DHSC from March 2020 to September 2021. Lord Bethell took a number of decisions as the 'Licensing Authority' during the Covid-19 pandemic.

    d. Maria Caulfield MP: variously Parliamentary Under-Secretary of State and Minister of State at the DHSC from September 2021 to July 2024. Minister Caulfield took a number of decisions as the 'Licensing Authority' during the Covid-19 pandemic.

35. As I explain more fully below, in September 2020 the MHRA agreed with the then Secretary of State that licensing decisions on Covid-19 medicinal products were exceptional by nature and therefore the MHRA should not take its usual delegated action. It was decided instead that a Minister should be designated as the "Licensing Minister" to take advice from the MHRA and take these decisions as the Licensing Authority. Recognising the potential for a conflict of interest, the identified Licensing Minister could not be involved with, for example, the purchase and deployment of vaccines or medicines, and could not liaise directly with interested pharmaceutical companies. Licensing decisions continued to be taken by the Licensing Minister until November 2022. On very rare occasions where minor changes to licences were proposed, which did not affect the benefit risk assessment of a product, the change was sent to the Licensing Minister for information only, rather than for decision-making. As a result, regular communication between MHRA policy officials and the Secretary of State took place. In most cases, communications would take place through submissions.

36. The Framework Agreement defines the working relationship between the MHRA and the DHSC. In March 2024 a new Framework Agreement was published [**JR/5 – INQ000507348**]. Before this, the Framework Agreement had been in place since 2016 [**JR/4**

– **INQ000283506**]. The working relationship is monitored through regular meetings between the DHSC Sponsor team and lead MHRA officials, and more formally through Quarterly Accountability Meetings with the Director of Medicines in the DHSC or her deputies, together with the MHRA Chair. These meetings continued throughout the pandemic period and covered the totality of MHRA business.

37. The MHRA worked closely with senior Civil Servants at the DHSC. On Covid-19 business, the main communications between the MHRA and senior civil servants at the Department was one of liaison between policy teams in the MHRA and the DHSC to ensure understanding of regulatory processes and timelines (while maintaining confidentiality around the MHRA's authorisation deliberations); to contribute to the development of new legislation as needed (in particular the amendment of the Human Medicines Regulations 2012 and insertion of regulation 174A to incorporate requirements on vigilance, advertising and NHS supply); to request and provide advice on the process of making regulation 174 requests from the DHSC to the MHRA; and liaison with the DHSC (as the applicant to the process) on these requests, once made (again respecting the independence of MHRA scientific deliberations and advice).

38. There was also liaison between communications teams within the DHSC and the MHRA to prepare for public announcements (under strict confidentiality rules) which I will elaborate on further below.

39. From early 2021 there were fortnightly meetings between the MHRA and the Department of Health in Northern Ireland, including the Chief Pharmacist, to address issues arising from the different regulatory situation for Northern Ireland following the UK's exit from the European Union. These meetings covered Covid-19 vaccines and therapeutics as well as wider medicines issues.

The Chief Medical Officer and Deputy Chief Medical Officer

40. During the pandemic, I had a close working relationship with the Chief Medical Officer (CMO), Professor Sir Chris Whitty, and the then Deputy Chief Medical Officer (DCMO), Professor Sir Jonathan Van-Tam. I appeared in a number of televised press briefings at Number 10, as well as featuring in a government vaccines confidence campaign, alongside Professor Whitty and Professor Van-Tam. Some of the key press briefings I attended with

the CMO and DCMO were on Covid-19 vaccine development, approval and availability, safety monitoring, and approval of vaccine boosters.

The MHRA's Independent Expert Advisory Committees

41. Decision making by the MHRA is supported by expert advice from several independent expert advisory committees (although not all of which advised in respect of Covid-19 vaccines or therapeutics). These expert committees include:
    a. The Commission on Human Medicines (CHM), which I explain below.
    b. Herbal Medicines Advisory Committee (HMAC).
    c. Advisory Board for Registration of Homeopathic Products (ABRHP).
    d. British Pharmacopoeia Commission (BPC).
    e. Device Expert Advisory Committee (stood down March 2022).
    f. United Kingdom Stem Cell Bank Steering Committee (UKSCBSC).
    g. The Review Panel.

42. These committees can also establish expert working groups to address specific issues. In the context of Module 4 of the Inquiry the most relevant committee is the CHM.

The Commission on Human Medicines

43. The CHM is the Government's independent expert scientific advisory body on medicines. It is an advisory non-departmental public body, sponsored by the DHSC. Its functions are set out in regulation 10 of the Human Medicines Regulations 2012. The CHM provides advice to ministers and the MHRA on the safety, quality and effectiveness of medicinal products and on the collection and investigation of information relating to adverse reactions to enable such advice to be given. The MHRA provides the CHM with a secretariat, attends CHM meetings, and regularly seeks CHM advice on licensing applications and safety concerns. As explained more fully below, the MHRA undertakes rigorous scientific assessments of all the available evidence on safety, quality and effectiveness of medicinal products provided by the manufacturer. The MHRA provides a scientific report and recommendations to the CHM, which considers those reports in detail and provides independent advice to health ministers. Except where it has been decided that a Licensing Minister themselves would take the decision (see paragraph 35 above), the MHRA acting as Licensing Authority then takes the regulatory decision.

44. During the Covid-19 pandemic, the CHM established Expert Working Groups ("EWG") including the Covid-19 Therapeutics EWG (established in March 2020 and stood down in May 2023), the Covid-19 Vaccines Safety Surveillance EWG (established in May 2020 and stood down in October 2020) and the Covid-19 Vaccine Benefit Risk EWG (established in August 2020 and stood down in May 2023). The remit and membership of each of the Expert Working Groups has been published online [**JR/6 – INQ000283558**]. The MHRA's scientific assessments of the benefit risk profile of each vaccine and medicinal product for which data were submitted were considered by the relevant EWG and the EWG then advised the CHM. The MHRA regularly sought independent scientific advice from the CHM throughout the pandemic on matters relating to human medicinal products.

45. In relation to authorisation of Covid-19 vaccines, the advice of the Covid-19 Vaccines Benefit Risk EWG (VBREWG) was sought on various ad hoc, interim and preparatory issues, prior to making a report to and recommending final authorisation decisions to the CHM. MHRA representatives attend all meetings of the CHM's EWGs and the CHM meetings. In all cases the advice of the CHM was conveyed to Ministers as the Licensing Authority for a final decision. There were no internal meetings deciding whether to follow CHM advice or not - the advice of the CHM is to Health Ministers.

Public Health England / the UK Health Security Agency

46. The MHRA maintained regular communication and information exchange with public health bodies, including Public Health England (PHE) and its equivalents in Wales, Scotland, and Northern Ireland. This involved discussions regarding data, research findings, and surveillance information related to Covid-19, including the spread of the virus, emerging variants, and the impact on public health, particularly where the MHRA would be responsible for approving tests. Public Health England officials also presented on topics related to their remit at CHM meetings where vaccine and medicine authorisations and benefit risk were discussed. The communications teams of the MHRA, DHSC and PHE worked together to prepare for announcements.

47. The MHRA collaborated with PHE to support the production of targeted communications, and this included information for pregnant women which invited their enrolment in the Yellow Card Vaccine Monitor (part of the Yellow Card Scheme). The MHRA collaborated with PHE on such information to ensure that details relating to the reporting of suspected side effects

were included within PHE's communications. The same MHRA feedback was also shared with devolved administrations for their vaccination information. Further, the MHRA inputted into training materials which described to vaccination teams when to report via a Yellow Card to the MHRA. The DHSC and Public Health England provided advice on stockpiling key medicines during the pandemic [**JR/7 – INQ000283519**], to which MHRA contributed through our guidance on the regulation of medicines and medical devices following the UK's exit from the European Union [**JR/8 – INQ000283560**].

NHS England and the Devolved Administrations

48. The MHRA liaised with NHS England in relation to multiple issues including: the vaccines and medicines programmes and other medicines supply issues, operational impact and potential risk mitigations. The MHRA also worked with NHS England as part of a group called RAPID C-19 ("Research to access pathway for investigational drugs for Covid-19", discussed below). To assist the DHSC's procurement efforts during the pandemic, the MHRA provided regulatory training to members of NHS England, Devolved Administrations and the DHSC.

49. The MHRA had meetings with PHE and NHS England in relation to incident management and ensuring that Yellow Card reporting information was included in materials for health care providers. For the other UK nations, the MHRA provided advice and support on the regulatory requirements relating to deployment, as needed. There were a number of deployment meetings held with NHS England and the Devolved Administrations throughout the vaccine roll out, and NHS England and the Devolved Administrations presented to the CHM setting out their plans for Covid-19 vaccine deployment [**JR/9 - INQ000400226**].

50. Following the authorisation of products, the MHRA held meetings to brief the devolved governments on the requirements and the conditions of the authorisations. This would relate to issues on patient safety monitoring and benefit risk evaluation concerning Covid-19 products, for example providing data on vaccine exposure, reports of anaphylaxis associated with vaccination, and epidemiological analysis of adverse events.

51. Officials from the MHRA also met regularly with the Chief Pharmacists and other policy officials in the Scottish, Welsh and Northern Irish Administrations. During the pandemic, meetings were held both bilaterally and with all four nations with the MHRA providing

regulatory advice on the vaccines. The devolved governments gave a presentation at the CHM regarding how their deployment would proceed and how they would implement the MHRA's regulatory decisions. For example, on 21 November 2020, the CHM's Covid-19 VBREWG held a meeting at which representatives of (amongst others) PHE, NHS England, NHS Scotland, NHS Wales and NHS Northern Ireland attended [**JR/9 – INQ000400226**].

52. The MHRA holds quarterly Cross-UK Partnership meetings with representatives from the Devolved Administrations and NHS England. These meetings are primarily to update the Devolved Administrations on agency work and priorities, including Covid-19 work. During the pandemic, they included updates on Covid-19 vaccines and regulatory flexibilities.

National Institute for Health and Care Excellence ("NICE")

53. The MHRA provided scientific input to inform the development of NICE's evidence-based guidelines, health technology assessments and recommendations related to Covid-19, by sharing data and analysis on the safety and effectiveness of Covid-19-related products. The MHRA also attended meetings of the RAPID C-19 oversight group, the multi-agency initiative which was set up and led by NICE. The group was established early in the pandemic to coordinate the activities of healthcare bodies and get treatments for Covid-19 to patients quickly and safely. The RAPID C-19 group monitored emerging trial evidence on the clinical effectiveness of potential Covid-19 treatments during the pandemic. The group reviewed the briefing documents prepared by NICE to see whether the current evidence supported the use of a treatment for Covid-19. The membership of RAPID C-19 comprised NICE; NHS England; the MHRA; the Scottish Medicines Consortium (Healthcare Improvement Scotland); the All-Wales Therapeutics and Toxicology Centre; the All-Wales Medicines Strategy Group; the Department of Health in Northern Ireland; and the Antivirals and Therapeutics Task Force at the DHSC.

NHS Test and Trace

54. From approximately January 2021 the MHRA attended weekly partnership meetings with NHS Test and Trace to discuss lateral flow tests and ensure safe and effective components of test kits. The MHRA also attended meetings to provide regulatory advice on sample collection devices to ensure that they were safe and compliant. Prior to January 2021, there had been regular, informal meetings with PHE designed to promote partnership working and collaboration.

NHS Digital

55. The MHRA worked with NHS Digital to ensure data were collected on vaccine administration, transferred to patients' GP records in a timely way and made available to the MHRA to enable effective implementation of the vaccine vigilance strategy for which accurate and up-to-date information on vaccine use was a key component. The MHRA's software team also worked with NHS Digital on the Covid-19 app in relation to the development of contact tracing and the lateral flow device reader.

International engagement

56. In addition to the above domestic working relationships, the MHRA worked closely with international partners during the Covid-19 pandemic. The MHRA is a member of the International Coalition of Medicines Regulatory Authorities ("ICMRA"), and I sit on the Executive Committee of the Coalition. The ICMRA is a voluntary leadership entity made up of national medicines regulatory authorities who work together on a variety of strategic initiatives, including supply chain integrity, antimicrobial resistance, crisis management, and public communication. During the pandemic, the Executive Committee met frequently to ensure strong liaison and information sharing on clinical trials, vaccines, and medicines approvals. Specific committees were also established including the ICMRA Public Health Emergency Clinical Trials Working Group, which was co-chaired by MHRA.

57. The MHRA also co-chaired the ICMRA Vaccine Pharmacovigilance Network with the Australian regulator, the Therapeutics Goods Administration ("TGA"). This served as a forum to share methodological approaches to vaccine pharmacovigilance and to share high level assessment positions on emerging safety signals. At various stages during the pandemic the MHRA also presented on critical issues to the ICMRA executive committee. As above, the MHRA continues to be part of the Executive Committee for ICMRA.

58. The MHRA worked, and continues to work, with other national regulators on a bilateral basis and is able to share confidential information, where we have the relevant agreements in place. Our Memoranda of Understanding generally contain the provisions for sharing confidential information on various aspects of the life- cycle of medicines and medical devices, such as pre-clinical studies, post-marketing safety signals, benefit risk assessments, and regulatory policy. During the Covid-19 pandemic, a Memorandum of

Understanding enabled the European Medicines Agency and MHRA to share confidential information on medicinal products intended for either prevention or treatment of Covid-19 disease. This enabled continuity of work with the European Medicines Agency after the end of the transition from the EU medicines regulatory system to the MHRA as a standalone regulator following the UK's exit from the European Union.

59. In October 2020 the MHRA joined the Access Consortium, commencing work-sharing applications in January 2021. The Access Consortium was formed in 2007 and was then known as 'ACSS' and comprised the Therapeutic Goods Administration (TGA) of Australia, Health Canada, the Health Sciences Authority of Singapore and Swissmedic. The Consortium works together on work-sharing procedures for the approval of medicinal products. The Consortium's goal is to maximise international co-operation between partners in the consortium, reduce duplication, and increase each agency's capacity to ensure patients have timely access to medicinal products of high safety, quality and effectiveness. In March 2021 the MHRA developed a regulatory approach for updating authorised coronavirus vaccines should mutations at any time make them less efficacious due to insufficient cross-reactivity, and this was agreed and published as Access Consortium guidance on strain changes in authorised Covid-19 vaccines.

Independence and Impartiality of MHRA

Independence

60. As outlined above, the MHRA is an executive agency of the DHSC. Whilst the MHRA is indistinguishable from the Secretary of State, it is operationally independent. It acts and takes decisions on behalf of the Secretary of State. The MHRA is accountable to the DHSC, on behalf of the Secretary of State who is accountable to Parliament. As stated in paragraph 35 above, scrupulous care was taken in the Covid-19 pandemic to separate Licensing Authority decisions on vaccines and medicines from procurement and deployment decisions.

61. In discharging those responsibilities on behalf of the Secretary of State, it is vital that the MHRA demonstrates its independence from any influence over the sectors and activities it regulates. The public understandably expect this of the MHRA, and it is the most fundamental element of our licence to operate, which we take very seriously. It is a topic that requires continual management to evidence the basis for, and maintain, public trust in

our independent decision-making. On a practical level, this means the MHRA need to be aware of the risk of, and put policies in place to manage, potential conflicts of interest in our staff, in our board members, in the members of the independent advisory committees that advise us and between different activities of the MHRA, where corporate conflicts of interest may potentially occur.

62. The below paragraphs set out our systems to ensure management of each of those differing types of potential conflict. However, ensuring impartiality and independence of decision-making is an ongoing responsibility of all staff and often features in discussions at the highest level of the MHRA. The MHRA utilise legal advice and the judgement of senior leaders, as needed, to ensure we avoid engaging with pharmaceutical companies other than in the proper conduct of regulation.

63. We also act to avoid the risk of perceptions of conflicts of interest in our dealings with wider government. An example of this is the decision taken in September 2020 by the Executive Committee at the direction of the CEO to withdraw MHRA representation from the Vaccines Task Force. This reflected the change of the Vaccine Task Force's focus from supporting the development of vaccines in general, where the MHRA could play a role in advising on likely requirements, to considering purchasing decisions for the UK government. I wrote to Dame Kate Bingham, then Chair of the Vaccine Task Force, advising on these grounds for our withdrawal from the Task Force [**JR/10 – INQ000400195**].

64. Given the MHRA's need to independently assess any and all potential vaccines on the basis of safety, quality and effectiveness, remaining a member of the Task Force could have been taken as predictive of a particular approach or outcome with respect to any regulatory submissions. This was not the case, nor is it ever the case that the MHRA considers factors beyond our statutory responsibilities to consider the safety, quality and effectiveness of the products we regulate.

Corporate conflicts of interest

65. A robust conflict of Interest policy during the pandemic was operated by several divisions or groups within the MHRA. For members of advisory bodies, conflicts of interest were overseen by the Operations team; for staff, it was owned by Human Resources; for

corporate activities, it was managed by the Policy team; and, for the Board, it sat with the Directorate.

66. When the MHRA's Governance Office was created in June 2021, as a result of the MHRA's transformation programme, the overall responsibility for conflicts of interest was brought together in one place in this new team. The Governance Office is responsible for overall co-ordination of MHRA policy on all types of conflicts and for supporting colleagues, such as the Human Resources Group or those supporting expert committees, to implement policies effectively. As part of our ongoing commitment to manage conflicts effectively, the MHRA has worked to update and improve our policies across the board. The MHRA's approach is continually monitored and assessed, with independent and objective assessment by the Government Internal Audit Agency (GIAA), as well as ongoing scrutiny by the Audit and Risk Assurance Committee of the Board.

67. At a corporate level, the MHRA follows its 'Corporate Conflicts of Interest Policy and Procedure' [**JR/11 – INQ000274037**]. The policy and procedures for 2020 and 2021 can be found here [**JR/12 – INQ000274043**] . These procedures require the MHRA to continually assess whether any activity that we undertake, or wish to undertake, will cause an actual or a perceived conflict of interest. The policy and procedures are based on the objective of enabling the MHRA to continue its activities and develop new areas of work, in the interests of public health, whilst identifying and taking steps to mitigate and/or avoid potential, actual or perceived conflicts of interest in a transparent way. The policy, and a tracker of our assessment of potential conflicts and the actions we have taken, are published on our website. The latest version of the 'Corporate 'Conflicts of Interest Policy and Procedure' was published in November 2023 [**JR/14 – INQ000503579**].

Board member conflicts

68. The MHRA's unitary Board does not have involvement in any regulatory decisions affecting medicines, medical devices or blood products; these are the responsibility of the Chief Executive and the Executive team. The Board's Terms of Reference are here: [**JR/15 - INQ000274034**]. MHRA Board members who are not covered by the staff policy (see paragraph 70) are required to declare interests in the pharmaceutical and medical devices industry under the MHRA's 'Policy on Declaring and Managing Interests for Members of the MHRA Unitary Board' (effective from March 2021) [**JR/16 – INQ000274033**]. This policy

also provides guidance on holding and declaring other relevant interests, and on how interests that have been declared will be managed.

69. At each Board meeting as well as annually and as part of the recruitment process, non-executive directors are invited to declare any relevant conflicts of interest. Any conflicts of interest are considered by the Chair, with the support of the Governance Office and noted in the minutes of each meeting (which are published online) and included in the annual list of declarations [**JR/17 – INQ000274032**], which is also published on the MHRA's website. The policy sets out a range of actions that the Chair may take where a Board member has a relevant interest, including removing the member from the meeting or for a specific discussion.

Staff conflicts

70. As civil servants, all MHRA staff are committed to the Civil Service's core values of integrity, honesty, objectivity and impartiality as set out within the Civil Service Code. During the period of the pandemic, the MHRA had a policy 'Dealing with Staff Conflicts of Interest' dated February 2017 [**JR/18 – INQ000274029**]. The policy sets out that staff cannot hold any direct financial interests in the industries the MHRA regulates (the pharmaceutical and healthcare product (medical devices) industries). This policy was updated in 2023 in line with Government Internal Audit MHRA ("GIAA") best practice [**JR/19 – INQ000400286**] to provide better technical support for declarations and to improve both declaration rates and line manager action. However, the underlying principles of avoidance of any conflict of interest remain the same and there were no significant changes to the requirements of staff.

71. Staff are required to declare all relevant interests on appointment, when they arise and annually so that they can be discussed, mitigated and/or disposed of as required. The Human Resources Group produces regular reports on declaration rates. Line managers are required to ensure conflict of interest declarations are completed and, where necessary, mitigations are agreed, implemented and sufficiently address the issue.

Expert members conflicts

72. Decisions relating to the safety, quality and effectiveness of medicines and medical devices are often taken in the face of significant uncertainties and can be complex in form, scope, and potential consequences. These difficult decisions involve making use of the best

available scientific evidence to weigh the respective benefits and risks of medicines and medical devices and, sometimes, involve intricate judgements to provide the greatest benefit to the affected populations. Consequently, decisions relating to the safety, quality and effectiveness of medicines and medical devices can benefit hugely from the involvement of independent experts, highly skilled professionals who have appropriate expertise and are well regarded in their respective fields.

73. As I have outlined above, the MHRA receives advice from a number of independent advisory bodies. On the basis of this advice, the MHRA takes decisions on behalf of Ministers on matters relating to the safety, quality and effectiveness of medicines and medical devices, remaining impartial at all times. Cost is not a factor in MHRA decision-making.

74. In July 2020 the report of the Independent Medicines and Medical Devices Safety ("IMMDS") Review (a review conducted by Baroness Cumberlege) was published [**JR/20 – INQ000361115**]. The review reflected the continued need for a robust management of Committee members' interests. Furthermore, public expectations of public sector transparency and reporting have continued to increase. It was identified that the practice of these advisory committees needs to develop to meet those expectations and demonstrate the best practice expected.

75. The Code of Practice in place before the IMMDS Review report for the MHRA's advisory committees required that committee members declare all interests for all medicines and devices both prior to joining the committee and for every product on the agenda at committee meetings [**JR/21 – INQ000507338**]. Interests declared by members of the CHM and its EAGs/EWGs are published in the Human Medicines Regulations 2012 Advisory Bodies Annual Report 2022. As the chair and members of the CHM provide advice directly to the Licensing Authority, they are not permitted to hold any current personal interests in the pharmaceutical industry.

76. In the context of the Code, a personal interest involved the payment, in any form, to an individual personally, by a pharmaceutical company whose business may be directly affected by the advice of the advisory body. At a meeting, personal interests must be declared as specific (that is, payment relates to a particular product under consideration), or as non-specific (that is, not related to the particular product under discussion). A non-

personal interest in the context of the Code, involved payment that benefits a department for which an individual is responsible, but is not received by the member personally. As with personal interests, non-personal interests at a meeting must be specific or non-specific. However, it is not only financial interests in the pharmaceutical industry that are relevant. Both the old and new codes of conduct capture a wide range of other matters which may also be considered relevant, depending on the circumstances and matters under consideration by a committee on which an individual serves, and could include non-financial interests.

77. There are no standard guidelines dictating whether "other" interests must be declared. In considering whether an interest is relevant and therefore should be declared, the guiding principle must be whether the matter might reasonably be perceived as affecting a member's impartiality. This relates to a recommendation of the IMMDS Review, which suggested that there should be a clear and transparent governance process to cover potential conflict of interests. The current Code provides that the processes to manage conflicts of interest are robust and clear to all, the role of patients and the contribution they make to committee advice is clearly defined and that they are properly supported to contribute effectively, and that experts remain independent and impartial.

78. Following publication of the IMMDS Review report, in April and May 2022, the MHRA held a public consultation on a proposal to reform the Code of Practice for MHRA advisory bodies [**JR/22 – INQ000274039**], resulting in the following changes:

    a. A single Code of Practice for all advisory committees to eliminate inconsistencies and remove any confusion **[JR/21 – INQ000507338]**.
    b. General prohibition for members of advisory committees to hold personal interests, except British Pharmacopoeia Commission.
    c. Created additional categories of members and other experts including 'Invited Expert', Patient Expert and Observer to support greater inclusion of patients or their representatives in committee discussions.
    d. Set out improved clarity on the scope of non-personal interests.
    e. Improved guidance for members particularly for 'other relevant interests' to promote accurate reporting and management of interest.

f. Provided for an advisory panel to provide advice where conflicts of interest are 'complex or novel', as needed, as well as a new conduct panel for dealing with breaches of the conflict-of-interest policy.

79. We will continue to monitor the impact of this new and improved policy, and records of the interests of members will continue to be published in the minutes of relevant meetings and in the annual reports of the statutory advisory bodies.

80. I believe that the safeguards described above are proportionate and robust. A GIAA audit on management of staff conflicts of interest in 2023 [**JR/19 – INQ000400286**] identified no significant control weaknesses in the implementation of the policy.

81. Following the publication of the IMMDS Review report in July 2021, the MHRA – reflecting its corporate Delivery Plan 2021 to 2023 – has initiated a substantial programme of work to improve how it listens and responds to patients and the public, is developing a more responsive system for reporting adverse incidents and is strengthening the evidence to support timely and robust decisions that protect patient safety. Further information is set out within the DHSC update report of December 2022 [**JR/518 – INQ000507359**].

82. The MHRA's 'Patient Involvement Strategy 2021-25' [**JR/23 – INQ000507358**] was published in September 2021 and is an important part of the response to recommendation 6 of the Cumberlege Review (i.e. that "*The MHRA needs substantial revision, particularly in relation to adverse event reporting and medical device regulation. It needs to ensure that it engages more with patients and their outcomes. It needs to raise awareness of its public protection roles and to ensure that patients have an integral role in its work.*").

83. The Patient Involvement Strategy has been developed in consultation with patients to understand what was important to them and included input from the review's independent Patient Reference Group, which was established to inform the 2021 government response. The MHRA continues to develop and introduce new systems, processes and training to ensure its teams have a means of engaging and involving patients and the public, embedding the patient and public voice in decision-making. The MHRA is working across the health sector to improve the effectiveness of patient engagement and share patient insight. A patient outcome evaluation framework will provide the agency with a robust

understanding of progress in delivering the MHRA's vision of being a patient focused regulator.

MHRA Funding

84. In 2021-2022, the MHRA's activities were funded as set out below:

    a. Medicines regulation is funded from fees charged to the regulated industry. In setting its fees the MHRA takes account of full cost recovery rules as set out in HM Treasury's Managing Public Money document.

    b. Devices regulation is funded by the DHSC with approximately 10% of its revenue from fees charged for services.

    c. The MHRA laboratories, formerly the NIBSC, derive approximately half of their revenue from fees charged for services, including the sale of biological standards, and from research funding. The DHSC provides the remaining funding to finance the MHRA laboratories' important public health functions.

    d. The Clinical Practice Research Datalink ("CPRD") is the MHRA's real-world data research service supporting retrospective and prospective public health and clinical studies. The CPRD collects de-identified patient data from a network of GP practices across the UK. Primary care data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset. The data encompass over 60 million patient records, including 16 million currently registered patients. CPRD recovers its costs via research service fees. Most of its revenue is through Multi-Study Licences to commercial clients. The balance is made up through the sale of a number of other service lines.

85. Further information about the Agency's funding arrangements can be found within its 'Annual Report and Accounts for 2020/21' [**JR/17 – INQ000274032**]. The MHRA provides bespoke scientific advice and guidance to manufacturers, for example on the development of a medicine. Under normal circumstances, the MHRA encourages manufacturers to contact the MHRA as early in the process as possible to seek regulatory advice. The MHRA charges fees to manufacturers for its regulatory, licensing and advice activities. Fees and the activities chargeable are published online [**JR/24 – INQ000274040**]. These reflect the charges provided for by regulations, such as The Medicines (Products for Human Use) (Fees) Regulations 2016 (as amended). The standard principle is to set charges to recover full costs. This in practice means that the regulated sector (rather than the taxpayer) bears

the cost of regulation. Another principle is to ensure that the MHRA does not profit from fees or make a loss which must then be subsidised by the DHSC or wider Government.

86. For certain projects, the MHRA receives grant funding which will include conditions of the funding as to the scope and the delivery of the work. The MHRA is accountable to the grant funding bodies for undertaking the work within the scope of the grant. In respect of Covid-19, the MHRA received such funding from the DHSC, the Coalition for Epidemic Preparedness Innovations and the World Health Organisation.

87. I am asked to comment on the impact, if any, which the MHRA's funding arrangements – specifically that it receives funding from industry – has on the MHRA's impartiality in making regulatory decisions. All of the MHRA's regulatory decisions are based on the safety, quality and effectiveness of the medicine under review and are in no way influenced by the set fees it charges for the services provided to industry. An organisation paying fees to the MHRA in no way guarantees that their product will gain licensing approval. As I have described above, there is a strict Code of Practice on managing conflicts of interest which is observed by all independent experts who provide scientific advice and there is a Corporate Policy for all staff to declare any interests annually.

88. The MHRA recovers 86% of its regulatory costs from the fees charged for the services we provide to industry. This is in line with many other regulators: the FDA recovers approximately 48% of its budget and the EMA recovers around 92% in the same way. Other parts of the agency, for example those involved in scientific research, obtain income from other sources, including grants.

89. Obtaining its income from the regulated sector in this way enables the MHRA to match resource with demand. If not funded in this way, the MHRA would be less flexible and less able to run its operations independently from central government. This flexibility was already somewhat diminished following the termination of the Trading Fund status formerly held by MHRA until 1 April 2022.

90. During the pandemic, the MHRA proactively approached manufacturers on the development of Covid-19 vaccines to support development and access to such products in the shortest possible time, for the benefit of UK public health. This took place both in relation to clinical trials and for prospective marketing authorisation applications. As these activities

were proactively undertaken by the MHRA, these fees were not chargeable. The MHRA did continue to charge fees for the marketing authorisation applications considered.

91. For Covid-19 products, the MHRA provided scientific advice to developers in teleconferences that could be arranged at very short notice. The MHRA did not charge for these Covid-19 vaccines and therapeutics scientific advice meetings.

92. As I will later address in more detail, the DHSC acted as the applicant for Covid-19 medicinal products to be considered under regulation 174. The applicant, under normal circumstances would typically be the manufacturer in a standard marketing authorisation process. There was no agreed charge for regulation 174 activities or on who was liable to pay and as such, these activities were not chargeable. Non-regulation 174 activities continued to be charged as normal.

93. The function of the MHRA's laboratories, formerly known as NIBSC, is set out above at paragraph 17. The laboratories are the UK's designated OMCL, responsible for independent regulatory testing of biological medicines within the framework of the European Union. Once approved for marketing and supply, the Covid-19 vaccines and biological medicines were batch tested by the MHRA OMCL before they were released for use in patients and the public.

94. The MHRA examines every batch of biological medicines (including vaccines) that is manufactured for use in the UK, independently of the testing required by the manufacturer. The MHRA levies a fee per service for OMCL independent batch release testing and certification. To release onto the UK market their Covid-19 vaccine in the UK, manufacturers need a certificate. The only statutory fees charged by MHRA laboratories to manufacturers are those for the batch testing and certificates.

The authorisation of vaccines and therapeutics

Authorisation of clinical trials

95. The first step in the development process of a new medicine involves researching the medicine in the laboratory and testing it in clinical trials. Companies developing new medicines, including vaccines (termed investigational medicinal products or "IMPs") first

need to obtain an authorisation to run clinical trials from the relevant national competent authority, which in the UK is the MHRA.

96. The MHRA regulates clinical trials in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 ("the 2004 Regulations") and provides scientific advice to applicants concerning clinical trial design and the data needed to support a clinical trial. The MHRA has responsibility for authorising clinical trials with medicinal products conducted in the UK. For each clinical trial, the sponsor/applicant submits a Clinical Trial Application for a clinical trial authorisation. The sponsor of a clinical trial is the person who takes responsibility for the initiation, management and financing of that trial. The type of trial must be specified as Phase I, Phase II, Phase III, or a combination. These phases are explained further below.

97. The MHRA's assessment of a clinical trial involves a detailed review of the clinical trial authorisation application and supporting documents (such as the Clinical Trial Protocol, Investigator's Brochure or Summary of Product Characteristics and the investigational medicinal product dossier). The prime concern is patient safety, and the scientific assessment is divided into three parts: non-clinical, pharmaceutical, and medical. When the assessment is complete the MHRA issues an opinion letter that either authorises the trial or requests further information. If further information is requested, the MHRA considers the applicant's responses before finally authorising or rejecting the trial proposal. During the course of the clinical trial, the sponsor may wish to amend the trial proposal and amendments are assessed and approved by the MHRA before they may be implemented.

98. During the pandemic, the MHRA proactively approached manufacturers of interest to support their development of Covid-19 investigational medicinal products in the shortest time possible to address the significant, urgent public health need. I am asked what effect, if any, did the abbreviated time frames for the Covid-19 vaccine clinical trials have on the reliability of data on safety and efficacy gleaned from those trials and what steps were taken to mitigate any risks of such an abbreviated approach. I seek to address these points at paragraph 138 below, however in summary: the assessment process although expedited, was as robust as for any clinical trial, ensuring the reliability of the trial outcomes. Safety and efficacy considerations gleaned from the trial data would have been considered in the

context of any limitations of the trial. A key step to mitigate any risks was close and frequent dialogue with the developers, especially in relation to the statistical questions.

99. Clinical trials are conducted via a series of phases to test the safety and effectiveness of the trial medicine. Earlier phases are smaller trials which test the safety of the medicine usually in healthy volunteers and identify any side effects it may cause. Later phases progress to testing medicines on their target patient population, then in larger groups to identify whether the new treatment is acceptably safe and efficacious and to find the appropriate dose. In most cases, all medicines will go through Phase I, II and III trials, and some medicines will also undergo Phase IV trials where the safety, side effects and effectiveness of the medicine are evaluated in clinical use.

100. In summary, the phases are:

    a. **Phase I study** – this is an initial safety trial involving a small group of participants to assess whether the medicinal product is safe in humans and the appropriate dosage. Phase I trials will test the medicinal product in healthy adults in the UK, or in a more 'relevant' target population.
    b. **Phase II study** – this is a trial to look at the safety and immune response (immunogenicity) if relevant, in a larger group of participants. The participants usually comprise the target group for whom the medicinal product is intended, for example adults, children, and/or infants. In Phase II, a study will often seek to determine the optimum product dosage for efficacy.
    c. **Phase III study** – this involves a larger group (many hundreds or thousands of trial participants) to gain statistically significant evidence of efficacy and to collect further safety data for inclusion in the product information (the Summary of Product Characteristics and Patient Information Leaflet).
    d. **Phase IV** – this phase supports post-marketing surveillance and collects data across a wider population that is using the product, to detect rare adverse effects and assess long term effectiveness.

Assessment of applications for product licences

101. If the data from the trials undertaken with the medicinal product shows efficacy in the indicated population, at the dose under investigation with an acceptable safety profile, the manufacturer may then decide to apply to the relevant regulatory authorities, such as the

MHRA, for a product licence (termed in EU regulations, a marketing authorisation). Applicants are asked and expected to provide assurance to the MHRA that they have provided all information and evidence available both for and against their product. A scientific review is then undertaken by a team of scientific and clinical assessors within the MHRA with reference to internationally agreed standards.

102. I am asked whether the MHRA is entitled to withhold any information from the public in relation to its assessment of an application for authorisation. The MHRA may withhold information submitted as part of a marketing authorisation application including commercially sensitive information, personal data, information protected by legal privilege and information that, if disclosed, could harm public health or safety. Information may also be withheld during a procedure where to disclose would harm the integrity of the procedure.

103. For Covid-19 vaccines, prior to the start of data submission the MHRA participated in World Health Organization ("WHO") and ICMRA workshops which were attended by international regulators where the regulatory aspects of Covid-19 vaccine development were discussed. Regulators agreed several aspects of vaccine development, e.g., the need for randomised, double blind, controlled trials with laboratory-confirmed Covid-19 infection of any severity as the primary trial endpoints. Agreement was also reached on statistical evaluation of the trial results, e.g., the minimum vaccine efficacy that would be considered acceptable and the lower limit of the confidence interval.

104. The MHRA adopted these requirements and followed normal regulatory requirements, as set out in medicinal product guidance documents issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH"), EMA and other bodies. For example, all quality-control release tests, including key tests for vaccine purity, identity, and potency, were required to be validated and shown to be suitable for the intended purpose. Demonstration of the stability and expiry date of the vaccine in its final container when maintained at the recommended storage temperature, were required.

105. The results of the clinical trials and other data on safety, quality and effectiveness received from vaccine developers were summarised in a scientific assessment report together with a critical appraisal of benefit risk prepared by MHRA assessors. This report was provided to the CHM, which was formally consulted at a meeting for its independent advice on benefit

risk, on any warnings or precautions, on the risk management plan and on the information for healthcare professionals and patients.

106. The MHRA requires that the manufacturing process for the investigational medicinal products used in clinical trials is consistent with the process used for the final product submitted for authorisation. In some instances, improvements were made by the manufacturer to the manufacturing process, or 'Process 1', to adjust the scalability, robustness, and productivity in preparation for large scale manufacture (designated 'Process 2'); scaling of manufacturing processes is a common occurrence in the manufacture of medicines. Manufacturing steps that were not scalable were replaced with those designed to provide a similar or better impurity profile. This 'Process 2' drug substance was required to be shown comparable through side-by-side comparability studies and heightened characterisation testing. New processes were validated at all manufacturing sites and submitted for review and approval. Vaccines produced by both 'Process 1' and 'Process 2' were included in the clinical trials.

107. For the approval of new medicines for marketing, i.e., those including new active substances, the MHRA follows established procedures in line with regulatory practices and standards internationally.

108. Until 31 December 2020, the MHRA was subject to EU medicines legislation. The only new medical products for Covid-19 approved before 31 December 2020 were the antiviral medicine remdesivir (Veklury), the Pfizer/BioNTech (Comirnaty) Covid-19 vaccine and the Oxford/ AstraZeneca (Vaxzevria) Covid-19 vaccine, as set out later in my statement. From 1 January 2021, after the UK's withdrawal from the EU, the MHRA could authorise all medicinal products on a national basis for Great Britain.

109. Following the UK's departure from the EU, the MHRA developed some different regulatory pathways as part of its national authorisation procedures. Manufacturers could apply to the MHRA for a full national consideration of their marketing authorisation (product licence) application or could alternatively use a new European Commission Decision Reliance Procedure: see the Standard Operating Procedure in [**JR/25 – INQ000283528**]. An example of this procedure being used was in respect of tocilizumab (brand name RoActemra). On 14 December 2021 the MHRA received a variation application for tocilizumab through the

Reliance Procedure to add a new indication for the treatment of Covid-19 in hospitalised adults who were receiving systemic corticosteroids and who required supplemental oxygen or mechanical ventilation. The variation was granted on 7 January 2022 after 24 days. This shortened timeframe was possible because the MHRA relied on the decision of the European Commission made on 06 December 2021.

110. As indicated above, from 1 January 2021, the MHRA was able to grant national marketing authorisations (product licences) for Great Britain as it was no longer subject to the European Medicines Agency regulatory regime. These marketing authorisations could be 'full' or 'Conditional'.

111. A Conditional Marketing Authorisation ("CMA") is granted on less comprehensive clinical data than is normally required for a marketing authorisation when there is a public health need, if all the following criteria are met:
    a. the benefit risk balance of the medicine is positive on the evidence available.
    b. it is likely that the applicant will be able to provide comprehensive data post-authorisation.
    c. the medicine fulfils an unmet medical need; and
    d. the benefit of the medicine's immediate availability to patients is greater than the risk inherent in awaiting the additional data that are still required.

112. A CMA is valid for one year and can be renewed annually. Once a CMA has been granted, the marketing authorisation holder must fulfil specific obligations within defined timelines. These obligations could include completing ongoing or new studies or collecting additional data to confirm the benefit risk balance of the medicine remains positive. I address what is meant by the assessment of benefit risk later in the statement.

113. During the pandemic, the EMA continued to authorise new Covid-19 medicinal products (including for Northern Ireland), but not always at the same time as the MHRA. The DHSC and MHRA worked to ensure parity of access between all four nations of the United Kingdom and ensure that the same products were available in Great Britain and Northern Ireland at the same time. From 1 January 2021 onwards, this was achieved, in appropriate cases, by considering new Covid-19 medicines, including vaccines, under regulation 174 of the

Human Medicines Regulations 2012. The operation of regulation 174 is explained later in the statement.

114. In all cases, and outside a public health emergency, the MHRA endeavours to complete all initial marketing authorisation application reviews within 210 days in line with the Human Medicines Regulations 2012. Details of the process for the approval of new medicines can be found in the MHRA's Standard Operating Procedure [**JR/26 – INQ000283530**]. For compliant marketing authorisation applications which meet the requirements as explained in the MHRA's guidance [**JR/27 – INQ000283606**], the MHRA offers a 150-Day Assessment Procedure timeline [**JR/26 – INQ000283530**].

115. Common to all these procedures is the continuous focus on the evaluation of the robustness of the evidence presented on the safety, quality and effectiveness of the product. This focus was never compromised during the pandemic. The review of an application is conducted by a team of assessors, with different specialist expertise to ensure a thorough and broad assessment of the product; these include: a clinical assessor; a quality assessor; a non-clinical assessor; a risk management plan assessor; a statistical assessor; and a clinical pharmacology assessor.

116. Independent expert advice from the CHM and its expert advisory groups is sought for all applications for marketing authorisations for medicines and vaccines containing new active substances through the national route. Advice from the CHM is also sought for any other application where the assessment team has identified major concerns and where the assessment decisions are likely to have a significant impact on public health. Schedule 11 to the Human Medicines Regulations 2012 details the requirement (and exceptions to this) for the Licensing Authority to consult the appropriate committee.

117. At the time of authorising a new medicine, including a new vaccine, information on its safety is necessarily limited due to the relatively small size of clinical trials. Consequently, applicants are required to provide a risk management plan outlining the known and possible safety issues, and to propose pharmacovigilance activities to generate data to address gaps in evidence and risk minimisation measures to address any concerns. To illustrate: Paxlovid is an antiviral that stops SARS-CoV-2 from multiplying in the body, comprising the active ingredient nirmatrelvir which is separately given with another medicine ritonavir as a

pharmacokinetic booster. Ritonavir can also interact with or affect how other medicines work, hence in the Paxlovid risk management plan these drug interactions are designated as an identified risk for this product and there is a requirement to study these. The product information contains warnings about use with the other medicines with which Paxlovid may interact, posing a risk to the patient. In addition, the MHRA worked with NHS England and the UKHSA to develop information resources to support prescribers and highlight the need to be aware of the potential for drug interactions with Paxlovid [**JR/28 - INQ000283564**].

118. In addition to the above processes, since April 2014, there has been an early access to medicines scheme ("EAMS"), which aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The scheme is voluntary and operates within the current regulatory structure. The MHRA is responsible for the scientific aspects of the scheme and will give a scientific opinion on the benefit risk balance of the medicine. Further information about EAMS can be found in the guidance 'Early access to medicines scheme (EAMS): task group and principles' (published in May 2016) [**JR/29 - INQ000274042**] and the schematic overview of the EAMS [**JR/30 - INQ000274028**]. The EAMS scheme was put onto a statutory footing in the UK on 7 March 2023 (Human Medicines (Amendments Relating to the Early Access to Medicines Scheme) Regulations 2022).

Pre-approvals

Benefit risk decision-making

119. As stated above, the MHRA is responsible for ensuring that vaccines and medicines in the UK are effective and acceptably safe. This responsibility begins at the approval stage and continues throughout the period for which a medical product remains licensed in the UK.

120. I am asked to explain the term 'acceptably safe'. No medical product is completely risk-free because all have the potential to cause side effects. The term 'acceptably safe' means that based on the assessment of the MHRA, the benefits, or expected benefits, associated with a particular product are considered to outweigh any risks associated with that product at a population level, and that the risks are acceptable in the context of the expected benefits.

121. Within the MHRA, a team of suitably qualified and experienced staff is assembled to undertake the various aspects of the safety, quality and effectiveness assessments, to review and finalise a risk management plan and to quality-assure the product information. I expand upon these processes throughout this statement. However, in summary, this employs a comprehensive approach to benefit risk assessments for vaccines, which includes a structured methodology that follows international guidance, incorporating scientific evaluation, independent expert advice, and robust post-authorisation surveillance. The post-approval assessment process includes access to epidemiological expertise in the evaluation of real-world data and special considerations for the needs of vulnerable populations.

122. There have been various efforts to quantify benefit risk analysis by regulatory authorities, but there is no one consensus method. The qualitative approach to benefit risk analysis taken by MHRA is best described as 'critical appraisal', weighing the strength of the evidence on efficacy and safety in the context of what would be expected for a particular product with its mode of action, used in a particular indication, current treatment options and taking into account the disease and the patient population in question. Increasingly, the view of patients with lived experience of a condition are involved in MHRA benefit risk decision-making.

123. In practice, in order to make an assessment of the benefit risk of a medicinal product for authorisation, the MHRA considers in particular all evidence from the pre-clinical studies and clinical trials on how well a given medical product works and its safety profile. However, clinical trials can only study a finite number of patients over a defined period, and as such the understanding of benefit risk is determined by the data available at the point of approval. For example, it is recognised that it is unlikely that very rare and rare adverse reactions would be identified through clinical trials alone as an adverse reaction which occurs at a rate of 1/300,000 would require a clinical trial involving more than 300,000 participants to be identified.

124. As such, medicinal products are authorised by the MHRA with a requirement that there is a robust post-authorisation surveillance system in place through which the benefit risk balance can be revised as real-world data becomes available as clinical usage expands. Post authorisation safety surveillance is additionally supported by a risk management plan, which sets out a medicine's safety profile, how any risks will be prevented or minimised in patients, any plans for studies or other activities to gain more knowledge about the medicinal product

and the plans to measure the effectiveness of any risk minimisation measures. I address the issue of post-authorisation surveillance later.

125. In addition, following authorisation, product information accompanying every authorised medical product specifies the conditions of use and details of any risk minimisation measures. There are two principal documents which make up this information: the Summary of Product Characteristics ("SmPC") and the Patient Information Leaflet ("PIL"). The SmPC is directed to healthcare professionals, and contains a description of a medicinal product's properties, the indication(s) and contraindication(s), how it should be used and prescribed, as well as warnings and precautions and the side effects which are considered reasonably causally related to the medicine. The PIL complements information from the healthcare professional and provides the patient with information about how to use the product safely. It reflects fully all the information contained in the SmPC in terms that are comprehensible for the lay reader.

126. Using the Pfizer/BioNTech (Comirnaty) COVID-19 vaccine as an example; in support of the regulation 174 authorisation in December 2020 for individuals aged 16 years and over, the efficacy of the Pfizer/BioNTech (Comirnaty) vaccine to prevent COVID-19 was 95% with a lower bound of the 95% confidence interval of 90%. At the time of authorisation, clinical safety data was available from more than 43,000 participants, of which more than 19,000 had been followed up for at least 2 months post second dose. As expected, there were short-lived localised and generalised reactions to vaccination, with at least 10% of recipients reporting injection site pain, fatigue, headache, muscle pain, joint pain, fever or chills. There was no evidence of serious side effects based on the clinical trial data. Thus, the vaccine was judged to be acceptably safe at the point of approval, in the knowledge that robust post-authorisation surveillance was in place to monitor the ongoing safety of the product. The SmPC and PIL for Pfizer/BioNTech (Comirnaty) can be found here: [**JR/31 – INQ000274035**] In the EMA Public Assessment Reports (see, for example, pages 134-135 of the EMA's report in respect of the Pfizer/BioNTech (Comirnaty) Covid-19 vaccine: [**JR/32 – INQ000274041**] favourable and unfavourable effects are further quantified.

127. The MHRA also considers international guidance when assessing the safety, quality and effectiveness of a medicinal product and if it should be licensed. There are guidance documents available from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH"), and from the EMA. Quality

guidelines address, among other issues, the studies required to demonstrate that the product is stable for the specified shelf life, that analytical tests are adequately validated, that impurity levels are appropriate, and that the manufacturer has demonstrated that it can reproducibly manufacture the medicine to the required specification. These quality guidelines, which are updated from time to time, are available through the ICH's website [**JR/33 - INQ000274048**].

128. Efficacy and safety guidelines address, for example: the choice of control groups, statistical considerations, the safety pharmacology studies expected to be submitted, the reproductive toxicology studies expected, etc. These safety and efficacy guidelines can be found here: [**JR/34 - INQ000274047**]; **JR/35 – INQ000274046**].

129. In November 2020 the EMA published specific guidance on clinical requirements for marketing authorisations for Covid-19 vaccines [**JR/36 – INQ000274031**]. This document sets out expectations for the design and statistical power of the pivotal Phase III trials that would provide convincing demonstration of efficacy. Guidance was also provided by the EMA on the number of participants expected to be enrolled in the trials, the period of post-vaccination safety data collection required in the marketing authorisation application and the post-approval follow up period.

Covid-19 vaccine benefit risk decision-making

130. As described, the principles of benefit risk decision-making did not change during the pandemic and importantly, assessment procedures for safety, quality and effectiveness remained the same. However, given the urgent public need for vaccines and the scale at which they would be administered, additional considerations were necessary.

131. An important example of a benefit risk consideration in the context of the Covid-19 pandemic, was vaccine dosing intervals. At the point of authorisation of the first Covid-19 vaccines, including Pfizer/BioNTech (Comirnaty) on 1 December 2020, due to the limited stocks of Covid-19 vaccines and the rapid spread of a new virus variant and significant risk to public health, there was a desire for the NHS to have the operational flexibility to enable a larger proportion of the population to receive a first dose. As such, on 22 December, DHSC asked the MHRA to consider whether the recommended interval between the two

doses of the Pfizer/BioNTech (Comirnaty) vaccine could be extended to enable a wider group to have protection from the first dose, before receiving a second dose [**JR/37 – INQ000416131**].

132. The MHRA sought advice from the CHM regarding an extension to the recommended timing of the second dose of the Pfizer/BioNTech (Comirnaty) vaccine to be supplied by the NHS. The CHM reviewed limited data on an extended dosing interval for the Pfizer/BioNTech (Comirnaty) vaccine and evidence for a dosing interval of greater than 21 days for the AstraZeneca (Vaxzevria) vaccine. In the light of these data and on immunological principles, the CHM supported a dosing regimen of at least 21 days for both the AstraZeneca (Vaxzevria) and the Pfizer/BioNTech (Comirnaty) vaccines [**JR/38 – INQ000400204**].

133. A submission outlining the assessment made by the MHRA and the CHM advice on the dosing interval was sent to the Licensing Minister on 29 December 2020 [**JR/39 – INQ000400197**] who accepted the advice.

134. At the time, this decision was also not universally accepted by other regulators, but following real world data which demonstrated the benefit of this strategy in protecting the maximum numbers of UK subjects [**JR/40 - INQ000274045**] many other regulators later adopted similar positions.

135. The MHRA scientific assessors are experienced in making benefit risk considerations in relation to innovative biological medicines, such as the novel Covid-19 vaccines. As such, in its temporary authorisation of the Covid-19 vaccines, and in decisions on dosing intervals, the MHRA was able to draw on existing expertise in vaccine technology. For example, while specific aspects of the mRNA vaccine technology are relatively new, the principal science behind the mRNA Covid-19 vaccines pre-dominantly arises from research dating as far back as the late 1970s.

136. I am asked whether mRNA vaccines have been characterised as 'gene therapies' or 'pro drugs' as distinct from traditional vaccines and if so, what the implications are from a regulatory and/or safety perspective and how these are addressed. mRNA lipid nanoparticle vaccines are a relatively new class of medicinal product formulation which does not have its own specific regulatory classification. While they share some characteristics with gene

therapy products and with pro-drugs, they are still classified as vaccines to protect against infectious diseases. Regulation 2A of the Human Medicines Regulations 2012 provides that "*A vaccine against infectious diseases is not to be treated as a gene therapy medicinal product*". Prodrugs are generally pharmacologically inactive small molecules that are converted into pharmacologically active agents by metabolic action, e.g. cleavage of a chemical linker. The prodrug approach is often used to overcome some biopharmaceutic limitation, including poor chemical stability, limited solubility or extensive drug metabolism to optimise oral bioavailability, which does not apply in the case of the vaccines. It is not clear that classification of mRNA vaccines as prodrugs would enhance the regulation of these products.

137. The mRNA COVID-19 vaccines are classified and regulated as biotechnology medicinal products and their safety was carefully considered by the MHRA, the CHM and also by international regulatory bodies around the world. The widespread use of the mRNA lipid nanoparticle Covid-19 vaccines around the world has confirmed the favourable benefit risk balance of these products.

The MHRA's Innovations for product approval during the pandemic

138. As explained above, while the MHRA's scientific standards remained unchanged and in line with international standards during the pandemic, flexible regulatory approaches were adopted. None of these flexibilities compromised the rigour of our scientific scrutiny. Flexibilities included expediting the 'rolling review' processes to ensure that medicinal products were made available in the shortest possible time as soon as the benefit risk in relation to the evidence of safety, quality and effectiveness was found to be positive.

Clinical Trials

139. The MHRA's approach to the regulation of clinical trials for vaccines and medicines to treat Covid-19 was broadly the same as that for any other clinical trial, namely, to assess the proposed study in terms of patient safety and authorise those trials and any subsequent amendments in line with the 2004 Regulations. However, during the pandemic the MHRA recognised the need for flexible and rapid clinical trial management. To that end, on 19 March 2020 at the outset of the pandemic, the MHRA published guidance on managing clinical trials during the Covid-19 pandemic to assist those involved [**JR/41 – INQ000283562**].

140. The MHRA enhanced its engagement with trial sponsors to advise on trial designs and regulatory flexibilities already available within the regulatory framework to minimise disruptions to the conduct of trials and to ensure the integrity of the data generated, while maintaining patient safety. For example, the MHRA advised on building flexibilities into protocols, remote monitoring of patients, and sending medicines to patients by post. In response to a rising number of enquiries about how to minimise disruption to the conduct and integrity of clinical trials, further guidance was published on 11 November 2020 [**JR/42 – INQ000283563**]. This included support for the commercial developers of Covid-19 vaccines and also for key non-commercial Covid-19 trials such as Panoramic, Principle, COV-BOOST and RECOVERY.

141. Clinical trial authorisation applications for Covid-19 medicinal products were also expedited, accompanied by a process of 'rolling' submission and review of the clinical trial documents as they became available. This allowed for the MHRA Clinical Trials Unit assessors to provide Sponsors of clinical trials with feedback on their documentation, prior to formal submission which significantly reduced the time taken to address any grounds for non-acceptance. The Clinical Trials Unit assessors also provided a single point of contact for trial Sponsors which simplified and streamlined the communications with the Agency. The clinical trial application assessment, although expedited, remained as robust as for any clinical trial authorisation application, still with full consideration of the same clinical trial documentation.

142. To ensure that any bias in the design of these trials is avoided, all clinical trial designs are reviewed by the MHRA assessors and clinical trial authorisations are only granted if the high standards of the MHRA are met. Measures taken by trial sponsors to eliminate bias are reviewed as part of this process. Bias is also monitored in trials through the MHRA's oversight and monitoring activities, which includes a central review of clinical trial data documents, reports and feedback from questionnaires sent to investigators. This process also involved close, regular dialogue between the MHRA and researchers as the Covid-19 vaccine trials proceeded.

143. As with all clinical trials, the MHRA required the reporting of all suspected unexpected serious adverse reactions (SUSARs). Accurate reporting of adverse reactions in clinical trials is further monitored through the MHRA's data management processes, its statistical review of the data from a trial and regular review meetings (e.g. sponsor with Contract Research Organisation / Chief Investigator). In addition to this, as part of oversight activities to assess

the conduct of a clinical trial and to ensure that trial data are being accurately reported, audits and visits to the investigator site by a trial monitor and audits were conducted for all UK clinical trials. Every trial has a data safety and monitoring board, or committee separate from MHRA which continually oversees the safety data as it is received.

144. Monitoring of clinical trials that are conducted outside of the UK is beyond the remit of the MHRA and would instead be the responsibility of the relevant regulatory body for the country in which the trial is conducted. That said, where a clinical trial was conducted globally across multiple sites with at least one in and one outside of the UK, the MHRA would require that SUSARs that occurred at the non-UK sites were reported to the UK licensing authority by trial sponsors through the usual routes of either MHRA Gateway or individual case safety report (ICSR) submissions as they remain relevant to UK trial participants. The MHRA is also provided with all safety data for all trials conducted up until the point of licence application for any medicine, as was the case for the Covid-19 vaccines.

145. This process was subsequently formalised by the MHRA's Clinical Investigations and Trials Unit through a standard operating procedure for the processing of clinical trial authorisation applications in a public health emergency, including a pandemic [**JR/43 – INQ000283524**]. This standard operating procedure was based on the processes that were successfully put in place during the Covid-19 pandemic and reflects some of the lessons learnt by the MHRA during the pandemic in respect of clinical trials. It aims to address the optimal approach in a pandemic for managing clinical trial continuity and trial participant safety, and how to support global efforts in finding safe and effective vaccines and treatments in the shortest possible time. It also describes other clinical trial processes which are part of responding to a pandemic, such as responses to queries, requests for scientific advice and working collaboratively with other MHRA units or divisions and external stakeholders.

146. I am asked whether clinical trials were sufficiently diverse in terms of age (including children), ethnic background and sex and, if not, what impact this had on assessing the safety implications for different groups. Whilst it is the responsibility of the trial sponsor to design the trial and set the inclusion and exclusion criteria, the MHRA requires that these criteria must be relevant to the target patient population and must align with the trial aims. The MHRA follows the ICH guidelines, specifically ICH guideline E8(R1) Step 5 published in 1997 and updated in 2022, which emphasises the importance of including population groups likely to use the medicinal product in the clinical trials to ensure they are adequately represented

[**JR/44 – INQ000507370**].The MHRA closely followed the demographics of the vaccine clinical trial participants in terms of age, ethnicity and sex and reported on their diversity in our public briefings. Trials were sufficiently representative to draw conclusions on safety in the indicated populations.

147. The primary consideration when conducting clinical trials is on the safety of the participants. Therefore, in some cases, certain populations or groups of people will be excluded from trials if it is considered that they might be at greater risk. Often, these at-risk groups include pregnant women, immunocompromised patients and those with certain co-morbidities. At the time of authorisation of the Pfizer/BioNTech (Comirnaty), AstraZeneca (Vaxzevria) and Moderna (Spikevax) vaccines, the CHM and VBREWG advised that sufficient reassurance of safe use of the vaccines in pregnant women could not be provided. Data from animal studies to support use in pregnant and breastfeeding individuals became available from mid-December 2020. These studies found no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development.

148. On that basis, the CHM advised that the Covid-19 vaccines should be considered for use in pregnancy, when the potential benefits outweighed any potential risks for the mother and foetus i.e., a more permissive approach allowing an individual benefit risk judgment to be made by women with their healthcare professional.

149. For groups excluded from clinical trials, an effective post-authorisation surveillance strategy is critical in understanding risk in these groups. As described in paragraph 329 certain strands of the surveillance strategy including Yellow Card Vaccine Monitor focussed on groups who were likely to have been excluded from clinical trials. Data from the Yellow Card Vaccine Monitor system as well as international studies and observational studies contributed to the advice that the use of Covid-19 vaccines in pregnant and breastfeeding individuals did not raise any safety concerns.

Regulation 174 and 174A

150. As I have outlined, after the end of the period of transition from the EU medicines regulatory system to that of a standalone sovereign regulator on 1 January 2021, the MHRA was able to grant national licences (marketing authorisations) for Great Britain as it was no longer subject to the EMA regulatory process. However, Northern Ireland remained within the European pharmaceutical regulatory system.

151. Before the UK left the EU on 1 January 2021, new Covid-19 medicinal products could be considered under regulation 174 of the Human Medicines Regulations 2012 to enable MHRA action to be taken on behalf of the UK outside of the EMA's centralised procedure. After 1 January 2021, to ensure that there was equal access to medicines and vaccines across all four nations of the UK during the pandemic, in appropriate cases new Covid-19 medicines and vaccines were considered under regulation 174 of the Human Medicines Regulations 2012 in order to extend supply to Northern Ireland at the same time as for Great Britain.

152. Regulation 174 operates to disapply, on a temporary basis, the standard authorisation procedures and regulations where that is in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation, which may cause harm to human beings. The Covid-19 pandemic met this definition and therefore new Covid-19 medicines could be considered under regulation 174.

153. It should be noted that regulation 174 approval is not the same as a marketing authorisation, however through the amendment to the Human Medicines Regulations 2012 which inserted a new regulation 174A on 17 October 2020, and the statutory framework setting out the action to be taken in the event of a breach of the conditions, the MHRA was able to define safeguards for the supply and use of unlicensed products which mirrored the conditions of a licence. More information on regulations 174 and 174A can be found at [**JR/45 – INQ000283549**]. The first uses of the regulatory framework for Covid-19 products, including the referral to the Licensing Minister and the use of regulation 174, were for Covid-19 vaccines.

154. I am satisfied that the disapplication of the standard authorisation procedures via regulation 174 had no impact on the MHRA's rigorous assessment of the safety of the Covid-19 vaccines. The MHRA's scientific standards remained unchanged and in line with international standards during the pandemic. The rigour of our scientific scrutiny of the vaccines for authorisation, and in post-marketing surveillance, was exactly the same as it would have been for a CMA or MA process. In addition, the amendment to the Human Medicines Regulations 2012 to insert a new regulation 174A on 17 October 2020, made it clear that the MHRA was able to define conditions and safeguards for the supply and use of products authorised for supply under regulation 174. This precisely mirrored the conditions of

a licence (CMA or MA). In addition, the new regulation 174A set out the statutory framework for the action to be taken in the event of a breach of the conditions. It is relevant that the temporary authorisation of supply of Covid-19 vaccines under regulation 174 was accompanied by terms set out in Regulation 174 Information for UK Healthcare Professionals and Patients [**JR/46 – INQ000507357**], and that the subsequent approvals by other jurisdictions, in particular by the EMA and FDA, did not differ in any material respect.

155. Currently, patients in Northern Ireland can still access medicines and vaccines that are authorised in Great Britain if they are authorised in the EU first. If, however, there is a medicine authorised in Great Britain that has not been authorised in the EU, then regulation 174 could be used to ensure Northern Ireland can access medicines and vaccines at the same time as Great Britain. The Northern Ireland MHRA Authorised Route (NIMAR) has been developed as an alternative to the use of regulation 174. The NIMAR enables wholesale dealers to supply medicines from Great Britain to Northern Ireland. This provides a route for the lawful supply of medicines in compliance with UK and EU rules, where there is a risk that the clinical need in Northern Ireland for that medicine cannot otherwise be met. This includes the supply of medicines that are unlicensed in Northern Ireland, but which are licensed and approved in Great Britain. Supplying a medicine via NIMAR is justified if it is essential on public health grounds. Having this additional route for supply means prescription-only medicines can be supplied to Northern Ireland to meet clinical need in accordance with their Great Britain marketing authorisation.

156. The licensing of medicines is addressed within the Windsor Framework (as explained within guidance produced by the MHRA: [**JR/47 - INQ000507356**]. The Framework will come into effect from 1 January 2025. From this point, novel medicines such as vaccines, will be, and can only be, licensed on a UK-wide basis. This provision means that medicines will be authorised at the same time and on the same basis, across the UK.

Accelerated Rolling Reviews

157. During the Covid-19 pandemic, to increase efficiency and to progress the regulatory review in the shortest possible time, evidence in support of the assessment of Covid-19 medicines and vaccines was considered in an expedited and flexible 'rolling review' procedure. This allowed companies to provide 'packages' of data as they were generated so that the review process could start as early as possible, with the provision of further data

packages as the review was ongoing [**JR/48 – INQ000283529**]. Normally, the MHRA would ask companies to put together a finalised set of packages of information covering all the required types of evidence before submitting their marketing authorisation application.

158. As already described, the overall process usually takes approximately 210 days from receipt of a final set of packages of data to determination of the application but the processes for Covid-19 medicines and vaccines were expedited in the context of a public health emergency, with timelines dependent on what and when data packages were available throughout the process. The general aim was to have completed all inspections, pre-clinical, quality and risk management planning assessments by the time the final clinical trial evidence of efficacy and safety was available, so that once a positive benefit risk balance was demonstrated there were no further delays in approving the vaccine or medicine. It provided for extended time for requests for information to be met and addressing any potential causes of non-approval. The use of the flexible rolling review procedure meant that the MHRA authorised some medicines and vaccines significantly sooner than would otherwise have been the case. For example, Paxlovid (nirmatrelvir with ritonavir) was authorised in 37 days, the Pfizer/BioNTech (Comirnaty) vaccine was authorised in 58 days and Lagevrio (molnupiravir) was authorised in 127 days. The days mentioned above include the total review time, which was dependent on the data available, and issues identified during the review process, and advice from the CHM and its EWGs.

Priority variations procedure

159. The MHRA implemented priority and expedited assessment for national variations (including batch-specific variations) of Covid-19 medicines and other medicines that the DHSC confirmed were in short supply. A variation here refers to a change to the terms of a marketing authorisation. As part of an expedited process, the MHRA assessment teams were emailed directly with advance notifications by the companies that a variation application was to be submitted. Once the assessment teams received the variation application, they followed the normal variation assessment process but provided a prompt response to the applicant with the decision based on the evidence of safety, quality and effectiveness.

Batch testing

160. Once approved for marketing and supply, the Covid-19 vaccines and biological medicines were batch tested by the MHRA Official Medicines Control Laboratory ("OMCL"), described

further at paragraph 186, before they were released for use in patients and the public. The purpose of this testing is to ensure that each batch of products meets the quality standards defined in their marketing authorisations (product licences), and it involves the thorough laboratory evaluation of their quality and biological activity. The MHRA examines every batch that is manufactured for use in the UK, independently of the testing required by the manufacturer. Medicines batches (including vaccines) that comply with the required specifications are certified, the manufacturer is issued with a certificate specific to the batch that has been tested, and the batch can then and only then be released by the manufacturer onto the UK market.

161. While manufacturers were in the process of developing vaccines, the MHRA prepared to batch test multiple vaccines simultaneously (once approved) in the MHRA OMCL by a process known as 'technology transfer'. This is a standard approach for any new product and involves MHRA laboratory scientists liaising with the manufacturers to have access to the methods that manufacturers have developed and tailored to their product. The MHRA scientists establish the methods in their own laboratories under the quality system, confirming that these methods work in that setting, are reproducible, that the data is comparable to that from the manufacturer, and that these meet the proposed product specifications.

162. The MHRA agreed to the request of the then Deputy Chief Medical Officer to prepare the process for COVID-19 vaccine batch testing at scale. This process ensured the MHRA were able to test a sufficient number of batches across an increasing number of vaccines, to enable the manufacturers to send sufficient doses to the UKHSA (at the time PHE) to meet the targets. The MHRA greatly exceeded these targets. For example, the first Government target was 15 million doses by mid- February 2021. From the date of authorisation of the first vaccine, the MHRA released batches that meant an average of 2 million doses per week were available, resulting in 22.9m doses available for this February target.

163. I am asked about inspections and regulation of Covid-19 vaccine manufacturing facilities. Vaccine manufacturers, as for any medicines manufacturers are subject to an initial inspection by the MHRA which is then followed up by risk-based inspections, under the appropriate inspection programme. Our model is outlined in SOP M206 GMP Risk based inspection programme and is based on the EMA approach [**JR/49 – INQ000507349**]. These inspections verify the standards of the facility, that operations comply with Good Manufacturing Practices,

and that products are manufactured in accordance with the details in the approved marketing authorisation. As well as inspection of the manufacturing facility, when a marketing authorisation holder wants to release a batch of a vaccine or a blood product to market, they must get the batch tested by an OMCL, as described above.

The MHRA's evaluation of pre-approval innovations

164. There was significant benefit to patients and the public from the approval of safe, effective medicines and vaccines for Covid-19 in the shortest possible time. The four main areas of innovation were in the scientific advice service, in clinical trials approvals, in accelerated rolling review assessment and in consulting the independent expert committees who made themselves available at an increased meeting frequency. The pre-approval innovations did not in any way reduce the scientific rigour or standards applied when evaluating the evidence. The innovations did, however, require working in new ways, with close oversight from managers to ensure that the integration of data assessments was robust and timely. Assessment staff responded without hesitation to the clear public health need to work differently but this meant all concerned, in particular managers, accepting the challenge. Expert Committee members also devoted considerable effort to providing independent advice as soon as it was needed.

165. The MHRA adapted its established scientific and regulatory advice service during the pandemic. Usually, MHRA was able to offer in-person scientific advice meetings with subject experts, on average, three months after the request. During the pandemic, to facilitate rapid development of new products, scientific and regulatory advice was provided promptly. These advice meetings were arranged at short notice and conducted by teleconference. Advice was provided through rapid minutes rather than formal letters. A single point of contact across the MHRA facilitated consistent and comprehensive advice from the licensing division, inspectorate, clinical trials unit and laboratory teams. Rapid interactions also allowed planning of dossier content and rolling review submission timings to align assessor resource.

166. Since the pandemic, the MHRA has retained virtual company meetings and increased flexibility thus allowing companies to accelerate their development plans. In a future public health emergency, the rapid advice service would be reinstated. The MHRA would also wish to introduce an enhanced service for transformative products in areas of public health need.

167. As described, overlapping clinical trial phases were permitted, allowing rapid progression to phase III. It is the MHRA's opinion that this approach should be adopted for future pandemic settings. This experience will also inform the overhaul of the clinical trials legislation announced by the government in March 2023.

168. As above, the Accelerated Rolling Reviews were used during the pandemic in response to the emergency context to expedite the MHRA's standard review processes. The enablers of the Accelerated Rolling Reviews were the agile and intensive use of MHRA resources in the context of extremely compact timelines for the MHRA to provide companies with its assessments. Accelerated Rolling Reviews often involve significant duplication of work for assessors, partly because the same datasets may need to be reviewed on multiple occasions as new data packages are received. Additional project management was needed to support more frequent interactions with manufacturers to manage timelines in light of data availability. Overall, the Accelerated Rolling Reviews are more challenging and require a greater level of resources than standard procedures. The MHRA's recommendation is that Accelerated Rolling Reviews should be used in cases of high public health need or during pandemics.

169. The final area of pre-approval innovation related to regular and frequent meetings of EWGs and of the CHM. The EWGs were set up early in the pandemic and scheduled frequently (e.g. fortnightly), to support rapid advice with the addition of ad hoc meetings as required. The EWGs provided advice on clinical trial protocols and minimum data requirements to support safety, quality, and effectiveness and allowed for frequent consultation of experts on these subjects. These discussions fed into international discussions at WHO, ICMRA and the Access Consortium. During the pandemic, the Covid-19 EWGs met a total of 129 times.

170. The EWGs advised on data packages in close to real-time to support the accelerated rolling reviews. Where necessary, the independent experts reviewed the data in parallel with the MHRA assessors, while always preserving separation of the roles. Although resource intensive, without doubt access to timely independent expert advice was key to achieving early access to Covid-19 vaccines and therapeutics in the UK. A similar approach has been adopted to support the current development of cancer vaccines and would be reinstated in the event of a further pandemic.

Involvement of other bodies in the MHRA's approval process

171. I have been asked to outline the respective roles of the following organisations (and any other relevant bodies) in the MHRA's approvals process for medicines and vaccines:

i. The Department of Health and Social Care ("DHSC");

ii. The Commission on Human Medicines ("CHM") and its Expert Working Groups (Covid-19 Therapeutics Expert Working Group, Covid-19 Vaccine Safety Surveillance Expert Working Group, and Covid-19 VBREWG);

iii. The Joint Committee of Vaccination and Immunisation ("JCVI");

iv. The National Institute for Health and Care Excellence ("NICE");

v. The Research to Access Pathway for Investigational Drugs for COVID-19 ("RAPID C-19");

vi. The Therapeutics Taskforce and the Antivirals Taskforce;

vii. The UK Covid-19 Therapeutics Advisory Panel ("UKCTAP"); and

viii. The MHRA's laboratories (formerly the National Institute for Biological Standards and Control ("NIBSC")).

172. The MHRA always guards its independence as the UK regulator for medicines and medical devices. As such, the organisations listed above which are outside of the MHRA play no direct part in the MHRA's marketing authorisation approval process. As the Chief Executive of the MHRA, I am ultimately accountable for all decisions taken by the MHRA, and this remained the case throughout the pandemic response. I was assisted by my Executive team, the MHRA Board and wider MHRA officials. While maintaining its regulatory independence, the MHRA worked with government departments, agencies and wider, and did so continuously throughout the pandemic. The procedural and advisory involvement of other relevant bodies in the MHRA's marketing authorisation approvals process is described below.

The Department of Health and Social Care

173. I have earlier set out the working relationship between the MHRA and the DHSC. Under normal circumstances, the DHSC does not play a role in the MHRA's regulatory processes. However, during the pandemic the MHRA was required to liaise with DHSC in respect of all public announcements including announcements on marketing authorisations. From June 2020 the MHRA was required to both formally 'grid' announcements with DHSC and No 10 and, for the duration of the pandemic, to clear all content ahead of publication with Ministers via their private offices in a separate clearance process [**JR/50 – INQ000400193**]. Also, during

the pandemic and as a result of the UK's exit from the European Union, the DHSC and the MHRA worked to ensure parity of access to vaccines and medicines between all four nations of the United Kingdom and ensure that the same products were available in Great Britain and Northern Ireland at the same time. From 1 January 2021 onwards this was achieved by, in appropriate cases, considering new Covid-19 medicines under regulation 174 of the Human Medicines Regulations 2012 as set out at paragraph 150.

174. During the pandemic the DHSC acted as an 'applicant' by requesting the MHRA's consideration of the suitability of new medicinal products for Covid-19 for temporary authorisation under regulation 174. In each instance, the MHRA would undertake a rigorous scientific assessment of the evidence of safety, quality and effectiveness relating to a medicinal product or vaccine and provide this assessment to the CHM. The CHM would consider such scientific reports (in addition to the recommendations of its Covid-19 Therapeutics Expert Working Group (Covid-19 "Therapeutics EWG" and "Vaccines Benefit Risk" EWG) and provide its advice which was put by the MHRA to the Secretary of State (in practice delegated to a junior Minister, referred to as the Licensing Minister).

The Commission on Human Medicines and its Expert Working Groups ("EWGs")

175. I have earlier outlined the role of the CHM and its EWGs in providing independent expert advice on vaccines and medicinal products to health ministers, which continued during the pandemic. As an independent expert advisory body, the CHM provided independent scientific advice to health ministers, the in practice 'Licensing Minister'. Where the Licensing Minister accepted the CHM's advice (which in practice occurred on all occasions), the MHRA then issued the temporary authorisation for supply under regulation 174. All key decisions on Covid-19 vaccine and therapeutics were taken by the Licensing Minister, supported by the MHRA's recommendations. It was open to the Licensing Minister to reject the MHRA's recommendation should they have reasons to do so, although this did not in fact occur.

176. The Covid-19 Therapeutics EWG was established in March 2020 and stood down in May 2023. Its role was to advise the CHM on the safety and efficacy of treatments and prophylaxis considered for use in Covid-19. This EWG also advised the CHM on measures to minimise risks and optimise the benefit risk balance of anti-viral agents and supportive therapies proposed for the treatment of Covid-19 infection and its complications. The CHM considered

the recommendations of the Covid-19 Therapeutics EWG in deciding whether to support the approval of authorisation applications for Covid-19 medicines.

177. The CHM established the Covid-19 Vaccine Safety Surveillance EWG in May 2020. This group worked to establish the core principles and methodologies of a robust surveillance strategy for Covid-19 vaccines in the event that they gained regulatory approval. It was anticipated that, based on previous mass immunisation programmes, there would be large numbers of reports to the MHRA of suspected adverse reactions generating safety signals which would require real-time monitoring to identify, evaluate and take prompt regulatory action on.

178. The Covid-19 Vaccine Safety Surveillance EWG convened on four occasions between May and October 2020. The output of these meetings was the Report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance [**JR/51 – INQ000274036**] which defined the key components of the surveillance strategy for the Covid-19 vaccines which I address later in this statement. The Covid-19 Vaccine Safety Surveillance EWG was not involved in the approval of any Covid-19 vaccines or medicines, nor was it involved in advice on any safety signals.

179. Of particular significance for the Covid-19 vaccine approval process, the VBREWG was established in August 2020 to advise the CHM on the safety, quality and effectiveness of Covid-19 vaccines and the balance of benefit and risks prior to and following initial authorisation, based on rigorous scientific evaluation by the MHRA teams of scientists and clinicians. The MHRA's assessments of the benefit risk profile of each vaccine for which data were submitted were considered by the EWG and the EWG advised the CHM. The VBREWG reported its conclusions and recommendations to the CHM about marketing authorisation and the conditions for marketing authorisation of the Covid-19 vaccines. Further details of the activities of the Covid-19 Therapeutics EWG and the VBREWG in 2021 are described in the Human Medicines Regulations 2012 Advisory Bodies Annual Report of 2021 [**JR/52 – INQ000274038**].

The Joint Committee on Vaccination and Immunisation

180. The Joint Committee of Vaccination and Immunisation ("JCVI"), an independent expert body established in 1963, provides advice to UK health departments on immunisation policy for all vaccines used in the UK, including Covid-19 vaccines. Immunisation policy includes determining eligibility and priority groups for vaccinations, as well as the timing and frequency of vaccine administration. The JCVI's advice is based on considerations of evidence on the burden of disease, vaccine safety and efficacy, and on the impact and cost-effectiveness of immunisation strategies. The JCVI is informed of the benefit risk assessment by the MHRA and the advice of the CHM on vaccine safety in its consideration of immunisation policy.

181. The JCVI's decision-making processes and remit are entirely distinct from those of the MHRA. Therefore, while the JCVI is made aware of the advice of the MHRA and CHM, the JCVI is not involved in decisions concerning the authorisation of vaccines or medicines and has no influence on them. Similarly, the MHRA does not take part in formulating UK vaccine policy recommendations, such as whether to procure and deploy a vaccine for a particular group, or at all. Such decisions are within the remit of the JCVI alone. There is advantage in having the two approaches of separate regulatory and deployment decisions, side by side but taking into account different criteria: the regulatory approach which is strictly focussed on safety, quality and effectiveness provides the terms and measures which support effective and safe use, and the health authority's deployment advice, which can prioritise different products depending on wider factors including availability of vaccines, changing disease pattern and any vulnerable groups.

National Institute for Health and Care Excellence

182. The National Institute for Health and Care Excellence ("NICE") provides national guidance and advice for England about health, including vaccine uptake. It also advises on which therapeutic products (excluding vaccines) and treatments are to be made available on the NHS in England. The MHRA provided scientific input to inform the development of NICE's evidence-based guidelines, health technology assessments and recommendations related to Covid-19, by sharing data and analyses on the safety and efficacy of Covid-19-related products. NICE did not have any role in the marketing authorisation process for Covid-19 vaccines and/or therapeutics and had no influence on this.

Research to Access Pathway for Investigational Drugs for COVID-19 (RAPID C-19)

183. The RAPID C-19 group was a multi-agency initiative which was set up and led by NICE. The group was established early in the pandemic to coordinate the activities of healthcare bodies and get treatments for Covid-19 to patients quickly and safely. The RAPID C-19 group monitored emerging trial evidence on the clinical effectiveness of potential Covid-19 treatments during the pandemic. The group reviewed the briefing documents prepared by NICE to see whether the current evidence supported the use of a treatment for Covid-19. The MHRA attended meetings of the RAPID C-19 oversight group. The RAPID C-19 did not have any role in the marketing authorisation process for Covid-19 vaccines and/or therapeutics and had no influence on this.

The Therapeutics Taskforce and the Antivirals Taskforce

184. The Therapeutics Taskforce (established in April 2020) and the Antivirals Taskforce (established in April 2021) were amalgamated in April 2022 into a single taskforce led by the DHSC: the Antivirals and Therapeutics Taskforce which was stood down on 31 March 2023. The Therapeutics Taskforce was established to drive forward efforts to ensure that the UK population would have access to clinically safe and effective treatments as soon as possible. Its responsibilities were to: identify potential Covid-19 therapeutics; trial these as part of an advanced programme of clinical trials; and make effective treatments available to UK patients. It brought together key clinical, research and industry stakeholders to coordinate and provide oversight to identifying, procuring and deploying treatments for Covid-19. This taskforce did not have any role in the marketing authorisation process for Covid-19 vaccines and/or therapeutics and no influence on this.

The UK Covid-19 Therapeutics Advisory Panel

185. The UKCTAP was an independent advisory panel which considered potential Covid-19 treatments to be proposed for national publicly funded clinical trials established by UK Research and Innovation (UKRI). The panel reviewed available scientific evidence and made recommendations to the principal investigators of each trial, the Chief Medical Officer for England, and the Chief Scientific Adviser for the DHSC. The UKCTAP was attended by Professor Sir Munir Pirmohamed, Chair of the CHM. UKCTAP did not have any role in the marketing authorisation process for Covid-19 vaccines and/or therapeutics and had no influence on this.

The MHRA's Laboratories (formerly NIBSC)

186. I have discussed in brief the function of the MHRA's laboratories, formerly the single entity known as the National Institute for Biological Standards and Control ("NIBSC"). The laboratories are the UK's designated Official Medicines Control Laboratory ("OMCL"), responsible for independent regulatory testing of biological medicines under Regulations 60A and 60B of the Human Medicines Regulations 2012 (as amended). The MHRA carries out independent control testing of certain biological medicines, including vaccines and medicinal products that are made from human blood, as required by UK law and prior to use of the products. Independent control testing means that biological medicines including Covid-19 vaccines are batch tested to confirm that key safety and quality parameters meet the product specifications.

187. I can confirm that no other outside body undertook work or made recommendations relevant to the MHRA marketing authorisation process for licensing Covid-19 vaccines and medicines.

The MHRA's role in authorising Covid-19 vaccines and medicines

188. The MHRA authorised nine vaccines for Covid-19 in the UK, as well as four strain-adapted vaccines.

189. At time of drafting in December 2023, the nine vaccines authorised by MHRA are:

i. Covid-19 Vaccine Pfizer/BioNTech (Comirnaty) – messenger RNA ("mRNA") vaccine;
ii. Covid-19 Vaccine AstraZeneca (Vaxzevria) – adenoviral vector vaccine;
iii. Covid-19 Vaccine Moderna (Spikevax) – mRNA vaccine;
iv. Covid-19 Vaccine Janssen – adenoviral vector vaccine;
v. Covid-19 Vaccine Novavax (Nuvaxovid) – protein subunit vaccine;
vi. Covid-19 Vaccine Valneva – inactivated whole virus vaccine;
vii. Covid-19 Vaccine Sanofi-Pasteur (VidPrevtyn Beta) – protein subunit vaccine;
viii. Covid-19 Vaccine SK Chemicals (SKYCovion) – protein subunit vaccine;
ix. Bimervax (previously Covid-19 Vaccine HIPRA) – protein subunit vaccine.

190. The four strain-adapted vaccines that are authorised by MHRA are:

i. Moderna (Spikevax) bivalent Original/Omicron BA.1;

ii. Pfizer/BioNTech Comirnaty Original/Omicron BA.1;
iii. Pfizer/BioNTech Comirnaty Original/Omicron BA.4-5;
iv. Moderna (Spikevax) bivalent Original/Omicron BA.4-5.

191. The MHRA authorised the supply of six new medicines for Covid-19 in the UK:
v. Remdesivir (Veklury);
vi. Casirivimab and imdevimab (Ronapreve);
vii. Molnupiravir (Lagevrio);
viii. Sotrovimab (Xevudy);
ix. Nirmatrelvir with ritonavir (Paxlovid);
x. Tixagevimab and cilgavimab (Evusheld) as pre-exposure prophylaxis.

192. Two previously authorised therapeutics were approved by MHRA for use to treat Covid-19 which remain authorised for this use:
xi. Dexamethasone;
xii. Tocilizumab (RoActemra).

193. I have been asked by the Inquiry to set out the MHRA's role in approving each of the Covid-19 medicinal products. Further detail of the authorisation process for medicinal products both during Covid-19 and during business as usual is set out above from paragraph 95 onwards.

194. Here follows a summary of the key events with a focus on the three vaccines Pfizer/BioNTech (Comirnaty), AstraZeneca (Vaxzevria) and Moderna (Spikevax), which were the first to be authorised in the UK and made up the vast proportion of vaccinations administered in the UK during the pandemic. As of mid-2022, approximately 27 million first doses, 24.9 million second doses and 30.5 million third or booster doses of Pfizer/BioNTech (Comirnaty) had been administered. For AstraZeneca (Vaxzevria) at the same time, 24.5 million first doses, 24.1 million second doses and 57,900 third or booster doses had been administered. Finally, for Moderna (Spikevax): 1.7 million first doses, 1.5 million second doses and 9.3 million third doses had been administered by mid-2022.

195. With the authorised therapeutics, I have focused in detail on Dexamethasone, Tocilizumab (RoActemra) and Remdesivir (Veklury) as the most widely used therapeutics for Covid-19.

Weekly therapeutic usage of the authorised therapeutics during the pandemic can be found at england.nhs.uk website: [**JR/53 - INQ000371348**]. The remaining vaccines and therapeutics can be found in Annex B where their authorisations have been summarised through high-level timelines and key documents exhibited.

196. As described above, the MHRA is only responsible for authorising clinical trials which are conducted in the UK. Clinical trials carried out in other countries were authorised by the national regulators for those countries.

Vaccines

Pfizer/BioNTech (Comirnaty) vaccine

197. The Pfizer/BioNTech (Comirnaty) vaccine was the first vaccine for Covid-19 that was authorised for use by the MHRA, and the first vaccine against Covid-19 authorised worldwide. Ninety-year-old Margaret Keenan was the first person to receive the Pfizer/BioNTech (Comirnaty) vaccine at 6:31 am on 8 December 2020, making her the first person in the world to receive an approved Covid-19 vaccine. The Pfizer/BioNTech (Comirnaty) vaccine technology is based on Tozinameran, a single-stranded, 5'-capped mRNA, encoding the viral spike (S) protein of SARS-CoV-2.

198. In reaching this pivotal moment, marking the beginning of what was to be a historic mass vaccination programme, the MHRA worked quickly, innovatively, and flexibly, all whilst maintaining its standards of evidential rigour for safety, quality and effectiveness.

199. The Covid-19 Pfizer/BioNTech (Comirnaty) vaccine was evaluated in clinical trials involving more than 44,000 participants. Clinical trials for the Pfizer/BioNTech (Comirnaty) vaccine were authorised and conducted outside of the UK. The first interim efficacy analyses were made available to MHRA on 13 November 2020 and the results were extremely promising, showing the vaccine to be more than 90% effective in preventing Covid-19 in participants without evidence of prior SARS-CoV-2 infection. There were no reported Suspected Unexpected Serious Adverse Reactions ('SUSARs') within the clinical trials, including cardiac events. A SUSAR is the term used to refer to an adverse event that occurs in a clinical trial subject, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the

study drug. Reports of these reactions are subject to immediate consideration by the regulator or health authority.

200. Following this, on 17 November 2020 the MHRA was contacted by the DHSC requesting the MHRA's view on whether the Pfizer/BioNTech (Comirnaty) vaccine would be suitable for temporary authorisation for supply under regulation 174 of the Human Medicines Regulations 2012 ("regulation 174") [**JR/54 - INQ000071697**].

201. The MHRA undertook several strands of work simultaneously in connection with the Pfizer/BioNTech (Comirnaty) vaccine's authorisation and subsequent deployment. Alongside its rolling review of the vaccine's safety, quality and effectiveness, the MHRA regularly met with the manufacturer to monitor the progress of the vaccine's development. The MHRA also met with the DHSC to plan logistical elements of deployment because the vaccine required storage at a very low temperature.

202. As I have earlier described, the MHRA through its laboratories (then known as NIBSC) assures the quality of certain biological medicines, including vaccines. Only vaccines and medicines batches that comply with stipulated quality specifications are approved for release to be used. The MHRA is responsible for carrying out independent control testing/batch testing of medicinal products before they are used. The manufacturer is issued with a batch-specific NIBSC certificate which they require for release of that batch onto the UK market.

203. Through the NIBSC, the MHRA performed essential tasks to support the eventual deployment of the Pfizer/BioNTech (Comirnaty) vaccine. The NIBSC established laboratory methods required to assess the biological quality of the vaccine, including methods not applied to existing vaccines. To test Covid-19 vaccines, implementation of test methods through 'technical transfer of methodologies' from the manufacturer was undertaken. This was done 'at risk' in mid-2020 before any vaccines had been approved by the MHRA, so that batches would be ready for the UK vaccination programme in the event of authorisation.

204. The first discussions with Pfizer/BioNTech (Comirnaty) and AstraZeneca were initiated by the MHRA laboratories in May/June 2020, to discuss requirements for independent batch release testing of their vaccines. The timelines for technical transfer were necessarily short to ensure readiness for testing and certification of compliant batches. This was only possible due

to the NIBSC's specialised laboratory facilities and equipment, and the broad scientific and technical expertise across its staff. Regular communication with Pfizer/BioNTech (Comirnaty) and the laboratories technical team enabled the scientific experts to implement critical tests to be used for independent batch release testing in a timely manner.

205. The MHRA laboratories recommended that its independent testing of Covid-19 vaccines was performed in parallel with manufacturer testing to ensure timely NIBSC certification in the event of authorisation. Surge staff resource was brought on board to perform batch testing and release in the shortest possible time. This involved redeploying some staff and deprioritising other work programmes, to ensure that Covid-19 related activities could be promptly completed.

206. The MHRA was asked by the then Deputy Chief Medical Officer to position itself to test 2 million doses of vaccine/s per week. In order to be ready for such large-scale testing, funding from the DHSC was requested and approved for additional scientific and support staff resource, equipment and potential additional temporary facilities. Preparation for test readiness involved staff training, verification of materials, methods and equipment, and documentation within a Quality Assurance System. The processes were compressed from a typical period of 6-12 months to, in one case, less than 2 weeks, through reliance on existing experience and strict prioritisation of activities that would provide the most useful insight into product quality.

207. The MHRA sought advice from the VBREWG which met seven times to review and discuss the safety, quality and effectiveness aspects in relation to authorisation of the Pfizer/BioNTech (Comirnaty) vaccine. The data collected by NIBSC during its physical testing was provided to the VBREWG. The meeting minutes can be found here: [**JR/55 - INQ000400222**; **JR/56 - INQ000400223**; **JR/57 - INQ000400224** **JR/58** **INQ000400226** **JR/59 - INQ000400228**; **JR/60 - INQ000400229**; **JR/61 - INQ000400230**]. Neither the meetings with manufacturers nor the data discussions with the VBREWG impacted the independent nature of the batch release testing by MHRA laboratories.

208. The MHRA sought advice from the CHM which met on 30 November 2020 and considered the final recommendations from the VBREWG [**JR/62 - INQ000409481**] regarding the requirements for temporary authorisation for the supply of Pfizer/BioNTech (Comirnaty)

vaccine. The requirements for safety, quality and effectiveness were considered by the MHRA to be met and conditions for the product supply were discussed to ensure adequate standards of safety, quality and effectiveness were met. The CHM recommended the temporary authorisation of the proposed supply of Pfizer/BioNTech (Comirnaty) vaccine for active immunisation to prevent Covid-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older, under regulation 174.

209. On 30 November 2020, the MHRA sent a Ministerial Submission to the Licensing Minister which set out the evidence of safety, quality and effectiveness and conveyed the advice of the CHM. The MHRA recommended that the CHM advice should be accepted and that temporary authorisation for supply of the vaccine under regulation 174 should be approved [**JR/63 - INQ000400297**]. Importantly, the submission also included the plans for proactive safety monitoring on which the MHRA had previously consulted the CHM and included the report of the CHM Covid-19 Vaccine Safety Surveillance Expert Working Group which had made recommendations for safety surveillance of Covid-19 vaccines.

210. The Licensing Minister accepted the CHM advice in full and on 1 December 2020, a regulation 174 temporary authorisation for supply of the Pfizer/BioNTech (Comirnaty) Covid-19 vaccine was granted in patients 16 years of age and older [**JR/64 - INQ000410479**]. This authorisation, as described, was conditional on the fulfilment of certain conditions which the MHRA published on 2 December 2020 [**JR/65 - INQ000371351**]. The MHRA laboratory processes described above enabled it to certificate a compliant batch of the vaccine on the day of authorisation, which allowed for the prompt commencement of the UK vaccination campaign on 8 December 2020.

211. Shortly after, on 21 December 2020 the EMA granted a CMA ("EMA CMA") for the use of the vaccine in patients 16 years of age and older. This EMA CMA automatically applied in the UK as the UK remained subject to EU medicines legislation at that time. The terms of the EMA CMA aligned with those of the regulation 174 authorisation. The EMA CMA applied in Northern Ireland from 21 December 2020 and was converted to a full EMA MA granted on 10 October 2022. The Great Britain CMA was converted to a full MA by the MHRA on 9 November 2022.

212. As I have earlier described in detail, recommendations regarding dosing schedules for the vaccine were needed. Due to the rapid spread of a new virus variant and significant risk to

public health, there was a significant benefit to public health for the NHS to have the operational flexibility in relation to vaccine supply to provide a larger proportion of the population with a first dose of the vaccine by extending the dosing interval. As such, on 22 December 2020, the DHSC asked the MHRA to consider whether the recommended interval between the two doses of the Pfizer/BioNTech (Comirnaty) vaccine could be extended to enable a wider group to have protection from the first dose, before receiving a second dose [**JR/37 – INQ000416131**].

213. On 24 December 2020 the MHRA sought advice from the CHM regarding an extension to the recommended timing of the second dose. On reviewing the available data, the CHM supported a dosing regimen of at least 21 days between doses for the Pfizer/BioNTech (Comirnaty) vaccine [**JR/38 – INQ000400204**].

214. At the time of initial authorisation of the Pfizer/BioNTech (Comirnaty) vaccine, animal reproductive toxicity studies were under way, but the results were not yet available. In practice, medicinal products at the time of initial authorisation often have limited data on women of childbearing potential and pregnant and breastfeeding individuals, given that they are typically excluded from clinical trials. As such, at the time of supply under regulation 174, it was advised by CHM that sufficient reassurance of safe use of the vaccine in pregnant women could not be provided. However, it was advised that use in women of childbearing potential could be supported, provided healthcare professionals were advised to rule out known or suspected pregnancy prior to vaccination.

215. Data from animal studies for the use in pregnant and breastfeeding individuals became available from mid-December 2020. These studies found no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. On that basis, on 24 December 2020 the CHM advised that the vaccine should be considered for use in pregnancy when the potential benefits outweigh any potential risks for the mother and foetus i.e., a more permissive approach allowing an individual benefit risk judgment to be made by women with their healthcare professional. On 29 December 2020 a submission was sent to the Licensing Minister advising this amendment to the regulation 174 conditions [**JR/39 - INQ000400197**]. The advice was accepted by the Licensing Minister in full.

216. Given limited data on safety and effectiveness for other age groups at the time of initial authorisation, the Pfizer/BioNTech (Comirnaty) vaccine was initially only authorised for use in individuals 16 years of age and older. As I have earlier described, this is common for all medicinal products; in that limited licences are granted initially and then amended as new data on benefits and risks become available for assessment.

217. As new data for the Pfizer/BioNTech (Comirnaty) vaccine became available, the MHRA considered the safety, quality and effectiveness of the vaccine in younger age groups. This was an important consideration as, despite younger age groups generally experiencing less severe disease following infection with SARS-CoV-2 virus, those age groups still carried and spread the virus. As such, Pfizer sought approval to extend the indication to children aged 12 – 15 years old. On 27 May 2021 [**JR/66 - INQ000409494**] the MHRA consulted the CHM on an assessment of the results of randomised, placebo-controlled clinical trials in over 2,000 children aged 12 – 15 years.

218. The safety of the vaccine in 12–15-year-olds was reviewed carefully. No new adverse events were identified and the safety profile in adolescents was comparable with that seen in young adults. On 28 May a submission was sent to the Licensing Minister outlining the data in favour of amending the existing conditions of approval to include 12–15-year-olds [**JR/67 - INQ000400217**] and setting out the advice of the CHM, recommending that this was accepted. The Licensing Minister accepted the advice in full and approved the amendments to the authorisation.

219. Towards the end of 2021, an application by Pfizer was also made to extend the indication for the vaccine to 5–11-year-olds in a smaller 10 micrograms/dose (10µg) dose, and later, via the European Commission Decision Reliance Procedure as described below at paragraph 248, a new 3 micrograms/dose (3µg) in infants and children aged 6 months to 4 years. A line extension is a new product authorisation linked to the original marketing authorisation.

220. The MHRA sought advice from the CHM on the 29 November 2021 and 24 and 25 November 2022 for 5-11 years and 6 month – 4-year age group respectively, and the CHM advised that based on the safety, quality and effectiveness data, the amendments to the authorisations should be granted. Meeting minutes can be found here: [**JR/68 - INQ000400268**; **JR/69 - INQ000409563**]. Submissions were sent to the Licensing Minister on

16 December 2021 and 29 November 2022 respectively: [**JR/70 - INQ000400254**; **JR/71 - INQ000400273**] who accepted the CHM advice in full.

AstraZeneca (Vaxzevria) vaccine

221. The design of the AstraZeneca vaccine (Vaxzevria) is based on a chimpanzee adenoviral vector, encoding the SARS-CoV-2 S glycoprotein. The MHRA was already familiar with the AstraZeneca vaccine technology as a chimpanzee adenovirus vector utilised in the Middle Eastern Respiratory Syndrome (MERS) vaccine had been tested in previous clinical trials safely and provoked an immune response.

222. The Covid-19 Vaccine AstraZeneca (Vaxzevria) was evaluated in clinical trials internationally and in the UK involving more than 23,000 participants. The MHRA approved pre-authorisation UK clinical trials to be conducted for this vaccine at Phase I/II on 26 March 2020 and at Phase II/III on 4 May 2020. On 3 September 2020 the Phase I UK trial was suspended after a SUSAR report of transverse myelitis in a female participant. As is standard practice within clinical trials, SUSARs are monitored and thoroughly investigated before either re-starting the trial or terminating it. On 10 and 11 September 2020 the advice of the CHM [**JR/72 - INQ000400208**] was that, considering the information against a causal relationship and the report of the Data Safety and Monitoring Board ('DSMB'), the trial could be restarted. No cases of cerebral venous sinus thrombosis or cerebral haemorrhage were reported in the clinical trials, nor was there any signal for thromboembolic events.

223. In respect of the minutes from the CHM meetings on 10 and 11 September 2020 [**JR/72 - INQ000400208**], I am asked why (at paragraph 22.1.14 the Commission recommended that the Sponsor be notified: "It is expected that the DSMB will continue to monitor safety of participants and inform the MHRA as soon as possible if there is a potential new signal, particularly for neurological and thrombotic events." Thrombotic events were designated as Adverse Events of Special Interest (AESIs) before clinical trials commenced and as such were of particular interest to the MHRA, hence the reference within the minutes. AESIs associated with Covid-19 vaccines and therapeutics are discussed in further detail below.

224. I am also asked, in respect of the minutes from the CHM meetings on 10 and 11 September 2020, whether the case of a 34-year-old female subject, who suffered from a migraine following the AstraZeneca (Vaxzevria) Covid-19 vaccine during a clinical trial, was reviewed once investigations were complete, as well at the outcome of the case. This case

was reviewed in detail. A narrative was provided by the trial sponsor which described the symptoms, investigation and outcome and can be found in "section b - Clinical update on subject 020611183" of this document **JR/75 - INQ000507373**. Following review by a stroke consultant, the Serious Adverse Event was marked as resolved and unlikely to be related to the vaccination. The subject stated she was content to remain in the trial [**JR/74 –** **INQ000507371** **JR/73 - INQ000507372**].

225. Interim analysis based on 11,636 participants in the Phase III programme led by the University of Oxford was published in the Lancet on 8 December 2020 [**JR/76 - INQ000371344**]. The primary efficacy endpoint based on the pooling of two dosing regimens showed that the vaccine had 70.4% efficacy (with a 95.8% confidence interval ranging from 54.8% to 80.6%). The side effects observed with use of the AstraZeneca (Vaxzevria) vaccine in clinical trials were mild to moderate in severity and short-lived, similar to those seen for other vaccines.

226. On 24 November 2020 the DHSC requested the MHRA's view on whether the vaccine would be suitable for temporary authorisation for supply under regulation 174 [**JR/77 - INQ000059052**]

227. The VBREWG met seven times to review and discuss the safety, quality and effectiveness aspects in relation to authorisation of the AstraZeneca (Vaxzevria) vaccine. Meeting minutes can be found here: [**JR/78** **INQ000409491** **JR/79 - INQ000400233**; **JR/80 - INQ000400231**; **JR/81 - INQ000400235**; **JR/82 - INQ000400234**; **JR/83 - INQ000400237**; **JR/84 - INQ000400236**].

228. On 24 December, 2020, the CHM discussed the data on the dosing interval for the AstraZeneca (Vaxzevria) vaccine [**JR/38 - INQ000400204**]. The CHM was informed that increased efficacy for a subset of patients in the clinical trials was likely to have been the result of a longer dosing interval. Accordingly, the CHM advised the MHRA that, on the basis of the available data, the dosage interval should be between 4 to 12 weeks after the initial dose. In addition to the data available on the longer dosing interval, it is an established principle in vaccinology that immunological response tends to be greater with a longer interval between doses.

229. The CHM met on 29 December 2020 and considered the final recommendations from the VBREWG [**JR/85 - INQ000409488**] regarding the requirements for authorisation for the temporary supply of the AstraZeneca (Vaxzevria) vaccine. The requirements for safety, quality and effectiveness were considered and conditions of the product's use were discussed. The CHM advised that the proposed temporary authorisation for supply of the AstraZeneca (Vaxzevria) vaccine for active immunisation to prevent Covid-19 caused by the SARS-CoV-2 virus, in individuals 18 years of age and older, was suitable for approval.

230. On the 29 December 2020 the MHRA sought advice from the CHM on the use of the AstraZeneca (Vaxzevria) vaccine in pregnant or breastfeeding individuals. Advice was provided based on evidence from animal toxicity studies in rats which concluded there was no evidence of concern for use in pregnant or lactating individuals. Nevertheless, as described with the Pfizer/BioNTech (Comirnaty) vaccine, there were limited human studies due to the necessary limitations surrounding clinical trials in pregnant individuals. As such, the CHM advised that the vaccine should only be considered for use in pregnancy when the potential benefits outweigh any potential risks for the mother and foetus allowing an individual benefit risk judgment to be made by women with their healthcare professional.

231. Following the advice of the CHM on 29 December 2020, the MHRA sent a ministerial submission to the Licensing Minister which conveyed the CHM advice, supported by MHRA, recommending temporary authorisation of the vaccine for supply under regulation 174 be approved with these conditions [**JR/39 - INQ000400197**]. The Licensing Minister accepted the MHRA's advice. On 30 December 2020 regulation 174 temporary authorisation was granted for the supply of the AstraZeneca (Vaxzevria) in patients aged 18 years and older. On 29 January 2021 the EMA granted a CMA for the vaccine in similar terms which was valid in Northern Ireland. Unlike Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax) vaccines, the AstraZeneca (Vaxzevria) vaccine was not considered later for authorisation in younger populations due to emerging data on adverse reactions, which I will discuss later in 'Adverse Event Chronologies.'

232. On 3 February, DHSC (Antonia Williams, Director of Covid-19 Vaccine Deployment, and Professor Jonathan Van-Tam DCMO) wrote to the MHRA to seek the Agency's view on whether the three batches of the AstraZeneca (Vaxzevria) vaccine, manufactured by the

Serum Institute of India (SII), would be suitable for authorisation under regulation 174 [**JR/86 - INQ000400201**]. India supplies more than 50 per cent of global vaccines and 25% of NHS generic drugs and was one part of the supply chain for the AstraZeneca (Vaxzevria) vaccine, which also included production in parts of the EU as well as in the UK.

233. The MHRA carried out a rigorous scientific assessment of all the available evidence on safety, quality and effectiveness as well as a detailed inspection of good manufacturing practice (GMP) by Serum Institute India and its activities concerned with manufacture. Some issues identified during the inspection were quickly conveyed to staff, however there were no issues were found which were critical in nature, and which would prevent supply from the site.

234. Some issues are commonly identified at the point of inspection and managed through a corrective action and prevention plan. The Serum Institute India provided a robust corrective action plan on 19 February 2021 **[JR/87 – INQ000400336]**. The company's response to the inspection findings (in its corrective action and prevention plan) was reviewed by the inspection team as is normal practice during the inspection process. The detail provided to MHRA was deemed acceptable and a GMP certificate was issued 23 February 2021 to confirm that the SII operations met the required GMP standards. This is documented in the Inspection Report dated 3 March 2021 **[JR/88 – INQ000507333]**. Additionally, as standard, a follow up GMP inspection of the facility was conducted in April 2022. This inspection confirmed that the operations of SII remained GMP compliant. During this follow up inspection, the inspectors assessed the CAPA and confirmed that "*The deficiencies raised during the previous inspection were appropriately closed.*" GMP inspections of the SII manufacturing facility have subsequently been conducted by EU authorities, the conclusions of which also confirm the ongoing GMP compliant status of the operations. These are detailed in [**JR/89 – INQ000507339**].

235. The MHRA sought the advice of the VBREWG on 15 February [**JR/90 – INQ000409514**] and the CHM on **18 February** 2021 [**JR/91 - INQ000400264**], who advised that the batches should be authorised for supply under regulation 174.

236. On 18 February 2021 a submission outlining the advice was sent to the Licencing Minister [**JR/92 – INQ000400202**], who accepted the CHM advice in full. This assessment by the

MHRA supported the availability of an additional 4.5 million doses of the AstraZeneca (Vaxzevria) vaccine within the UK.

237. Finally, on 24 June 2021 a CMA was granted by the MHRA for the use of the vaccine in Great Britain alongside the existing regulation 174 temporary authorisation from 30 December 2020 to allow for batches with different specifications to continue to be supplied in the UK under both regulation 174 and CMA conditions, as well as allow the existing stock of vaccine supplied under regulation 174 to be used until depleted. A letter detailing the CMA and its conditions was sent to the manufacturer, AstraZeneca, on 24 June 2021 [**JR/93 - INQ000400300**].

Moderna (Spikevax) vaccine

238. The Moderna (Spikevax) vaccine is based on Elasomeran, a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

239. The Moderna (Spikevax) Covid-19 vaccine was evaluated in clinical trials involving more than 30,000 participants. Pre-authorisation trials for Moderna (Spikevax) were conducted outside of the UK. Phase III vaccine efficacy trials, known as COVE, began under Operation Warp Speed (OWS), a multi-agency collaboration working on accelerating vaccine development for Covid-19. The vaccine showed promising 94.1% efficacy in preventing coronavirus disease. No SUSARs were recorded during the UK Moderna (Spikevax) trials.

240. Given the promising data from the clinical trials, on 24 December 2020 the DHSC wrote to request the MHRA's view on whether the vaccine would be suitable for temporary authorisation for supply under regulation 174 [**JR/94 - INQ000401310**].

241. The VBR EWG met four times to review and discuss safety, quality and effectiveness data in relation to the Moderna (Spikevax) vaccine. Meeting minutes can be found here [**JR/95 - INQ000400224**; **JR/96 INQ000400231 JR/97 INQ000400237 JR/98 - INQ000400239**].

242. The MHRA sought the advice of the CHM which considered the final recommendation of its VBREWG on 31 December 2020 [**JR/99 - INQ000400263**]. The CHM advised that based on the data on safety, quality and effectiveness, and public health need, temporary approval for supply under regulation 174 could be given for the Moderna (Spikevax) Covid-19 vaccine.

243. A ministerial submission was sent to the Licensing Minister on the 6 January 2021 conveying the advice of the CHM and VBREWG on safety, quality and effectiveness and recommending temporary authorisation of the vaccine for supply under regulation 174 [**JR/100 - INQ000400198**]. This exhibit is the ministerial submission submitted, despite bearing a "draft" marking in error. The Licencing Minister accepted the MHRA's recommendations in full, and on 8 January 2021 regulation 174 temporary authorisation was granted for the supply of the vaccine in Great Britain in patients aged 18 years and older.

244. On 6 January 2021 the EMA authorised an EU CMA for the use of the Moderna (Spikevax) vaccine in the EU and therefore in patients in Northern Ireland aged 18 years and older [**JR/101 - INQ000371349**].

245. Unlike for Pfizer/BioNTech (Comirnaty), animal reproductive toxicity data was already available for the Moderna (Spikevax) vaccine at the time of initial authorisation which did not indicate direct or indirect harmful effects in pregnancy or lactation. As such, in line with the other Covid-19 vaccines authorised, it was advised by the CHM that the vaccine should only be considered for use in pregnancy when the potential benefits outweigh any potential risks for the mother and foetus allowing an individual benefit risk judgment to be made by women with their healthcare professional [**JR/102 - INQ000400199**].

246. There were ongoing discussions between the MHRA and the manufacturer regarding dose interval for the second dose of the Moderna (Spikevax) vaccine. The manufacturer proposed administering the second dose of the vaccine 28 days after the first dose and CHM advised that this was acceptable following discussions at its meeting of 11 March 2021 [**JR/103 - INQ000400265**]. The product SmPC specified a tolerance window of -7 to +14 days around the proposed 28 days for administration of the second dose.

247. On 27 March 2021 Moderna applied to the MHRA for a Great Britain MA via the European Commission Decision Reliance Procedure ('ECDRP') [**JR/104 - INQ000400211**]. Under this

process, the MHRA took into account the EMA assessment and would still have been able to refuse authorisation if there were concerns of safety, quality or effectiveness.

248. This reliance procedure was put in place following the UK's exit from the EU. For a period of 3 years from 1 January 2021 until January 2024, the MHRA may rely on a decision taken by the European Commission on the approval of a new marketing authorisation for Great Britain. The ECDRP enables the MHRA to "rely" on the decision of the European Commission in issuing or updating a marketing authorisation for a medicinal product and as such, to undertake a lighter touch review of the baseline data. Where a concern is identified (i.e. a safety concern) significant enough to create a negative benefit risk, applications are subject to more detailed scientific scrutiny and will potentially lead to a refusal of an application or changes to the product and patient information.

249. The MHRA reviewed the evidence with due consideration of the European Commission decision and on 31 March 2021 sent a ministerial submission requesting that the Moderna (Spikevax) vaccine be considered for a CMA via the ECDRP. [**JR/105 - INQ000400212**; **JR/106 - INQ000400213**]. This was accepted in full by the Licensing Minister and the CMA was granted. A letter detailing the authorisation and its conditions was sent to the manufacturer, Moderna, on the same date [**JR/107 - INQ000400299**].

250. Given limited data for other age groups at the time of initial authorisation, the Moderna (Spikevax) vaccine was initially only authorised for use in individuals 18 years and older. However, as new data became available, the MHRA was able to consider the safety, quality and effectiveness of the use of the vaccine in younger age groups. In August 2021, Moderna applied to the MHRA via the ECDRP to amend their existing CMA to extend the therapeutic indication of their Covid-19 vaccine to children and adolescents aged 12-17 years old [**JR/108 - INQ000400219**]. The EMA had approved the extension of use to 12-17 years on 23 July 2021.

251. As with its initial authorisation, the MHRA undertook an independent review of the evidence for an extension in the authorisation, taking into account the European Commission decision. On 16 August 2021 after considering the evidence, the MHRA sent a ministerial submission [**JR/109 - INQ000400240**] recommending a CMA extension via the ECDRP, be granted in Great Britain for patients aged 12 to 17 years old. The Licensing Minister accepted

this advice in full. A letter was sent to Moderna confirming this extension on 17 August 2021 [**JR/110 - INQ000400316**].

252. The VBREWG was informed on 4 March 2022 [**JR/111 - INQ000400276**] that a variation to extend the therapeutic indication to individuals 6 to 11 years had been submitted via the ECDRP and advised approval of the variation in the UK.

253. On 13 December 2022 the MHRA sought advice from the CHM [**JR/112 - INQ000400277**] regarding an application via the ECDRP to extend the use of Moderna (Spikevax) to the paediatric population aged 6 months to 5 years at a lower dose of 25 micrograms with doses 28 days apart. Moderna applied for this variation via the ECDRP, and CHM advised that based on the evidence of safety, quality and effectiveness, the variation could be approvable. A ministerial submission was sent to the Licensing Minister on 18 April 2023: [**JR/113 - INQ000400285**] and the Licensing Minister accepted the advice in full and the variation was granted.

Covid-19 Therapeutics

254. In the early stages of the pandemic, the MHRA proactively sought advice from the CHM Covid-19 Therapeutics EWG on a general review of all existing therapeutic agents with potential efficacy in the treatment of Covid-19 [**JR/114 – INQ000283507**]. In February 2020, at the time of the initial review, no medicines were identified as being suitable for repurposing. However, after the review of evidence available later, dexamethasone and tocilizumab (RoActemra) had indications added to their marketing authorisations for the treatment of Covid-19.

Remdesivir (Veklury)

255. Remdesivir inhibits viral replication and demonstrated in vitro and in vivo activity against SARS-CoV-2. In March 2020, the MHRA approved UK Phase III clinical trials to be conducted, with approximately 200 UK participants, and 4440 participants globally.

256. On 22 April 2020 the MHRA received an application from Gilead Sciences Ltd under the Early Access to Medicines Scheme ("EAMS") for a Promising Innovative Medicine ("PIM") designation for remdesivir. A PIM designation is required for companies to enter the EAMS Scientific Opinion procedure. The aim of EAMS is to provide earlier availability of promising

new unlicensed and repurposed medicines to UK patients that have a high unmet clinical need. An EAMS Scientific Opinion is not a marketing authorisation but supports prescribers and patients in making a decision on whether to use a medicine before its licence is approved. The EAMS Scientific Opinion is valid for one year but can be renewed.

257. Early results from clinical studies showed that remdesivir reduced the time of recovery from 15 days to 11 days in patients with severe Covid-19. There was a favourable trend for a reduction in mortality, though this did not reach statistical significance. On 7 May 2020 and 15 May 2020, the MHRA consulted the CHM Covid-19 Therapeutics EWG on the qualification of remdesivir for a PIM designation [**JR/115 - INQ000400279**; **JR/116 - INQ000400301**]. The MHRA requested and received additional data on safety and efficacy from Gilead Sciences Ltd following the CHM Covid-19 Therapeutics EWG meetings.

258. Based on the available clinical and non-clinical data on safety, quality and effectiveness, the MHRA considered that the risks associated with remdesivir were minor and did not outweigh the benefits. The MHRA subsequently consulted the CHM on the MHRA's proposal to issue a positive EAMS Scientific Opinion for adult and adolescent patients with severe Covid-19 [**JR/117 - INQ000400192**]. On 22 April 2020 the CHM recommended a positive EAMS Scientific Opinion be issued for adult and adolescent patients.

259. On 26 May 2020, the MHRA issued a positive EAMS Scientific Opinion to the manufacturer of remdesivir, Gilead Sciences Ltd [**JR/118 - INQ000371343**]. This allowed remdesivir to be made available for the treatment of 71,081 hospitalized patients aged 12 years and older with severe Covid-19 between July 2020 and July 2023. Details on weekly remdesivir administration can be found here [**JR/119 - INQ000408766**]. This was the only instance of the MHRA issuing an EAMS Scientific Opinion for a Covid-19 medicinal product.

260. The EMA received an application for a CMA for Remdesivir on 8 June 2020 [**JR/120 - INQ000371354**] and approved the application on 3 July 2020. This CMA took effect in the UK automatically because the UK was subject to EU legislation at that time. The EAMS Scientific Opinion was withdrawn on the same date because it was superseded by the CMA.

Dexamethasone

261. Dexamethasone is a potent corticosteroid, used to treat inflammatory conditions. It is one of two pre-existing medicines which had indications for the treatment of Covid-19 added to their marketing authorisations. Tocilizumab (RoActemra) is the second and is discussed from paragraph 265. The MHRA approved dexamethasone for evaluation in the treatment of Covid-19 in the RECOVERY trial. The RECOVERY trial was an 'Adaptive Platform Trial' embedded in clinical care that allowed multiple therapies to be evaluated at the same time under a master protocol. The clinical trial application for RECOVERY was received on Friday 13 March 2020 at 17:50 GMT [**JR121 – INQ000400190**] and was approved on Tuesday 17 March 2020 at 07:58, reflecting the expedited approval times provided by the MHRA for Covid-19 trials. The RECOVERY trial was then officially launched on 23 March 2020.

262. The dexamethasone arm of the RECOVERY trial was a randomised, controlled open label study with 6,425 patients, of whom 2,104 patients were randomised to receive dexamethasone with usual standard of care and the remainder to usual standard of care alone. In early June 2020, the investigators of the trial announced that data from the study showed that dexamethasone had a positive treatment effect in patients with Covid-19 and reduced mortality in people with serious Covid-19 illness. Dexamethasone treatment reduced deaths by one third in ventilated patients and by one fifth in other patients receiving oxygen without ventilation. It was not effective for participants not receiving any form of supplementary oxygen. As soon as the clinical trial results became available to the DHSC and the MHRA on 16 June 2020, the MHRA issued a Covid-19 Therapeutic Alert, also known as a Central Alerting System ("CAS") alert, from the Chief Medical Officer advising use of dexamethasone in the treatment of hospitalised patients with Covid-19 who required oxygen or ventilation [**JR/122 – INQ000283542**]. The alert enabled NHS England to provide clinical guidance immediately to the relevant target audience, in this case prescribers.

263. The position of the MHRA at that time was that the currently authorised indications within the Summary of Product Characteristics for dexamethasone in the UK were sufficiently broad [**JR/123 – INQ000283541**] and allowed the use of dexamethasone in Covid-19 patients without needing further regulatory action, such as a variation. On 24 June 2020 the Clinical Guidance section of the Central Alerting System (CAS) was updated by the Chief Medical Officer to advise that a clinically significant interaction between remdesivir and dexamethasone was unlikely [**JR/124 – INQ000283566**].

264. On 26 June 2020 the MHRA consulted the Covid-19 Therapeutics EWG and CHM on the RECOVERY trial results for dexamethasone. The EWG noted that the results were significant and were likely to positively affect clinical practice [**JR/125 – INQ000283540**]. The EMA considered the data under Article 5.3 of EC Regulation 726/2004, and on 18 September 2020, the EMA issued an opinion to support the change in indication for dexamethasone products in the treatment of patients with Covid-19 who had been admitted to hospital and who required oxygen therapy [**JR/126 – INQ000283567**]. Following the publication of the EMA's scientific opinion, the MHRA received applications for variations from marketing authorisation holders of dexamethasone products to update the indication for the treatment of Covid-19. These variations for use of dexamethasone in the treatment of Covid-19 were approved on 20 October 2020 [**JR/127 – INQ000400196**]. Dexamethasone remains authorised for this use.

Tocilizumab (Actemra/RoActemra)

265. Tocilizumab (Actemra/RoActemra) is a first-in-class anti-IL-6 receptor therapy. IL-6 is believed to play a key role in activating the inflammatory pathway that contributes to the signs and symptoms of inflammatory autoimmune conditions. It was the second of two pre-existing medicines which had a Covid-19 indication added to its marketing authorisation (dexamethasone, discussed above, was the first).

266. The earliest approved clinical trial for Tocilizumab (Actemra/RoActemra) for use in Covid-19 was a Phase II/III trial approved on 27 March 2020. Tocilizumab (Actemra/RoActemra) was later added to the RECOVERY trial in an amendment approved on the 16 April 2020 [**JR/128 – INQ000400191**]. Tocilizumab was first added to the REMAP-CAP trial in an amendment approved on the 15 April 2020. During the Covid-19 pandemic REMAP-CAP was set up as an 'Adaptive Platform Trial' embedded in clinical care that allows multiple therapies to be evaluated at the same time under a master protocol.

267. In January 2021, the REMAP-CAP trial reported that tocilizumab and sarilumab reduced the risk of death for patients with Covid-19 when administered within 24 hours of entering intensive care. On 11 February 2021, the RECOVERY trial announced results showing that Tocilizumab (Actemra/RoActemra) reduced the relative risk of death for hospitalised Covid-19 patients by 14% and reduced the time spent in hospital by 5 days when used for patients on oxygen and in addition to dexamethasone.

268. The CHM Covid-19 Therapeutics EWG reviewed the preliminary results from these trials on 12 February 2021 and 18 February 2021 [**JR/129 – INQ000400209**; **JR/130 – INQ000400264**]. During the meeting on 12 February 2021, it was noted that the preliminary RECOVERY trial results showed that Tocilizumab (Actemra/RoActemra) treatment was associated with a significant reduction in mortality compared with usual care alone, which may have included administration of dexamethasone (29% of patients in the tocilizumab group versus 33% of patients in the usual care group).

269. Based on this early, positive, clinical trial data, on 17 February 2021, the MHRA issued a Covid-19 Therapeutic Alert / CAS alert from the Chief Medical Officer recommending that Tocilizumab (Actemra/RoActemra) be considered for eligible hospitalised patients with Covid-19 pneumonia, typically as adjuvant treatment to dexamethasone as standard of care [**JR/131 - INQ000371353**].

270. During the CHM meeting held on 18 February 2021, the MHRA informed the CHM that three pregnant women were enrolled in the RECOVERY trial, but that limited further data was available at that time. The CHM noted that decisions on use in pregnancy should be made on a case-by-case basis by the individual patient and by their treating clinician [**JR/132 - INQ000400215**].

271. The European Commission approved an extension of the indication for Tocilizumab (Actemra/RoActemra) on 7 December 2021 to include the treatment of adults with severe Covid-19 being systemically treated with corticosteroids and requiring extra oxygen or mechanical ventilation [**JR/133 - INQ000371355**].

272. Following the European Commission decision, the MHRA received a variation application for Tocilizumab (Actemra/RoActemra) through the ECDRP on 13 December 2021 [**JR/134 - INQ000400253**] to add a new indication for the treatment of Covid-19 in hospitalised adults who were receiving systemic corticosteroids and who required supplemental oxygen or mechanical ventilation. The variation was granted by the MHRA on 7 January 2022, after 24 days. This shortened timeframe was possible because the MHRA relied on the decision of the European Commission.

Tixagevimab and cilgavimab (Evusheld)

273. Evusheld is a long-acting antibody combination of tixagevimab and cilgavimab for use as a pre-exposure prophylactic medicine to prevent Covid-19 disease. It may be suitable for people who are unlikely to mount an immune response from Covid-19 vaccination or for whom vaccination is not recommended.

274. A Phase III, randomised, double-blind, placebo-controlled clinical trial reported that participants who took Evusheld had a reduced risk of Sars-Cov-2 infection when compared to placebo with a relative risk reduction of 77% (confidence interval 95% ranging from 46% – 90%). The side effects observed with use of Evusheld, including allergic reaction, injection site reaction or hypersensitivity reaction, were considered to be typical for this type of treatment.

275. The CHM Therapeutics EWG was consulted about the evidence of safety, quality and effectiveness for Evusheld on three occasions. Meeting minutes can be found here: [**JR/135 - INQ000400280**; **JR/136 - INQ000400334**; **JR/137 - INQ000400272**].

276. The MHRA consulted the CHM on the safety, quality and effectiveness data supporting authorisation of Evusheld on 3 and 4 March 2022. The meeting minutes are found at: [**JR/138 - INQ000400282**]. The CHM advised that the evidence of safety and efficacy for Evusheld was satisfactory for approval with certain conditions as part of its authorisation. Given that during trials the effectiveness of Evusheld was not tested against the Omicron variant (given Omicron was not a variant of interest at the time of the trial), the CHM advised that wording be added to the SmPC to highlight that the effectiveness against the Omicron variant of Covid-19 was unknown, and that the company should provide real-world evidence of the effectiveness of Evusheld.

277. On 15 March 2022, the MHRA conveyed the advice of the CHM to the Licensing Minister that a CMA should be approved for Evusheld [**JR/139 - INQ000400257**] and the Licensing Minister accepted the CHM recommendation in full. The MHRA issued a CMA for Great Britain on 17 March 2022. On the same date, the MHRA wrote to AstraZeneca, the manufacturer, detailing the CMA and its conditions [**JR/140 - INQ000400312**]. The only other medicine approved as prophylaxis for Covid-19 was casirivimab/imdevimab (Ronapreve), as set out in Annex B.

278. The RAPID C-19 group, as I have earlier described, began to review the evidence for Evusheld in February 2021, and carried out periodic reviews thereafter over an 18-month period. As with Covid-19 vaccines, antibodies such as Evusheld attach to a specific part of the virus and can be rendered ineffective against new variants. In May 2022, RAPID C-19 considered non-clinical data from the UK Health Security Agency and others on the efficacy of Evusheld against Omicron variants and advised the Chief Medical Officer that these data did not provide sufficient evidence of efficacy to support recommending patient access. On 24 August 2022, a RAPID C-19 Oversight Group reviewed real-world evidence, which was summarised in a report found at: [**JR/141 - INQ000283349**].

279. Following the review of real-world evidence by RAPID C-19, the group's conclusion was that the data supporting a favourable benefit risk of Evusheld were insufficient to support patient access before the completion of NICE's technology appraisal, which would otherwise determine the drug's clinical and cost-effectiveness. The RAPID C-19 group considered that there remained uncertainty that Evusheld would prevent symptomatic Covid-19 caused by (the then) current Omicron variants in the vulnerable population who would potentially be eligible. RAPID C-19 concluded that there was insufficient evidence that Evusheld was effective against the current Covid-19 variants at that time. The collective advice given to the Government was that there was insufficient evidence of benefit to justify the deployment of the medicine.

280. In August 2022, Government ministers announced their decision not to procure Evusheld. A letter from the DHSC about this decision was sent to patient groups and published in October 2022, and is found at: [**JR/142 - INQ000283336**]. Decisions about the procurement and deployment of medicines such as Evusheld are not within the remit of the MHRA.

Effectiveness of therapeutics and new variants

281. I have been asked by the Inquiry how effectiveness of therapeutics was affected by new variants. As part of their conditions of authorisation, marketing authorisation holders were required to monitor real world effectiveness and the generation of viral variants in patients treated with their products. The MHRA receives and considers data on effectiveness through various sources, including annual renewals and variation applications. Reports of lack of efficacy in any product for new virus variants submitted to MHRA would be reviewed and

followed up with the marketing authorisation holder, and where appropriate, requiring them to submit further data and discuss the continued positive benefit risk analysis.

282. As with Evusheld discussed above at paragraphs 273-280, the product remains authorised by MHRA as the regulator, given it still has a positive benefit risk assessment for the original coronavirus strain. However, decisions on its supply to patients based on its effectiveness lie with the health authority. Marketing authorisation holders may remove their product from the market given poor effectiveness against other agents and resulting lack of supply.

Prophylactic medicines not authorised by the MHRA

Ivermectin

283. Ivermectin is authorised as a topical treatment for inflammatory skin lesions of rosacea (papulopustular) in adult patients amongst other pathologies. Ivermectin is not licenced to be taken orally in the UK. On 28 October 2021, the MHRA sought advice from the CHM because there was significant public interest in the potential use of ivermectin in preventing or treating Covid-19. The meeting minutes are found here: [**JR/143 - INQ000400267**]. The CHM advised that there was insufficient evidence of safety and efficacy to support the use of ivermectin for the prophylaxis or treatment of Covid-19. It was noted that both the US Food and Drug Administration ("FDA") and European Medicines Agency ("EMA") had stated that this drug should not be used to treat or prevent Covid-19. The MHRA did not receive any applications for marketing authorisation for ivermectin. The Agency does not assess medicinal products for marketing authorisation without an application from the manufacturer.

284. In light of the conclusions reached, the Summary of Product Characteristics for ivermectin was varied to record a clear recommendation that ivermectin should not be used for the treatment of patients suspected to be infected with Covid-19, given the absence of convincing evidence of a favourable benefit risk for this purpose [**JR/144 - INQ000371346**].

Chloroquine and hydroxychloroquine

285. Chloroquine is authorised in the UK to prevent and to treat malaria in adults and children. It is also used in adults only to treat amoebic hepatitis and abscess, rheumatoid arthritis and some types of lupus erythematosus. Hydroxychloroquine is authorised in the UK in adults to treat immune conditions such as rheumatoid arthritis, some types of lupus erythematosus and

certain dermatological conditions. In children, hydroxychloroquine is authorised in the UK to treat some types of lupus erythematosus and is also used alongside other medicines to treat types of childhood arthritis. Chloroquine and hydroxychloroquine share similar pharmacodynamic activities and have similar chemical structures and clinical indications.

286. Chloroquine and hydroxychloroquine were approved by MHRA to be added to the RECOVERY and REMAP-CAP trials, which I outline above, for the treatment or prophylaxis for Covid-19.

287. The UK's RECOVERY trial provided robust evidence of no meaningful mortality benefit from hydroxychloroquine in hospitalised patients with Covid-19. The MHRA sought advice from the CHM regarding this data on 1 and 5 June 2020 [**JR/145 - INQ000400206**; **JR/146 - INQ000400207**]. The CHM advised that recruitment of patients to hydroxychloroquine trials be suspended. As a result, on 16 June 2020 the MHRA instructed those conducting clinical trials using hydroxychloroquine to suspend recruitment into those trials.

288. The MHRA consulted the CHM Covid-19 Therapeutics EWG on the available data on the safety and efficacy relating to hydroxychloroquine at its meetings on 24 April 2020, 26 June 2020 and 24 July 2020. The minutes from the respective meetings are found here: [**JR/147 - INQ000400278**; **JR/125 - INQ000283540**; **JR/148 - INQ000400194**]. Neither hydroxychloroquine nor chloroquine were authorised by the Agency to treat Covid-19.

Convalescent plasma

289. Convalescent plasma is the antibody rich plasma from a patient who has recovered from infection with Covid-19. Convalescent plasma in this context refers to immunoglobulins extracted from convalescent plasma. Use of 'whole' convalescent plasma is outside the remit of the MHRA as it is not considered to be a medicine. It only becomes a medicine when the immunoglobulins are extracted from the plasma.

290. The MHRA sought advice from the CHM Covid-19 Therapeutics Expert Working Group on the safety and efficacy of convalescent plasma in Covid-19 at its meetings on 23 and 24 April 2020 [**JR/149 - INQ000409484**]. At that time, the CHM advised that any Agency decision about convalescent plasma should be deferred until there could be a review of evidence from ongoing clinical trials.

291. There was no conclusive evidence available that immunoglobulins from convalescent plasma provided any benefit for Covid-19 patients. The MHRA did not receive any applications to approve immunoglobulin products derived from convalescent plasma.

Post-Approvals

The need for post-authorisation surveillance

292. With the development of any new vaccine or medicine, the limited size of clinical trials invariably means that rare side effects can only be identified or fully characterised when the products are used in large populations. It is also the case that certain groups who may benefit from, and be recommended to receive, a vaccine, such as those with underlying chronic illnesses or pregnant women, may have been excluded from clinical trials.

293. It is for these reasons that post-authorisation, 'real world' safety vigilance of new vaccines and medicines is a crucial part of the MHRA's responsibility for keeping under review the benefit risk of medicines and vaccines in clinical use in UK, and for provision of up-to-date information on product safety to inform the decisions of prescribers, patients and the public. Part 11 of the Human Medicines Regulations 2012 provides the statutory responsibility of the MHRA for undertaking post-authorisation safety monitoring in the UK. The MHRA also oversees the manufacturers' legal responsibilities to undertake such vigilance.

294. Medicines and vaccines in use internationally, as would be expected in a pandemic, may generate safety signals relevant to UK healthcare professionals, patients, and the public, and therefore pharmacovigilance is an international undertaking in which MHRA is an active participant. The MHRA contributes to global pharmacovigilance as a member of the WHO's Advisory Committee on Safety of Medicinal Products, which established subgroups on Covid-19 therapeutics, and of the WHO's Global Advisory Committee on Vaccine Safety, which kept the safety of Covid-19 vaccines under continual review. The MHRA's leadership of the international 'Smart Safety Surveillance' initiative, in co-operation with the WHO and the Bill and Melinda Gates Foundation, was the basis for regular signal detection meetings on Covid-19 adverse reaction reports for several African countries (Ghana, Nigeria, South Africa and Ethiopia).

295. The MHRA is also a member of the International Coalition of Medicines Regulatory Authorities ("ICMRA"), a voluntary leadership entity made up of national medicines regulatory authorities who work together on a variety of strategic initiatives, including supply chain integrity, antimicrobial resistance, crisis management, and public communication. During the pandemic the MHRA co-chaired the ICMRA Public Health Emergency Clinical Trials Working Group and the ICMRA Vaccine Pharmacovigilance Network. The Pharmacovigilance Network served as a forum to share methodological approaches to vaccine vigilance and to share high level positions on assessment of emerging signals. This was an important opportunity to enable the experience of safety monitoring of Covid-19 vaccines and therapeutics, introduced in large populations for the first time in UK, to support other countries' safe use of the vaccines.

The role of manufacturers in post-authorisation surveillance

296. Manufacturers holding a UK marketing authorisation for medicinal products are required to submit safety surveillance data to the MHRA, including:

i. UK and non-UK Individual Case Safety Reports;
ii. Periodic Safety Update Reports;
iii. Risk Management Plans; and
iv. Post-Authorisation Safety Study protocols and final study reports.

297. I am asked about pharmaceutical companies' obligations to collect data and/or conduct safety trials post-authorisation. Marketing authorisation holders must carry out signal detection for potential safety issues for as long as the licence is extant and notify the MHRA of any information that might impact on the benefit risk of the product and terms of the marketing authorisation (pursuant to regulation 190 of the Human Medicines Regulations 2012). Marketing authorisation holders in this context are the pharmaceutical companies. In the event of a marketing authorisation holder identifying an emerging safety issue from any source, regulation 190 states that the information must be provided to the regulator without delay. As set out in the MHRA's guidance, this new information must be communicated to the MHRA within three working days.

298. In addition to this requirement, Periodic Safety Update Reports (PSURs) are comprehensive documents that must be prepared and submitted by the marketing authorisation holder at defined intervals post-authorisation of a medicine. Initially, PSURs are required to be submitted every six months after a product is authorised, then annually for two

years, and thereafter every three years unless specified otherwise. These reports focus on summary information, scientific assessment, and integrated risk-benefit evaluation, considering any new or changing risks, including the clinical importance, nature, seriousness, frequency, and whether a safety issue can be prevented or minimised.

299. Post-Authorisation Safety Studies (PASS) are studies conducted after a medicine has been authorised, to gather additional information about its safety and to evaluate the risk of adverse events. A PASS study can be required by the MHRA either at the time of marketing authorisation or post-authorisation if new safety concerns arise. A PASS study must follow the guidelines set out in the Good Pharmacovigilance Practice ("GVP") Module VIII and be registered in the EU Post Authorisation Studies ("PAS") Register, with results submitted to the MHRA.

300. In addition, a marketing authorisation may contain conditions which require the company to comply with obligations on recording and reporting of suspected adverse events which are stricter than those detailed above. Marketing authorisation holders must carry out signal detection for potential safety issues and notify the MHRA of any information that might impact on the benefit risk of the product and terms of the marketing authorisation (see regulation 190 of the Human Medicines Regulations 2012). Marketing authorisation holders are responsible for ensuring that the product information is kept up to date with current scientific knowledge (see regulation 76 of the Human Medicines Regulation 2012).

301. In the context of the pandemic, regulation 174 of the Human Medicines Regulations 2012 was used to approve several medicinal products and vaccines as soon as the available data supported a favourable benefit risk balance. Regulation 174 operates to disapply on a temporary basis the typical authorisation procedures and regulations where that is in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation, which may cause harm to human beings. The Covid-19 pandemic met this definition and therefore new Covid-19 medicines could be considered under regulation 174.

302. It should be noted that regulation 174 approval is not the same as a marketing authorisation. However, through the amendment to the Human Medicines Regulations 2012 which inserted a new regulation 174A, and the statutory framework setting out the action to be taken in the event of a breach of the conditions, the MHRA was able to define safeguards for the supply and use of unlicensed products which mirrored certain conditions of a marketing

authorisation, including stipulating vigilance requirements. More information on regulations 174 and 174A can be found at [**JR/45 – INQ000283549**

303. In practical terms, this meant that a manufacturer with regulation 174 temporary approval for supply of a Covid-19 vaccine or medicine was required to provide safety data to the MHRA in the same manner as if they had obtained 'full' or conditional marketing authorisation. By way of example, the regulation 174 approval for the Pfizer/BioNTech (Comirnaty) Covid-19 vaccine was subject to clinical and pharmacovigilance conditions (among others): [**JR/65 – INQ000371351**]. The conditions included a requirement for Pfizer/BioNTech (Comirnaty) to operate a comprehensive pharmacovigilance system for the vaccine in accordance with UK legislation for licensed products, as if they were holders of a market authorisation.

304. Risk Management Plans ('RMPs') are a requirement for all new products at the time of approval and comprise 1) what is known about the safety of a product at the time of authorisation, detailing important risks of the medicine, 2) the gaps in the evidence base, such as use in immunocompromised patients or pregnant women, and how more information can be obtained about benefit risk in these populations, and on any potential risks based on current knowledge of the product, and 3) risk minimisation measures. Thus, the RMP includes important identified risks which have been demonstrated to be associated with the medicine and which require additional measures to minimise any potential risk to users as part of the authorisation. Gaps in the evidence are reflected in medicinal product information for healthcare professionals and patients, for example use of vaccines may not have been studied or monitored in pregnant women. Manufacturers must submit a proposed RMP for approval when applying for marketing authorisation.

305. The MHRA may also request the submission of a new RMP or an update to an existing RMP at any time during the product's lifecycle. Whenever relevant new data become available, the marketing authorisation holder should consider whether changes to its RMP are required. Situations where an updated RMP is required include when new safety concerns arise or where there is a new or significant change in the existing safety reporting pattern or trends, or additional risk minimisation activities are justified to maintain a favourable benefit risk balance. An example of the RMP provided to the MHRA by AstraZeneca during the pre-approvals process for its vaccine, which includes the company's proposed Pharmacovigilance Plan, is found at [**JR/150 – INQ000494267**].

306. The MHRA continually assesses safety surveillance data provided by marketing authorisation holders, alongside the data from other sources as described later, to identify any safety issues which are then factored into its ongoing evaluation of the benefit risk balance throughout the currency of a product's licence.

307. Throughout the pandemic the MHRA held regular meetings with marketing authorisation holders to ensure that they understood MHRA requirements and expectations, and to facilitate requests for emerging data on safety issues.

Development of Covid-19 vaccines surveillance strategy

308. In March 2020, well in advance of the envisaged availability of vaccines and therapeutics, the MHRA began the development of its vigilance strategy for Covid-19 vaccines, led by vaccine expert Dr Phil Bryan in the then Vigilance and Risk Management of Medicines (VRMM) Division. The aim was to develop initial proposals for a scientifically robust strategy which would enable real-time safety monitoring in the context of mass exposure to new Covid-19 vaccines and which would make use of the latest available tools and methodologies. These early discussions built on experience from the 2009 H1N1 swine flu pandemic in terms of systems required for surveillance of both antivirals and vaccines, whilst also utilising emerging knowledge about Covid-19, including from China and Italy.

309. One of the successes and learnings from the swine flu pandemic was the importance of dedicated surveillance systems and public web portals for reporting suspected adverse reactions. In 2009, the pandemic specific systems deployed by the MHRA served both to de-risk the potential impact of large volumes of suspected adverse reaction reports adversely impacting on the surveillance of non-pandemic products, but also to enable specific and focused surveillance activities for the products deployed during the pandemic. The dedicated portal also served as a focal point both for the public and for healthcare professionals.

310. Early discussions of the surveillance response in the MHRA's internal Covid-19 Task Force noted the importance of robust and flexible incident reporting and data collection systems for both medicines, vaccines and medical devices, and the potential need for more proactive data collection. The group, reporting to daily meetings of the Corporate Executive

team, considered the capacity, capability, and robustness of each of the components of the vigilance system to ensure that maximum potential volumes of safety data at the peak of reporting could be managed and assessed.

311. The MHRA Covid-19 Task Force agreed the VRMM recommendations that:

i. A dedicated Coronavirus Yellow Card web portal should be established to enable patients, the public and healthcare professionals to report suspected adverse reactions based on modern flexible IT.

ii. Though primarily developed for Covid-19 vaccines, the surveillance strategy should be incorporated within separate workstreams on devices, antivirals and therapeutics and vaccines.

iii. A dedicated cross-agency team would be required with an immediate focus on resourcing the areas of work required, exploring opportunities for proactive engagement on external studies and research and development, and agreeing funding for delivery of reporting systems.

iv. In parallel, activities for establishment of the assessment and communications activities should be prioritised to connect with other Arm's Length Bodies and to respond to media interest and commentary.

The Covid-19 Vaccine Safety Surveillance Expert Working Group (VSSEWG)

312. The MHRA also considered the need for independent expert advice on the developing surveillance strategy to ensure its scientific robustness. In relation to vaccines, in May 2020, the CHM established the Vaccine Safety Surveillance Expert Working Group (VSSEWG) to advise the CHM on its safety monitoring strategy for Covid-19 vaccine(s) in May 2020. The VSSEWG held four meetings from May to October 2020, during which it considered proposals and methodologies for MHRA-led vigilance activities. I exhibit the minutes of those meetings which took place on 28 May 2020 [**JR/151 – INQ000409569**]; 25 June 2020 [**JR/152 – INQ000409572**]; 23 July 2020 [**JR/153 – INQ000409570**]; and 27 October 2020 [**JR/154 – INQ000409571**].

313. As recorded within the minutes of 27 October 2020 the next meeting of the VSSEWG was to take place on 11 November 2020. The meeting was cancelled due to a lack of substantial business to warrant a full meeting, as well as the meeting date being difficult for members to attend as some had conflicting commitments. The final report of the safety monitoring strategy,

which is further discussed at paragraph 328, was due to be discussed at this cancelled meeting, and was instead circulated via email for the group's comments before being discussed at the CHM meeting. The cancellation of the EWG meeting scheduled for 11 November 2020 had no effect on finalising the EWG's recommendations to the CHM.

314. The VSSEWG members consisted of experts in medicine, infectious disease, pharmacoepidemiology and data analytics to provide the CHM with a breadth of independent oversight and advice on the MHRA's Covid-19 vaccine vigilance activities. To support the VSSEWG deliberations, the MHRA developed a four-stranded approach to vigilance which I detail at paragraph 328. Pillar one was spontaneous reporting via the Yellow Card Scheme which is operated jointly by the MHRA and the CHM.

315. The VSSEWG discussed potential clinical events likely to be reported under the Covid-19 vaccine safety surveillance, which led to the development of a list of adverse events of special interest ('AESIs') for Covid-19 vaccines. In this context AESIs are medically significant events which could potentially be causally associated with vaccines. Pre-specified lists of AESIs are frequently developed for proactive vaccine pharmacovigilance to identify the events which should be more closely monitored (given they are predicted to have a greater likelihood of association) as part of ongoing vaccine safety monitoring processes. For example, the Brighton Collaboration, a program committed to promoting and improving vaccine safety, partnered with the Coalition for Epidemic Preparedness Innovations (CEPI) to create AESI lists for Covid-19 vaccines.

316. Throughout the pandemic, the MHRA considered AESI lists developed and updated by the Brighton Collaboration, as well as lists published internationally, for example by the EMA and the WHO. Included events are those that were observed in clinical trials and events that could theoretically be associated because they may have been reported or associated with other vaccines in the past, or based on the fact that they are immune-mediated events. Events are also included despite having no previous causal association if they can occur naturally in groups eligible for vaccination, and reporting a single or small number of events is likely to cause unnecessary concerns about the safety of the vaccine, such as myocardial infarction. Any reports of death temporally associated with vaccination are subject to review and follow-up for additional information to help assess likelihood of any association with that vaccine. All these events were subject to close monitoring by the MHRA and the vaccine manufacturers.

317. The initial list of AESIs developed by the MHRA for the Covid-19 vaccines was:

i. Covid-19 disease enhancement
ii. Sudden death
iii. Guillain-Barré syndrome, and other peripheral and polyneuropathies
iv. Multiple sclerosis, transverse myelitis and other demyelinating disorders
v. Optic neuritis
vi. Encephalitis
vii. Myasthenia gravis
viii. Bell's palsy
ix. Seizure disorders
x. Myocardial infarction
xi. Myocarditis/pericarditis
xii. Stroke and other cerebrovascular events
xiii. Venous thromboembolism
xiv. Idiopathic thrombocytopenic purpura and autoimmune thrombocytopenia
xv. Rheumatoid arthritis
xvi. Polyarthritis
xvii. Autoimmune thyroiditis
xviii. Chronic Fatigue Syndrome / Myalgic encephalomyelitis / Post-Viral Fatigue Syndrome, Fibromyalgia
xix. Post Orthostatic Tachycardia Syndrome, Narcolepsy.
xx. Paediatric inflammatory multisystem syndrome (or otherwise a recently defined condition associated with Covid-19 in children and adolescents)
xxi. Kawasaki syndrome
xxii. Pregnancy related events (pre-term labour, stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, foetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, or neonatal renal failure, chorioamnionitis, major structural congenital malformations, all serious events that can occur naturally in pregnancy).

<u>Coronavirus Yellow Card for individual reports</u>

318. The MHRA immediately took steps to establish a dedicated Coronavirus web portal for healthcare professionals and the public to report via Yellow Card any suspected side effects associated with Covid-19 treatments and events related to medical devices. We ensured rapid

establishment of the portal through an expedited internal governance process. As part of MHRA's new SafetyConnect Programme, which is delivering an IT vigilance system for all medicinal products, the expedited process allowed for the delivery of external-facing systems to be brought forward and delivered at pace. A cross-agency team worked to deliver the project, from initial documentation, project planning, and user journeys to development and testing in parallel work-streams to facilitate the rapid deployment of core functionality. This was deployed on 28 April 2020 for medicinal products with an associated press release [**JR/150 - INQ000494267**] and medical devices reporting was added on 28 May 2020, with support of vaccine ADR reporting to be available at the time of approval of a Covid-19 vaccine.

319. In parallel to establishing the IT systems for the public and healthcare professionals to report, in June 2020 the MHRA undertook a detailed analysis of potential numbers of Yellow Card reports that might be received in the context of a mass vaccination campaign. Reporting rates from established vaccines (such as HPV) scaled up to a whole population were projected to result in 100,000 reports based on 100m doses. The analysis can be found here: [**JR/155 – INQ000494375**]. However, given the enhanced public awareness and serious nature of the pandemic, actual numbers were expected to be substantially higher.

320. The MHRA has historically received a maximum of 60,000 reports of suspected adverse reactions per year for all products. Given the expected increased reporting when healthy people are vaccinated during a pandemic, further steps were taken to ensure that capture and evaluation of Covid-19 vaccine reports was rapidly progressed to enable safety signals to be detected in as close to real time as possible. This included Increasing the number of mandatory 'fields' within a Coronavirus Yellow Card form and improving the automation and coding applied to data received directly from the reporter. The MHRA incorporated artificial intelligence using natural language processing to ensure that descriptive or narrative information that may be important for signal detection was automatically captured in our database.

321. These IT system changes were designed to ensure highly structured, more consistent and complete data collection. It enabled large numbers of reports of suspected side effects associated with vaccines to be captured and ensured they were rapidly available for analysis and signal detection as well as onward transmission to the World Health Organisation and relevant pharmaceutical companies.

322. As discussed in greater detail below at paragraph 329, under "Targeted Active Monitoring-Yellow Card Vaccine Monitor", the MHRA rigorously tested each of its new and enhanced tools and surveillance systems prior to roll-out. The Coronavirus Yellow Card system was continually developed and enhanced throughout the pandemic to deliver additional functionality to meet real-time surveillance needs.

Exposure data from vaccination records

323. As a key aspect supporting the vigilance strategy, the MHRA worked in close collaboration with public health partners across the UK, including PHE (now UKHSA), the respective public health authorities in Scotland, Wales and Northern Ireland, as well as the DHSC, NHS England and NHS Improvement ('NHSEI'), NHS Digital and NHS-X to understand the infrastructure supporting potential mass deployment of vaccines, including the operation of vaccination sites, data collection and data transfer requirements. The MHRA also incorporated scientific collaboration for data analysis with the National Institute for Health and Care Research-funded Health Protection Research Unit, within the London School of Hygiene & Tropical Medicine.

324. Data from suspected adverse reaction reports need to be evaluated in the context of use of the vaccine, termed 'exposure data'. The MHRA worked with NHS Digital (now part of NHS England) to ensure that data on vaccine administration, including details on dose number, brand, batch, and adverse effects reported at each vaccination centre were captured in point of care systems and transferred to the patient's GP record within 48 hours. For the MHRA to effectively implement the vaccine vigilance strategy, it was critical to know how many people had been administered each vaccine, which would provide a denominator for the numbers of Yellow Card reports. Details of the vaccine which had been administered also needed to be available to patients and their healthcare professionals so that these details could be included in a Yellow Card report in the event of a suspected adverse reaction. Details on the vaccine were also needed to support the analyses of electronic healthcare record databases, such as rapid cycle analyses and epidemiological studies, which constitute the third and fourth pillars of the vaccine strategy.

325. In parallel to the assessment of clinical trials and other pre-approval data for Covid-19 vaccines and without pre-judging the outcomes of such assessments, the MHRA worked

cross-government to ensure that appropriate systems were in place for safety monitoring of Covid-19 vaccines in the event of their approval. The system preparedness that was enabled by 'front-loading' this work supported the approval of the vaccines as soon as there was satisfactory evidence of efficacy and the prompt vaccine roll-out. System requirements were established to collect sufficiently detailed point of care vaccination information and any acute adverse event data, to rapidly collate this, and enable linkage of the data to other health datasets, with feedback of the data captured to the individual patient and their healthcare providers. These requirements were conveyed to DHSC, NHS England and NHS-X, including engagement through September 2020 in line with recommendations from the CHM Expert Working Group on Covid-19 Vaccine Safety Surveillance.

326. Implementation of the IT systems to support the vaccination programme was led by NHS Digital from the beginning of November 2020, following an escalation of the requirements to commence the programme through the Vaccine Task Force. The MHRA participated in regular meetings with PHE, NHS Digital and NHSEI to ensure that discussions were coordinated to address any potential issues that might arise in delivery of the DHSC vaccine programme.

327. The MHRA also worked with the UKHSA on the development and planning of the surveillance approach for vaccines, monitoring and evaluating individual safety signals as these were identified during deployment. The MHRA maintained regular communication and information exchange with public health bodies, including the UKHSA and its equivalents in Wales, Scotland, and Northern Ireland. These involved discussions and information exchange relating to data, research findings, and surveillance information related to Covid-19, including the spread of the virus, detection of emerging variants, and the impact of the vaccine programme on public health.

Covid-19 Vaccines Surveillance Strategy

328. As above at paragraph 328, there were four 'pillars' to the MHRA's Covid-19 vaccine vigilance strategy, which combined to address the relative strengths and weaknesses of each form of vigilance and build the most comprehensive strategy capable of providing close to real-time vigilance. Those four pillars were:

i. Enhanced passive surveillance – 'observed versus expected' analysis
ii. Rapid Cycle Analysis and Ecological analysis
iii. Targeted active monitoring – the Yellow Card Vaccine Monitor
iv. Formal epidemiological studies.

329. As to those four pillars, the report of the CHM Expert Working Group on Covid-19 vaccine safety surveillance [**JR/156 – INQ000274107** set out (relevant extracts below):

> "***1. Enhanced passive surveillance – 'observed vs expected' analysis***
>
> *"…As with any system of safety vigilance, the ability to very rapidly detect a new safety concern in the midst of a mass immunisation campaign is dependent on the early presentation and diagnosis of symptoms. The key strength of the Yellow Card scheme is that it allows any member of the public or health professional across the UK to immediately alert us to any concerns they have without a formal diagnosis. And because anyone across the UK can report to the MHRA at any time, unlike studies which are limited in size, the scheme is able to identify the rarest of side effects.*
>
> *A team of MHRA scientists will continually review individual reports and will contact reporters to obtain more information, where required. Scientific and clinical assessment will be used to determine if an individual or series of reports indicate a new safety 'signal'. An established statistical approach known as empirical Bayes geometric mean (EBGM) will be used to facilitate signal detection.*
>
> *Whilst Yellow Cards in isolation are sufficient to allow signal detection, the MHRA will enhance the system by analysing reports in the context of near real-time information on the number of doses of vaccine administered at the relevant time point, stratified by age and gender, and the background rate of the event of interest in the absence of vaccination. This will allow continuous evaluation of the 'observed' number of reports of a suspected serious side effect compared to 'expected' numbers – i.e. based on the naturally-occurring rate that would normally happen in a given time period in the same sized cohort and in the absence of vaccination.*

The background rate used to estimate the expected numbers of cases will be extracted from anonymised GP electronic healthcare records and linked secondary care records within the Clinical Practice Research Datalink (…) (CPRD) supported by additional analyses using full England-wide secondary care data for the rarest events…

…Because every passive surveillance system suffers from variable under-reporting, the MHRA will conduct sensitivity analyses based on a range of under-reporting assumptions. Everyone receiving a vaccine should be provided with an information leaflet, which will provide a link to the Yellow Card site, and which should help to reduce any under-reporting."

2. Rapid Cycle Analysis and Ecological analysis

…[A]s Covid-19 vaccination records (i.e. those given outside of GP surgeries) begin to get updated within GP systems, the MHRA will implement a form of active surveillance known as 'Rapid Cycle Analysis' (...). This method involves proactive, weekly analysis of a range of pre-defined events (theoretical side effects) to quickly identify safety signals – it again involves 'observed vs expected' analyses (i.e. comparing rates after vaccination to rates in unvaccinated comparator groups) but doesn't rely on people directly reporting any concerns through the Yellow Card scheme. It is also a more robust way to quickly determine if rates are likely to be consistent with a coincidental association…

…The MHRA will also use the CPRD data to conduct 'ecological analyses' (…). This involves monitoring trends in the rates of pre-defined events within given population cohorts, based on prioritisation groups for vaccine roll out, to see if they are occurring to a greater extent amongst those targeted for vaccination after it is deployed compared to historical rates from the pre-deployment period. Comparisons can also be made to trends seen in groups not targeted for vaccination at the same time. This approach is most useful when we see high vaccine uptake and is another way to quickly detect a potential safety signal.

Each of these methods will need very careful evaluation to tease out any change in rates over time that may be a direct or indirect consequence of the SARS-CoV-2 epidemic, rather than an effect of the vaccine.

3. Targeted active monitoring – Yellow Card Vaccine Monitor

Another form of vigilance that the MHRA will implement is targeted active monitoring of certain groups of vaccinees, focused particularly on those who may have been excluded or under-represented in clinical trials. Through the call/recall system which the NHS will use to invite people to register to receive the vaccine, a random selection of vaccinees from certain cohorts will be invited to voluntarily register for follow-up via a new platform, called the Yellow Card Vaccine Monitor, which the MHRA has developed.

This vigilance activity will seek enrolment prior to vaccination (and thereby before any suspected side effect is experienced) and vaccinees will then be contacted at set intervals (for example 7 days, 28 days, 3-6 months) to ask whether any adverse reaction occurred. The objective of this is not necessarily to detect very rare risks, as the intention is to recruit the same numbers that are generally included in a clinical trial (i.e. several thousand), but to compare the frequency and severity of side effects to groups that were included in trials to allow further characterisation of the safety profile. This would allow, for example, further evaluation of the safety profile in people with underlying immunosuppression.

4. Formal epidemiological studies

The above three methods are essentially 'signal detection' and 'signal strengthening' tools – i.e. their main purpose is to quickly flag up whether there might be a new, rare side effect and to build the volume of data on safety. They cannot confirm if it is a side effect. Similarly, whilst they can provide some strong evidence to indicate if something is likely to be

coincidental, they cannot always confirm this. A formal epidemiological study, designed and powered specifically to test a given hypothesis in an unbiased way, is usually necessary to confirm and quantify a suspected rare side effect. These will be undertaken on an ad hoc basis should the need arise based on other vigilance activities.

Examples of such studies undertaken by the MHRA in the past include the association between human papillomavirus (HPV) vaccine and chronic fatigue syndrome and the safety of pertussis vaccine in pregnancy...

…The self-controlled case-series method was specially designed for rapid unbiased assessment of vaccine safety issues (…). In this approach, cases act as their own controls as the incidence of the event of interest in pre-defined risk-periods following vaccination is compared to the incidence outside the risk period. However, as with the choice of data set it is important that the most appropriate study design is used for the issue identified.

Engaging with academia and other experts

The conduct of independent studies is also highly valuable and so the MHRA is working with PHE and the Health Protection Research Unit in Immunisation at LSHTM [the London School of Hygiene and Tropical Medicine] *to establish a framework for the rapid conduct of epidemiological studies in OPENSAFELY (…). A template protocol is being written which will allow the investigation of key theoretical adverse events in the first instance and which can be rapidly updated to include additional events if the need arise.*

What the MHRA does with the data we generate

The main objective of the safety monitoring process is to identify any new risks that may emerge as the vaccines are used. Such risks could include a new side effect, an apparent change in the nature of a known side effect, identification of factors that increase the chances of having a side effect,

batch-related problems or issues related to inappropriate use of the vaccines.

If a new risk is confirmed, this will be fed into a continuous evaluation by the MHRA of the balance of benefits of a vaccine versus risks. The MHRA will consult the Commission on Human Medicines (CHM) and its Expert Groups and, if deemed necessary, regulatory action would be taken to minimise risk and support safe use of a given vaccine (e.g. adding warnings to the product information, sending out communications to healthcare professionals and patients, restricting its use). This would also be communicated to DHSC, PHE, devolved Governments, and public health partners in the devolved nations to inform any decisions regarding the immunisation programme."

330. The EWG report concluded by explaining that the MHRA intended to operate a transparent process and to that end would publish online, on a regular basis, a summary of adverse reaction reports: [**JR/157 – INQ000274109**]. Weekly reports of the latest ADR data for the Covid-19 vaccines, any trends in reporting and the results of evaluation, together with independent expert advice where relevant, were published from February 2021 to 23 June 2022. These were changed to bi-weekly and then transitioned to monthly publications from August 2022. Importantly, these reports aimed to set the ADR reports received by MHRA in the context of similar events which would be expected in a similar population.

331. I am asked why the Covid-19 Vaccine Safety Surveillance Strategy was not published before the first Covid-19 vaccines were administered. As with any strategic vigilance proposal, particularly one involving the Yellow Card Scheme which is jointly operated by the MHRA and the CHM, the first priority is to seek agreement from the CHM and its advisory subgroup, in this case a dedicated EWG set up for the purpose. This was sought at a meeting on 27 November 2020, where the CHM agreed to the special four-stranded strategy for the Covid-19 vaccines. During this meeting, it was also agreed that the strategy should include details on the regularity and expectations for the public concerning publication of ADR data, to help boost public confidence and maintain transparency.

332. Since the then Secretary of State was responsible for the final decision-making concerning ADR data publication, the publication of the strategy was dependent on his decision. On 3 December 2020, the MHRA sent a submission to the then Secretary of State outlining the four strands of the vaccine strategy agreed with the CHM. With regular ADR data publication now a part of said strategy, the MHRA finalised grid slots with Number 10 and DHSC planners, to publish the first ADR data on reported suspected ADRs of the Covid-19 vaccines on 14 January 2021, along with a rolling weekly publication of reported ADR data. The timing of this publication was chosen to align with the publication of Public Health England's surveillance plans to better reassure the public that there were robust plans in place to monitor the safety, efficacy and uptake of the Covid-19 vaccines.

333. On 4 January 2021, a meeting was held between the then Secretary of State and the MHRA communications team. During this meeting, the Secretary of State advised that planned publication of Covid-19 Vaccine ADR data by the MHRA should not go ahead at this time, to ensure maintained confidence in the vaccination programme and as such the publication of the vaccine strategy would also have to be delayed until such a time that the data could be published.

334. On 21 January 2021, a ministerial meeting was held wherein the MHRA updated Ministers on a pending decision regarding the optimal approach to publishing ADR data, aimed at enhancing transparency and understanding of vaccine risks. Subsequently, on 25 January 2021, a phone call took place between the Secretary of State, Dr Phil Bryan and me. During this call, I requested an earlier publication of ADR data, which was agreed upon.

335. This ultimately led to the MHRA publishing the results of the work undertaken in its 'Report of the Commission on Human Medicines Expert Working Group on Covid-19 Vaccine Safety Surveillance' [**JR/158 – INQ000274107**] on 5 February 2021. By this time, the MHRA had authorised the supply of the Pfizer/BioNTech (Comirnaty), the AstraZeneca (Vaxzevria) and the Moderna (Spikevax) vaccines.

336. It could be argued that earlier publication of the Covid-19 Vaccine Safety Surveillance strategy may have played some part in bolstering public confidence and timely publication of the relevant strategies will be sought in future pandemics. However, prior to the publication of the strategy the MHRA was engaged in a wider government communications strategy which

saw the production and publication of a number of communications aimed at highlighting the favourable benefit risk profile of the Covid-19 vaccine and bringing attention to its surveillance activities by encouraging online Yellow Card reporting through the coronavirus Yellow Card reporting site. This is detailed further in paragraphs 342-353.

337. As explained within the report of the CHM EWG on Covid-19 Vaccine Safety Surveillance published on 5 February 2021, given the then (correctly) anticipated scale of a Covid-19 mass immunisation programme, with many millions of doses of one or more novel vaccines administered across the UK over a relatively short time, the MHRA's vigilance activities needed to be continuous, proactive and as near real-time as was possible.

338. The importance of this vigilance strategy was two-fold. First and foremost, the aim was to rapidly detect, confirm, characterise and quantify any new risks that were not detected in clinical trials, to weigh these against the expected benefits and take any necessary action to minimise risks to individuals. Secondly, the MHRA needed to establish very quickly if any serious events which were temporally related to vaccination were merely a coincidental association or causal, and to do this in a robust, evidence-based way so that any steps necessary to minimise risk could be promptly taken and public confidence in a vaccine would not be eroded. Such associations were considered potentially more likely whilst the UK was still in the midst of a national epidemic, and because most of the millions of people offered the vaccine in the early phase of a vaccination campaign would be elderly and/or have underlying medical conditions, which increases the likelihood of unrelated illnesses or death occurring soon after vaccination.

Implementation of the surveillance strategy

339. Equal focus was placed upon both ensuring that systems were in place to capture and process the data required for surveillance, and also that the scientific and clinical assessment team was well placed to assess the data in advance of commencement of vaccinations. The VRMM division established a dedicated assessment team for Covid-19 vaccines, comprising experienced scientific and medical assessors, alongside vaccine, epidemiological and system experts. As more Covid-19 vaccines were approved additional assessors were added to the surveillance team after an appropriate induction based on the skills and experience of the individuals to ensure continuity of dedicated expertise for each product.

340. The MHRA also took great care in the implementation of each aspect of surveillance to ensure the quality of both individual components and the robustness of the system as a whole. While IT systems were iteratively improved throughout the pandemic, each system was rigorously tested to ensure the necessary functionality was in place before commencement of the vaccination programme. The relevant functionality and data transfers were established in advance of the approval of the vaccines, with validation that the necessary tools and systems were in place prior to the commencement of vaccination. As a result, when vaccinations began, the four elements of the vigilance strategy were already in place to detect any potential safety issues arising in clinical use.

341. Importantly, there was advanced MHRA preparedness for the kinds of safety issues which might arise and readiness for communication and regulatory action such as risk minimisation measures. The VBREWG met 93 times over the course of the pandemic to review emerging safety signals at the earliest possible time and make recommendations. The considerations and subsequent actions taken by the MHRA are described in further detail in the vaccine "ADR Chronologies" section below.

Signal detection

The Yellow Card Scheme

342. In accordance with the first pillar of the surveillance strategy, as described in paragraph 328, Yellow Card reports of suspected side effects or adverse drug reactions (ADRs) associated with any medicines or vaccines, as well as medical device incidents, were evaluated by scientists and clinicians together with additional sources of evidence, to identify any new safety issues or side effects. Those additional sources of evidence included information provided by the manufacturers, other epidemiological studies (including analyses of data on national vaccine deployment), anonymised GP-based electronic healthcare records, data from organisations such as the UK Teratology Information Service (UKTIS) which captures information on exposure to drugs in pregnancy, the published literature and other healthcare data. The MHRA also took into account the international experience based on safety data from other countries including from other international regulators which had experience of deployment of the same products.

343. I am asked about the MHRA's interrogation of the Yellow Card database for batch-related vaccine safety issues and other temporal associations. Batch testing is the primary way in

which batch-related issues with purity and potency could be identified (see paragraphs 160-163for details). The temporal association of a suspected ADR in relation to exposure to the vaccine is captured through the Yellow Card scheme when reported and is an important consideration when establishing a relationship between a vaccine and an ADR. Providing a batch number is an option when submitting an ADR report for a medicine or vaccine via the Yellow Card scheme, but it is not mandatory. Analyses of batch number data, were and are, able to be undertaken where these have been provided through the Yellow Card.

344. The MHRA's analysis of Yellow Card reports did not result in any safety concerns considered to be batch-related issues. Manufacturing site details for each batch are included in the information supplied by the marketing authorisation holder and reviewed as part of the MHRA independent batch testing process. When assessing for any batch-specific issues, numbers of Yellow Card reports were considered alongside information about the size and source of the batch.

345. On 8th December 2020, mass vaccinations were commenced in the UK at which point the MHRA initiated dedicated Covid-19 vaccine signal detection meetings. These meetings ran daily throughout the early stage of the pandemic, with attendance of suitably qualified and experienced staff depending on vaccine usage and report numbers. Examples of minutes from signal detection meetings are found here: [**JR/159 – INQ000494281**; **JR/160 – INQ000494319**; **JR/161 – INQ000494329**; **JR/162 – INQ000494331**; **JR/163 – INQ000494343**].

346. A safety signal is information on a new or known adverse event that may be caused by a medical product and requires further investigation. It is not possible to determine a specific number of reports that constitutes a safety signal nor a specific rate of reporting. Many adverse events that are reported in association with vaccination will occur naturally in the population and have no association with the vaccine itself. The MHRA does not, therefore, have a threshold for a particular number of suspected ADR reports required before regulatory action is taken. The MHRA may, for example, take action based on a single suspected ADR report.

347. The number of Yellow Card reports received by MHRA therefore needs to be placed into the context of the size and characteristics of the vaccinated population and the background rate of the event in question in that population to understand how many events might be expected. There are uncertainties in the estimates of the background rates. The validity of

using these rates based on a comparison with routinely recorded healthcare data needs to be considered on a case-by-case basis. Further, reporting levels, such as via the Yellow Card scheme, are highly variable depending on the type of issue and public awareness.

348. Our signal detection processes focus on highlighting drug event associations of concern based on a combination of statistical disproportionality (associations occurring more than would be expected compared with other associations) and a rule-based approach. For established medicines there are statistical thresholds which trigger alerts to review the association which include rule-based criteria (i.e. if a report is fatal or concerns a child). For new medicines and those under additional monitoring all reports are flagged and reviewed by assessors. Drug-event associations of concern are assessed by a group of scientists, physicians and pharmacists for likely causality and to determine if risk minimisation measures need to be implemented, taking into account other sources of information and independent expert opinion where appropriate. Therefore, there is not an absolute threshold for intervention by the MHRA. The MHRA would take action on a signal from any data source if we had concerns and other available data warranted it.

349. The MHRA did not rely solely on Yellow Card data for Covid-19 vaccine safety monitoring, but also utilised data from electronic healthcare records, including through rapid cycle analyses of the AESIs (as described in paragraph 317) where appropriate and feasible Rapid cycle analysis compares the rate of events in a time period following vaccination to a pre-pandemic rate in the same data source. As part of the second pillar of the surveillance strategy, the rapid cycle analyses were designed to address the challenges of comparing data across different data sources, in contrast with other observed versus expected analyses which try to contextualise spontaneous reports from patients and healthcare providers through the use of non-spontaneous routinely captured diagnosis data. The rapid cycle analyses were implemented by the MHRA using data from the Clinical Practice Research Datalink 'Aurum' dataset and the statistical maximum sequential probability ratio testing (MaxSPRT) methods, as used within US FDA surveillance systems in the Biologics Effectiveness and Safety (BEST) Initiative. Further information on US surveillance systems can be found at the FDA's BEST website.

350. To support these rapid cycle analyses, pseudonymised patient level data on vaccinations were sent by NHS Digital to the Clinical Practice Research Datalink and linked by the MHRA

to their patient cohort and analysed in conjunction with data on events recorded in the patient record on a weekly basis. Outputs of rapid cycle analyses were monitored by the MHRA and presented alongside ADR reporting data to the VBREWG. The rapid cycle analyses were, however, themselves limited by variable delays in the availability of data on diagnosed events and the unknown impact of the pandemic on presentation, diagnosis and recording in electronic healthcare records. Ecological analyses, showing event rates over time before the pandemic, prior to vaccine deployment and after deployment were also used. These were also calculated using data from the CPRD and supplemented with analyses from UKHSA using Hospital Episodes Statistics data.

351. Additionally, to further facilitate rapid assessment of safety data, the MHRA implemented daily data mining runs within its Empirical Signal detection software. This enabled daily provision of all newly received or updated UK ADR reports from all sources in relation to the Covid-19 vaccine(s) to the dedicated product assessment team each morning, for their clinical and scientific review and assessment, ahead of the afternoon (4pm) signal detection meeting. The meetings also considered information and signals received from vaccine manufacturers as well as data from other regulators under data sharing agreements. Using this information, the group worked to reach decisions on next steps.

352. A line listing of all newly received or updated ADR reports was provided to the MHRA's assessment team each day, alongside a count of the number of Yellow Card reports received per reaction. A statistical score, known as 'EB05', was provided for each reaction on both a combined 'medicines and vaccines' and 'vaccine only' background. This score was used to provide an indication of whether a reaction was being observed more than expected and therefore needed urgent scientific and clinical assessment. These criteria, as well as signal detection and evaluation processes, were evaluated by the MHRA in a paper titled: "Impact of Covid-19 vaccine reports on disproportionality analyses for other vaccines" [**JR/164 – INQ000494328**]. This study validated that the large numbers of ADR reports and the methodologies deployed for Covid-19 vaccines had not adversely impacted signal detection for other vaccines and drugs at this stage of the pandemic.

353. In order to implement observed versus expected analyses to enhance the passive surveillance systems, the MHRA utilised age-specific pre-pandemic background rates for the pre-specified AESIs calculated prior to vaccine deployment using data from the CPRD and

Hospital Episode Statistics data. The UKHSA and the public agencies in the devolved administrations sent weekly aggregated data on the number of vaccinations by age, gender, vaccine brand, and dose, from the start of deployment. This enabled the weekly calculation of observed-expected analyses using the MaxSPRT approach to support signal detection and signal strengthening. Ad hoc analyses were calculated for signals arising for events not in the AESIs list to trigger further assessment.

Engagement between the MHRA and relevant bodies

Marketing Authorisation Holders

354. Under regulation 205A read with schedule 12A (part 6) of the Human Medicines Regulations 2012, marketing authorisation holders are required to communicate reports of suspected adverse reactions to authorised products in the form of UK and global Individual Case Safety Reports ("ICSRs"), to the MHRA. This follows an international standard. As explained above, the MHRA implemented systems to ensure not only that legal deadlines were met, but that reports were available for assessment both within the MHRA and by relevant bodies substantially more speedily than has historically been possible, despite anticipated increased numbers of suspected adverse reaction reports.

355. The MHRA implemented weekly meetings with individual vaccine manufacturers, both to exchange information on evolving safety assessments, and to monitor and provide feedback on the resilience of manufacturers' vigilance systems.

356. The MHRA does not have specific powers to compel marketing authorisation holders (including pharmaceutical companies) to provide relevant clinical information for MHRA safety investigations. However, under the Human Medicines Regulations 2012, a UK marketing authorisation holder is required to submit any new information to the licensing authority that may necessitate a modification of the authorisation. This includes any additional information the holder considers might influence the evaluation of the benefits and risks of the product, including relevant clinical information.

357. Information must be provided by the marketing authorisation holder as soon as is reasonably practicable after the holder becomes aware of it. Additionally, a UK marketing authorisation holder is obliged to transmit reports of suspected adverse reactions to the MHRA within strictly defined reporting timeframes, including both the initial report and any subsequently received follow-up information (including clinical details). Therefore, although

the MHRA does not have powers to compel, the current legislation does provide a mechanism to ensure all relevant data are communicated.

Other bodies

358. Effective partnership working was established with PHE (now UKHSA), NHS-E and the devolved administrations for the rapid exchange of information on any incidents that occurred at vaccination sites, with clear guidance that reporting via Yellow Card should be undertaken, leading to additional capability for rapid communication between teams.

359. The MHRA agreed approaches for sharing safety assessments with the JCVI including via attendance at their meetings, sharing signal assessment reports, and having JCVI representatives observe the meetings of the VBREWG. On request by JCVI, the MHRA presented safety updates on the Covid-19 vaccines, typically based on recent presentations to EWG and CHM, and focussing on the current safety topics being assessed. Further detail about sharing safety data with the UK public and national and international stakeholders can be found here: [**JR/165 – INQ000494301**].

360. Updating healthcare professionals and the UK public on the emerging safety profile of Covid-19 vaccines in clinical use was primarily via the weekly Yellow Card ADR summary publications, and via media briefings at key points. Regular meetings of the ICMRA Covid-19 ICMRA Covid-19 Vaccine Pharmacovigilance Network proved vital in exchanging the latest safety information with other regulators, and this was supplemented by bilateral engagement as appropriate. For example, the then head of the Australian regulator, the TGA, has expressed the opinion that access to the MHRA's safety data saved Australian lives. Additionally, Memoranda of Understanding and Data Sharing Agreements [**JR/166 – INQ000494275**; **JR/167 - INQ000494363**] were used to share assessments with key international regulatory partners.

361. I am asked about how the MHRA comes to review post-mortem data in relation to potential safety signals. There is no systematic interaction between the Yellow Card system and the coronial system. Paragraph 7 of Schedule 5 to the Coroners and Justice Act 2009 provides coroners with the duty to make reports to a person, organisation, local authority or government

department or agency where the coroner believes that action should be taken to prevent future deaths. Such reports are sometimes referred to as reports to prevent future deaths or regulation 28 reports.

362. The MHRA receives regulation 28 reports from Coroners considered relevant to medical products and rigorously reviews these for actionable information. The MHRA also rigorously reviews the findings of inquests and follows up post-mortem data, when available, for potential safety signals. The MHRA may also attend inquests and / or provide evidence.

363. When the MHRA receives a regulation 28 report, the Yellow Card database is searched to determine if a report for the patient and event already exists. If not, a Yellow Card report is created and processed to look for potential signals according to standard operating procedures. The MHRA fully assesses the event to determine whether regulatory action is required. The MHRA will seek further data and independent expert advice in order to support this assessment. A full response is provided to the coroner on every regulation 28 report and as CEO I review each response and any follow-up action.

Formal epidemiological studies

364. The fourth pillar of the Covid-19 vaccine vigilance strategy related to conducting formal observational epidemiological studies on the benefits and risks of Covid-19 vaccines, using data on vaccinations and outcomes from electronic healthcare records and other national data sources. Central to this pillar was ensuring that the MHRA was aware of studies being undertaken by research groups nationally and internationally, liaising with the research groups to encourage their timely engagement with key questions relating to specific safety issues, and seeking data for consideration by the EWG and the CHM.

365. Evidence generated by MHRA epidemiologists supplemented the assessment of vaccines benefit and risk. For example, a self-controlled case series, analysing primary care data from 17 million patients in England, investigated the potential association of Covid-19 vaccination with three acute neurological events: Guillain-Barré syndrome ('GBS'), transverse myelitis and Bell's palsy [**JR/168 – INQ000274106**]. This was conducted in collaboration with a group from LSHTM using data from OpenSAFELY and another study, also looking at the risk of GBS, that was conducted with scientists from University College London Hospitals using data from the National Immunoglobulin Database.

366. Other descriptive studies were implemented to support the assessment of other safety concerns, for example CPRD data were used to evaluate rates for serious menstrual disorders and these were presented at the VBREWG on 18 March 2022 [**JR/169 – INQ000409539**].

Signal Assessment processes

The Yellow Card system

367. Those reporting via the Yellow Card system are asked to indicate whether they are the patient, or otherwise, their relationship to the patient. The MHRA can therefore identify whether the Yellow Card is self-reported, reported by next of kin, or by a healthcare professional. Patients do not always have access to diagnostic information, or may report based on symptoms, which can add to the complexity of interpreting their reports. Patients who self-report are asked for permission for the MHRA to contact their healthcare professional for further information.

368. The Yellow Card reporting system asks the reporter to detail characteristics including age, weight, height, ethnicity, pregnancy, past medical history and co-morbidities. These data may produce a safety signal among particular patient groups. However, the MHRA does not rely solely on Yellow Card data to identify risks for certain groups, and epidemiological studies can also identify the prevalence of safety signals in certain groups.

369. The MHRA's scientific and clinical assessors continually reviewed Yellow Card and other adverse reaction data associated with Covid-19 vaccines and therapeutics received from all sources to consider whether new reports may represent new safety concerns, or a change in the safety profile as assessed from the clinical trials. Signal meetings attended by assessors determine whether independent expert advice should be sought from the CHM's VBREWG, or whether further evidence or analysis (such as cumulative review of relevant reports and other relevant data or observed-expected analyses) would be required to establish a potential association with a vaccine. The signal meetings also considered information and signals received from vaccine manufacturers and under data sharing agreements with other regulators.

370. It is important to note that Yellow Card data cannot be used to derive side-effect frequencies or compare the safety profiles of Covid-19 vaccines, as many factors can influence adverse reaction reporting. In assessing emerging trends from Yellow Card data,

the MHRA considered all sources of evidence from the surveillance strategy, including observed versus expected rates of events from healthcare data and international information. Additionally, it is important to note that a Yellow Card report of a suspected adverse reaction can include reference to more than one vaccine for example where different vaccines have been used as third or booster doses.

371. Throughout the pandemic, the MHRA actively encouraged healthcare professionals to report suspected Covid-19 vaccine side effects. The MHRA published guidance to healthcare professionals on reporting adverse events via the Yellow Card Scheme [**JR/170 – INQ000507363**]. This was updated six times between 19 March 2020 and 1 January 2021 to provide the most up to date advice. This included encouraging online Yellow Card reporting instead of paper submissions, sharing a link to the newly created coronavirus Yellow Card reporting site, and sharing updated documents highlighting the role of Yellow Cards in identifying safety issues. The MHRA also provided information on the Yellow Card scheme to all vaccinators and vaccinees at the point of care through information leaflets before and after vaccination, and through NHS training materials. Additionally, all authorised vaccine information included a statement to encourage the reporting of suspected side effects to the Yellow Card scheme and stated why it was important.

372. The MHRA's team of safety assessors follows up Yellow Card reports for additional information as necessary, based on the completeness, severity, outcome and clinical details provided in the report. We actively follow up Yellow Cards of special interest, including reports with a fatal outcome, for any information that would benefit our assessment and encourage all reporters to send relevant updates on their reports. Not all Yellow Card reports require follow up by the MHRA. For example, the reporter may provide a comprehensive account of the clinical details upon first submission including outcome. Reporters may not provide permission for the MHRA to contact them again. In July 2023, the Yellow Card reporting system was updated to allow users to update their own reports. This change aimed to enhance the flexibility and accuracy of the data, enabling users to amend their submissions with new information or corrections as needed.

373. I am asked about whether the MHRA's analysis of Yellow Card reports concerning Covid-19 vaccines and background rates of conditions changed during the course of the pandemic. The MHRA's analysis of Yellow Card data was dynamic throughout the pandemic as we

continuously reviewed the evolving data that became available post-approval of the vaccines. This is described in detail within the "ADR Chronologies" section of this statement. Background rates provide an indication of how often a condition would have occurred naturally in the population, outside of the pandemic. Background rates were monitored throughout the pandemic, during both the pre-vaccination period and vaccine roll-out, allowing sensitivity analyses incorporating background rates to be conducted. For example, the MHRA conducted observed versus expected and rapid cycle analyses where there was evidence that background rates had changed due to other factors (such as reduced socialising during lockdowns and changing prevalence of infection with Covid-19).

374. I am asked about making the Yellow Card reporting process a simpler experience for lay people, including those who may be suffering from ill health or bereavement. The Yellow Card scheme was continually enhanced prior to and during the pandemic (see paragraph 832). In February 2022, a new Yellow Card website was launched, building on enhancements from the Coronavirus Yellow Card site introduced in May 2020. The update simplified the reporting process, removing the need for the public to differentiate between medicines and medical devices, a change driven by user feedback. Forms also support dictation via a mobile device to provide easier completion. New Yellow Card functionalities also include patient-reported follow-up and customisable questions for more targeted data collection, enhancing MHRA's ability to monitor safety concerns responsively. Attachments such as photographs can now be added to reports, further improving communication and surveillance capabilities. The MHRA continually seek user feedback to understand further ways by which we may improve the usability of the Yellow Card Reporting System.

The Yellow Card Vaccine Monitor

375. The Yellow Card Vaccine Monitor was established to generate data which could be used alongside other sources of evidence to help quantify more frequent side effects and those in populations which had not been included in clinical trials, such as pregnant and breastfeeding women. Individuals were invited to register for the system through a call-recall process. The number of invitations sent to each cohort was designed to have a representative spread of registrations across the cohorts eligible for vaccination. Where numbers of registrations were noted to be lower than anticipated, additional invitations were sent to these groups in

subsequent waves. During the pandemic, close to 1.5 million invitations were sent, yielding over 33,000 registrations, including roughly 12,000 individuals over the age of 70 years and 2,500 pregnant women. Those who registered for the Yellow Card Vaccine Monitor were actively followed up to obtain information about potential side effects associated with the Covid-19 vaccines. Those who responded but were not invited to participate were encouraged to report any suspected adverse events via the coronavirus Yellow Card portal.

376. Data from the Yellow Card Vaccine Monitor System supported signal detection analysis and were used in routine signal detection activities alongside other data sources. For example, at its meeting on 23 July 2021, the VBREWG reviewed safety data for Covid-19 vaccines in pregnancy and breastfeeding and in relation to menstrual disorders [**JR/171 – INQ000409532**]. Data from the Yellow Card Vaccine Monitor system were reviewed alongside non-clinical and clinical trial data, spontaneous reports received via the Yellow Card Scheme and via the ZOE app. The ZOE app enabled Covid-19 safety data to be collected from over 4 million users. The ZOE COVID Symptom Study was supported by grants from the DHSC in 2020 and 2021.

377. The Yellow Card Vaccine Monitor system data contributed to the VBREWG's advice that the use of Covid-19 vaccines in pregnancy and breastfeeding did not raise any safety concerns, and that there was no evidence of an increased risk of menstrual disorders for the AstraZeneca (Vaxzevria), Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax) Covid-19 vaccines, with a very low rate of reporting (0.5%). It was recorded in the VBREWG meeting minutes at paragraph 3.4 that the data from the Yellow Card Vaccine Monitor System were reassuring. The Yellow Card Vaccine Monitor has not been discontinued. The MHRA is no longer recruiting new members to the YCVM but is still receiving and monitoring follow-up information through the system.

Epidemiological Studies

378. Epidemiological studies which were undertaken by the UKHSA and others on the effectiveness of the different vaccines were also used to contextualise risks when making benefit risk decisions. During the pandemic, a significant amount of data from epidemiological studies were considered by the EWGs, via presentations and publications. An example of the VBREWG receiving a presentation on an epidemiological study carried out by an external research body is found in the meeting minutes from 7 June 2021 [**JR/172 – INQ000494349**].

During the meeting, Professor Sudlow from the BHF Data Science Centre presented to the VBREWG an analysis of data for the Pfizer/BioNTech (Comirnaty) and AstraZeneca (Vaxzevria) Covid-19 vaccines from electronic healthcare records on thrombosis and thrombocytopenia.

Vaccine batch related signals

379. I am asked to explain what, if any investigations or batch analysis was undertaken to determine whether certain batches of Covid-19 vaccines were associated with higher rates of adverse events. I have explained the MHRA's approach to batch testing elsewhere in this statement (see, for example, paragraph 154 and onwards). Independent batch release testing was, and is, undertaken on all Covid-19 batches by NIBSC before they are released to patients, ensuring all batches meet the required specifications for purity and potency.

380. Our analysis of the Yellow Card reports considers product batch number, where provided by the reporter, however as above, it is not mandatory to provide batch numbers when submitting a suspected ADR report for a medicine or vaccine. Manufacturing site details for each batch are included in the information supplied by the marketing authorisation holder to MHRA laboratories and reviewed as part of the independent batch testing process. It is important to also note that not all batches of the Covid-19 vaccines are the same size, and some batches may have had more wastage than other batches or be distributed more widely outside of the UK. Therefore, the MHRA would not expect the number of suspected ADR reports for all batches to be the same as they have been administered to different numbers of patients. Different batches would have been used at different stages of the vaccination campaign, and in different patient groups, which could also impact reporting rates. For example, reporting rates were typically higher at the beginning of the vaccination campaign as individuals received their first dose. The likelihood of experiencing a reaction, as well as the propensity to report it, remains variable across patients of different ages.

381. Our ongoing safety monitoring of Covid-19 vaccines has not identified any batch- specific safety concerns and no regulatory action has been taken for individual batches of these vaccines.

Post-Authorisation Safety Studies

382. A post-authorisation safety study (PASS) is a study that is carried out after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. The MHRA has contacted marketing authorisation holders AstraZeneca, Pfizer/BioNTech and Moderna to understand the latest publication status of the studies where this was not provided in the RMP. The HMA-EMA Catalogues include information on the products, protocols and outcomes for all published PASS studies. This is available through the EMA's website [**JR/173** **INQ000507365** **JR/174 – INQ000507366**].

383. For the AstraZeneca (Vaxzevria) Covid-19 vaccine, a total of 17 clinical studies were conducted, or were previously included, as additional pharmacovigilance activities in the Risk Management Plan Of these studies, 9 are reported as phase 1,2 or 3 studies. Of the remaining studies, 6 are safety studies and 2 are vaccine effectiveness studies. AstraZeneca provided information on the publication status conducted as registered within HMA-EMA Catalogues of real-world data sources and studies. This included information on the 6 studies considered to be post-marketing safety studies, the 2 effectiveness studies and one phase 3 study. Of these 9 studies, AstraZeneca state that, currently 6 have made results publicly available online within clinical study reports (CSR) – as either an interim report (n=1) or final report (n=6). For the remaining two, the decision has not yet been made to publish by the Principal Investigator for one study, and no CSR was posted for the other study.

384. In respect of the Pfizer/BioNTech (Comirnaty) Covid-19 vaccine, a total of 22 clinical studies are included, or were previously included, as additional pharmacovigilance activities in the Risk Management Plan for the Pfizer/BioNTech (Comirnaty) vaccine. Of these studies, 9 are reported as phase 1,2 or 3 studies. Of the remaining studies, 10 are safety studies and 3 are vaccine effectiveness studies. Pfizer has not specified how many studies have been published but states that "Under EU and other obligations, all final study results will be published. Where studies have not yet been published, this is due to the study being ongoing, not yet commenced, or in the process of regulatory submission and review. Publication will be made via EMA, and other routes where applicable, in due course."

385. In respect of the Moderna (Spikevax) Covid-19 vaccine, a total of 16 clinical studies are included, or were previously included, as additional pharmacovigilance activities in the Risk

Management Plan for the Moderna (Spikevax) vaccine. Of these studies, 8 are reported as phase 1,2 or 3 studies. Of the remaining studies, 7 are safety studies and one is a vaccine effectiveness study. The MHRA does not have information on the publication status of these studies but understands that publication will be via EMA and other applicable routes in due course.

Benefit risk evaluation

386. If a new risk is confirmed by MHRA as a result of its vigilance activities, this is incorporated in continuous evaluation of the balance of benefits of a vaccine versus its risks. For potential safety issues detected from Yellow Card data or other sources, typically a decision was made to seek timely independent expert advice from the COVID-19 VBREWG. Meetings of the VBREWG were held virtually approximately once a week to allow for rapid advice to be sought and to facilitate prompt regulatory action. If the VBREWG recommended that regulatory action was required to minimise a risk to public health, then its recommendations were presented to the CHM whose advice would be conveyed for ministerial decision on the proposed action.

387. Benefit risk assessments were undertaken promptly, often requiring out of hours and weekend working, involving collaboration from multiple MHRA scientific, clinical and epidemiological assessors to collate and analyse the supporting evidence. The evidence included Yellow Card reports, data from clinical trials and information where available from other regulators, along with data on vaccine exposure at that point in time to help characterise what might be expected in the population exposed. While safety evidence accumulated at a rapid rate, as the vaccination programmes in the UK, and globally, progressed, the MHRA conducted multiple assessments for the most significant safety concerns to ensure that advice was continually sought on the most up-to-date evidence, taking into account any regulatory action in other jurisdictions.

388. For the assessment of a specific possible safety concern, the MHRA considered the biological plausibility of the event being caused by the vaccine based on knowledge of the kinds of events which that type of vaccine may induce (typically immune-mediated events for non-live vaccines) and associations with similar vaccine platforms (where applicable). In the event of a series of reports of the same or similar reactions, the characteristics of the reports were considered in terms of seriousness of the event (resulting in hospitalisation, or on the other hand self-limiting), outcomes (whether the patient recovered or not), the level of certainty

of the diagnosis (test results, diagnosis by a healthcare professional), time to onset, possible alternative explanations (underlying medical conditions, concurrent medications). Data on overall exposure to the vaccine and in specific groups were used to put the numbers of reports in context.

389. For adverse events of special interest, the MHRA routinely conducted enhanced signal detection using observed-expected analyses, where numbers of reports of an event are combined with age-stratified incidence rates for that event, along with numbers of individuals exposed, to provide an estimate of whether that event is occurring more frequently than would be expected under normal circumstances in the absence of vaccination. If these analyses suggested an increased incidence, then additional epidemiological analyses could be undertaken to determine whether there was a statistical association between the vaccine and the safety concern.

390. Information from signal assessment informs benefit risk assessment of a vaccine through evaluation of benefit risk at population level. In the early stages of the vaccine roll-out the benefits were inferred from clinical trial data on efficacy, but as real-world data on effectiveness of the vaccines accrued, it was possible to compare some of the more serious risks with numbers of hospitalisations and deaths prevented by vaccination. Risks were characterised in terms of their seriousness, frequency, and reversibility. Wherever possible, risks were stratified by age to identify whether a particular age group was more likely to be the basis of the signal (eg for Guillain-Barré syndrome this was typically older adults as opposed to younger individuals). For all the more serious safety concerns identified for the Covid-19 vaccines (thrombosis with thrombocytopenia syndrome, immune thrombocytopenia, Guillain-Barré syndrome, myocarditis), the estimated incidence rates were all either very rare (between 1 in 10,000 and 1 in 100,000 vaccinated) or less than 1 in 100,000.

391. Other considerations in benefit risk assessment include the implications of not using the product e.g. risks associated with Covid-19, or the risks of another product (e.g. a patient with an allergy to a component of another type of vaccine, such as an mRNA vaccine).

392. The general principles of benefit risk assessment for the Covid-19 vaccines were similar to a non-pandemic situation, although there was the added challenge of rapid delivery of the vaccination programme to the majority of the population to prevent the associated morbidity

and mortality and to slow the spread of infection and reduce the adverse impact of Covid-19 in the population. Regulatory options to maintain the positive balance of benefits and risks included risk communications, adding advice in the product information, and restricting use of a vaccine in a particular group of patients to prevent harm to those patients who may be at particular risk of certain ADRs, thus allowing continued use of the vaccine in other populations.

Post-approval safety monitoring of Covid-19 therapeutics

393. The MHRA's approach to safety surveillance for Covid-19 therapeutics was designed based upon the general principles of signal detection and risk management, taking into account the anticipated scale and different modes of deployment. Given these products were and are given to patients infected with Covid-19 most at risk of progression to severe disease or already suffering severe symptoms, the approach taken needed to account for the co-morbidities and characteristics of these patients and the potential for confounding while ensuring events presenting across a range of healthcare settings were identified.

394. For therapeutics, the primary route for post-approval monitoring undertaken by the MHRA (as distinct from the role of the manufacturers) was therefore, the Yellow Card scheme. The coronavirus Yellow Card portal was designed and updated to enable data capture on adverse events related to all products used in the treatment of Covid-19 including those authorised later in the pandemic. There were also strategies in place to deal with specific issues, including use in understudied populations such as pregnant and breastfeeding individuals and the risks of drug interactions. For example, in the light of pre-authorisation non-clinical data on Molnupiravir indicating a potential risk in pregnancy, it was agreed a Covid-19 Antivirals in Pregnancy registry should be established. The MHRA commissioned the UK Teratology Information Service to operate the registry and the advice of the EWG was sought on any suspected safety issues detected.

395. As set out earlier from paragraph 296, marketing authorisation holders for all types of medical products (including Covid-19 therapeutics) are required to report safety data promptly to the MHRA and to conduct further pharmacovigilance activities including those specified in the Risk Management Plan. The MHRA specifically requested that Covid-19 therapeutics manufacturers proposed studies on effectiveness in immunocompromised patients and pregnancy registries in some cases. The MHRA also required manufacturers to commit to monitoring the impact of viral variants on the efficacy of their products.

Surveillance outcomes

396. As described, a vast amount of data was considered by the MHRA as part of the surveillance monitoring for Covid-19 vaccines and therapeutics. Between December 2020 and May 2023, 186 papers were produced for consideration at the 93 VBREWG meetings. Between December 2020 to September 2022, there were 184 Covid-19 vaccine specific signal detection meetings and over 170 safety assessments produced by a team of 25 assessors, including expert assessors in vaccines and women's health, medical assessors, pharmacoepidemiologists, and toxicologists. These meetings were instrumental in decision-making on vaccine benefit risk and are described below in our "ADR Chronologies" section.

397. As of 23 November 2022, for the UK, 177,925 Yellow Cards had been reported for the monovalent and bivalent Covid-19 vaccine Pfizer/BioNTech (Comirnaty), 246,866 have been reported for the Covid-19 vaccine AstraZeneca (Vaxzevria), 47,045 for the monovalent and bivalent Covid-19 vaccine Moderna (Spikevax).

398. Assessment of the vast majority of suspected adverse reaction reports confirmed the safety profile seen in clinical trials with the overwhelming majority of reports relating to injection-site reactions (for example, a sore arm) and generalised symptoms such as 'flu-like' illness, headache, chills, fatigue, nausea, fever, dizziness, weakness, aching muscles, and rapid heartbeat. These types of reactions reflect the normal immune response triggered in the body by the vaccines.

399. Where the data suggested that medical events were directly associated with Covid-19 vaccines and not just temporally, coincidentally linked with vaccination, these were included within the product information and RMPs. I discuss these adverse reactions below.

The MHRA's role in provision of information to the public and healthcare professionals during the pandemic

400. The MHRA played a significant role in the provision of information to the public and healthcare professionals about the Covid-19 vaccines during the pandemic. During the public health crisis, from 8 June 2020, the Secretary of State for Health and Social Care approved all of the MHRA's national communications and public messaging, including those regarding vaccine approvals and safety communications **[JR/50 – INQ000400193]**. Additionally, it was agreed that the communications strategy and key messages from the DHSC and the MHRA

should align wherever appropriate. The DHSC and the MHRA therefore shared all specific communications strategies and key messages. The DHSC's Covid-19 Vaccine Communications Strategy was finalised and published on 23 October 2020 [**JR/175 – INQ000494264**].

401. In November 2020 the MHRA developed an overarching Covid-19 vaccines communications strategy [**JR/176 – INQ000494368**]. The principles of the strategy reflected the MHRA's normal communication principles, with a 'patient first' approach that demonstrated the MHRA's commitment to protect public health and safety, to be consistent with wider government, and to deliver fact-based, honest, transparent and scientifically rigorous communications. The aim was to reinforce the MHRA's independent science-based judgment and to increase confidence in the safety and efficacy of MHRA-approved Covid-19 vaccines.

402. In December 2020, the DHSC and MHRA additionally agreed on a Yellow Card Covid-19 Vaccine ADR Reporting Campaign Plan [**JR/177 – INQ000494277**]. The objective of the campaign was to encourage Covid-19 vaccine recipients who experienced suspected side effects associated with their vaccine to report their experiences via the coronavirus Yellow Card reporting site. Social media, advertisements, search engine optimisation and leaflets were all utilised to promote the Yellow Card scheme in targeted campaigns for various vaccination cohorts. Information on the Yellow Card scheme and the process for reporting suspected side effects was also provided to all vaccinators and vaccinees at point of care through information leaflets before and after vaccination, and it was provided in NHS training materials.

403. Finally, the MHRA worked in cooperation with other government health bodies such as the former Public Health England (now UK Health Security Agency, UKHSA) to ensure that up-to-date safety information about the Covid-19 vaccines was included in materials for healthcare professionals, such as the Green Book [**JR/178 – INQ000468861**]. This enabled the public to receive accurate vaccine safety information directly from their healthcare professionals.

404. I am asked whether I consider the information provided to the public was sufficient. Overall, I believe it was satisfactory before and at the time of vaccination. Regular and

frequent publication of ADR data and reporting trends also supported transparency. I note that the level of reporting of side-effects was about five times greater than predicted, suggesting that the messaging to report suspected side effects reached many of those who needed to hear it.

405. I am asked what process, if any, exists for updating people who have received a vaccine of subsequently discovered side effects, and if no such process exists, whether it should. There is no direct mechanism for MHRA to update individuals who have received a vaccine of subsequently discovered side effects. The MHRA published a regular report on its Yellow Card website during the pandemic where, as well as data on suspected adverse reaction reports associated with Covid-19 vaccines, trends in vaccine safety information was provided. A listing of all ADRs received via the Yellow Card reporting scheme on the Covid-19 vaccines is provided as Vaccine Analysis Prints on the MHRA website, updated regularly There are pros and cons to establishing such a mechanism to provide feedback to vaccine recipients that would need careful consideration.

The MHRA's understanding of public confidence

406. I am asked about the MHRA's understanding of levels of public confidence or causes of mistrust in the safety of the UK Covid-19 vaccines. The MHRA did not and does not collect specific data on public confidence or mistrust in the safety of medicines and medical products including the Covid-19 vaccines. The high vaccine uptake, particularly in the elderly and other vulnerable populations, indicates that there was a good level of public trust and confidence. As of 2 March 2023, Office for National Statistics figures indicate that 75.8% of people aged 18 and over had received at least three Covid-19 vaccinations. Older people were more likely to receive a fourth vaccination than younger people, with 94% of people aged 80 years and over receiving a fourth dose, compared to 66.4% in people aged 50 to 59 [**JR/179 – INQ000489455**].

407. However, there were large variations in vaccine uptake rates in different ethnic groups. As of October 2022, the proportion of unvaccinated adults was highest for those identifying as Black Caribbean (39.5%), followed by those identifying as White Other (25.8%) and Black African (25.6%). The lowest proportions of unvaccinated adults were in the White British (8.8%) ethnic group. In response to this the MHRA engaged with multicultural groups, including in devolved nations, to support dissemination of information about the benefits and

risks of Covid-19 vaccines, as discussed in the "Lessons Learnt" section of this statement. [**JR/180 – INQ000468868**].

408. I am aware that on 16 March 2022 the Office for National Statistics also published data from a study about barriers to vaccination among unvaccinated adults in England. The study found that the top three reasons why individuals had chosen not to be vaccinated were: (i) being worried about the side effects, (ii) feeling that the vaccine had been developed too quickly, and (iii) being worried about the long-term effects on their health [**JR/181 – INQ000489456**].

409. Below I set out our proactive, and, where necessary, reactive approaches to addressing public concerns in order to increase trust in the safety of the Covid-19 vaccines.

The MHRA's role in strengthening public confidence in the Covid-19 vaccines

410. The MHRA was part of wider government communications efforts to contextualise the benefits and risks of the Covid-19 vaccines. The MHRA sought to strengthen public confidence in the standards of its scientific assessment of the vaccines, its robust impartial decision-making processes and testing strategy, and its continual vigilance to ensure that the benefits of the vaccines continued to outweigh any risks for the majority of people. To achieve this, communications were produced to highlight the favourable benefit risk profile and provide timely safety information in relation to the vaccines available in the UK so that patients could be confident that any identified risks were addressed as quickly and comprehensively as possible.

411. Strategies for public engagement included patient and stakeholder engagement, proactive and reactive media engagement, social media, televised media briefings with large reach, GOV.UK updates and content (including the publication of the weekly Summary of Coronavirus Yellow Card reporting; see paragraphs 360), responding to enquiries and supporting campaigns led by other government departments.

412. As part of our commitment to public and patient engagement, lay and patient representatives were invited to participate in the CHM and EWG committee meetings, which ensured representation of the public and patient voice in decision-making. Summaries of CHM

minutes were published and can be found here [**JR/6 – INQ000283558**], which provided additional transparency and openness.

413. Minutes from meetings of EWGs are not usually published. Due to the urgent nature of the scientific assessment and committee support work during the Covid-19 pandemic and the resourcing which minute drafting and publication required, it was not possible to dedicate the time and staff needed to perform the necessary review and redaction for contemporaneous publication. Whilst the MHRA has made a commitment to publish all EWG meeting minutes before the end of 2024, it is true to say that this lack of resource led to a missed opportunity for transparency to which the MHRA is committed. Furthermore, it could be argued that more timely publication of the minutes would have better engaged the public in active surveillance. However, the MHRA was able to achieve engagement in relation to vaccine surveillance through regular fortnightly publication of Yellow Card ADR numbers and trends, as well as through the regular televised Number 10 briefings. Ultimately, however, the high uptake of the Covid-19 vaccines implies a level of trust had been generated. Regardless, the resources required and the potential benefits of more timely publication of the relevant EWG minutes during future pandemics will be considered closely.

414. To ensure access to timely information for the public, the GOV.UK website was utilised by the MHRA for Covid-19 public messaging. The GOV.UK website is well-known and provides an accessible platform for wide dissemination of critical safety updates. the MHRA published product information for the Covid-19 vaccines on the GOV.UK website when regulatory approval was given, starting from 2 December 2020 when the Pfizer/BioNTech (Comirnaty) vaccine was the first Covid-19 vaccine in the world to be approved [**JR/182 – INQ000507332**

415. This regular dissemination of information provided transparency and openness around the regulatory approval process. The MHRA aimed to publish information via multiple routes and formats to ensure it reached target audiences. These publications on GOV.UK were updated to incorporate subsequent changes to product information following the initial marketing authorisations, such as updates to the known side effects of the vaccines. This publication process continued until January 2024. Publishing product information in this more accessible way allowed for rapid and timely updates, providing up-to-date scientific advice which was deemed critical to the success of the vaccination campaign.

416. In December 2022, to expand the information available online on the safety of Covid-19 vaccines and improve transparency further, the MHRA introduced new interactive Drug Analysis Profiles (iDAPs) for vaccines, which are available online at https://yellowcard.mhra.gov.uk/idaps. The interactive and accessible format includes all spontaneous Yellow Card reports on suspected ADRs with contextual information to aid understanding and help prevent misinterpretation. This includes guidance on what data iDAPs provide and the limitations of this data, including the fact that the information does not present a complete overview of potential side effects associated with specific medicines. It guides users to refer to the patient information leaflet for the vaccine and to speak to healthcare professionals for comprehensive information about the risks of particular vaccines.

417. The MHRA also published a number of topic-specific public communications. One example of this was our messaging and dissemination of new advice about the link between the AstraZeneca (Vaxzevria) Covid-19 vaccine and extremely rare blood clots with lowered platelets. As the CEO of the MHRA, I spoke at a live televised press conference on 7 April 2021 alongside Professor Sir Munir Pirmohamed (CHM Chair), Professor Wei Shen Lim (JCVI) and Professor Sir Jonathan Van-Tam (DCMO). A press release was issued, including a link to the slides presented [**JR/183 – INQ000408453**; **JR/184 – INQ000494370**]. The MHRA notified healthcare professionals via a central alerting system (CAS) message and published the updated product information for the AstraZeneca (Vaxzevria) vaccine on our website [**JR/185 – INQ000507350**

418. The MHRA also used other communications products and alert systems, such as regular email updates to subscribers which provided general information on any new approvals, revision to product information, or alerts relating to Covid-19 [**JR/186 – INQ000494369**]. Drug Safety Update (DSU) bulletins and DSU summaries were regularly published for certain specific risks such as anaphylaxis/allergic reactions and myocarditis [**JR/187 – INQ000468825**; **JR/188 – INQ000489453; JR/189 – INQ000468831]**. CAS alerts were used to directly alert health care providers to important safety information [**JR/190 – INQ000069793**].

419. Additionally, with the known lower vaccine uptake among various groups in the general population (as discussed above), it was important to address the root causes and ensure

information was available in the right format for these groups. Cross-governmental plans were implemented to address this challenge, including the MHRA's engagement with multicultural groups and black and minority ethnic-specific media to support dissemination of information about the benefits and risks of Covid-19 vaccines and increase the confidence of these communities. This is further discussed in the "Lessons Learnt" section of this statement.

420. The MHRA also worked alongside the Cabinet Office to strengthen public confidence in the vaccines. As part of these efforts, I engaged in an interview with Reach Media that syndicated to its media titles, such as The Sun newspaper [**JR/191 – INQ000489454**]. Following a Q&A format, the interview provided a clear explanation of how the vaccines were developed and approved by the MHRA. This provided wide-reaching reassurance to the public that our usual robust standards of safety, quality and effectiveness had been upheld during vaccine assessments despite their approval in the shortest possible time and subsequent rapid deployment.

421. Further examples of how the MHRA strengthened public confidence and communicated risks associated with the Covid-19 vaccine to healthcare professionals and the general population are set out within the "ADR Chronologies" section of this statement.

422. Finally, in June 2021 the MHRA, as co-chair of ICMRA's Vaccine Pharmacovigilance Network, contributed to the publication of a joint Vaccines Confidence Statement between ICMRA and the WHO. This statement was further revised in March 2022 **[JR/192 – INQ000489459]**. In response to the public interest in vaccines and to support healthcare professionals in discussing vaccination, the statement covers the rigorous evaluation process of vaccine safety, quality, and effectiveness, and highlights the benefits of vaccination as well as addressing common concerns about vaccine safety, including the risk of adverse events and speed of vaccine development.

423. The MHRA sought to ensure that public messaging about the vaccines adequately reflected the risks of vaccination. The regular Number 10 briefings included information on the risks of the vaccines as appropriate. The MHRA also worked to make data on risks available to the public in accessible formats, as was exemplified in communication of age-related risk of blood clots with lowered platelets associated with the AstraZeneca (Vaxzevria) vaccine in collaboration with the Winton Centre. Patient information leaflets, which were given to patients

at the point of vaccination, held risk information and were promptly updated with any new risks, as is detailed in the "ADR chronologies" section of this statement, as was the Green Book, so that healthcare professionals would be able to convey the latest information on risks.

424. I am asked when providing information to the public about vaccines, whether both relative risk and absolute risk statistics be referred to and those concepts explained. The MHRA published data on the frequency and types of adverse effects reported following vaccination in the regular 'Summary of Yellow Card reporting'. This included absolute risk figures, such as the number of adverse events per million doses administered. The regular 'Summary of Yellow Card reporting' aimed to explain in lay language the context in which the absolute risk should be interpreted. Data on vaccine efficacy often includes relative risk reductions, showing how much the vaccine reduces the risk of contracting the disease compared to not being vaccinated. As described earlier in my statement, the MHRA's benefit risk analysis includes both relative and absolute risk assessments. The MHRA is always looking for ways in which to improve risk communication, hence seeking the advice of the Winton Centre, to ensure the public has a clear understanding of risk.

425. The MHRA believes that continuing to focus on maintaining public trust in regulatory systems, and engaging openly with public concerns, as they are raised will continue to increase public trust in the safety of the Covid-19 vaccines. The first of four strategic priorities in the MHRA's Corporate Plan 2023-2026 is to "maintain public trust through transparency and proactive communication" **[JR/193 - INQ000489451]**. The efforts being made to achieve this priority goal will, the MHRA believes, bolster the UK public's trust and confidence in our decision-making for any future pandemics. The Corporate Plan sets out a patient involvement strategy, as well as a communications and reputation strategy, outlining specific actions that the MHRA is taking to increase confidence and to continue to be transparent with the public. This includes continuing to have patient representatives both on our scientific advisory committees and in our patient group consultative forum.

Tackling misinformation and disinformation

426. My understanding of the term 'misinformation' (from The Health Counter-Disinformation Playbook) [**JR/194 – INQ000494338**] is the inadvertent spreading of false information. I understand 'disinformation' to refer to the deliberate creation and dissemination of false and/or manipulated information that is intended to deceive and mislead audiences. I understand

'malinformation' to refer to information that stems from the truth but is exaggerated in a way that misleads and may cause harm. I am aware that a number of theories and publications have been produced as a result of the pandemic and the development and deployment of the Covid-19 vaccines in particular, which might be considered mis/disinformation.

427. The DHSC took the lead in combatting mis/disinformation about the Covid-19 vaccines and set out its approach to tackle this issue within the communications strategy published on 23 October 2020 [**JR/175 – INQ000494264**]. I am unable to speculate about the different causes and motives behind vaccine mis/disinformation, however I note at page 5 several research sources which were used to inform the content of the DHSC strategy.

428. During the pandemic, the MHRA received numerous reports of mis/disinformation. In deciding how to prioritise and focus our responses, the key factor to consider was the impact on UK public health, and in this context, whether the information was adversely impacting on vaccine uptake. The MHRA sought the advice of the DHSC Covid-19 Vaccine Security group on 25 August and subsequently on 7 September 2021 (including colleagues from the Department of Digital, Culture, Media and Sport, DCMS) and again in October 2021, January 2022 and May 2022.

429. In June 2022, the MHRA was subsequently invited to join the cross-Whitehall Health Counter-Disinformation Working Group, which was led by the UK Covid-19 Vaccine Security group (UKCVS). Largely, the groups provided us with intelligence on the population impact of mis/disinformation, which informed the prioritisation of the MHRA response. The meetings provided initial feedback on handling the misinformation which the MHRA was seeing and what support we could be offered. Generally, it was found that mis/disinformation surrounding the Covid-19 vaccines did not significantly impact on vaccine uptake, and it was decided that responding to public statements that described these claims would only bring attention to them.

430. For example, the MHRA received emails with links to articles containing information claiming that Covid-19 vaccines caused infertility **[JR/195 – INQ000494340; JR/196 – INQ000494332; JR/197 – INQ000494330].** These emails were sent in large email chains to various organisations and did not contain specific concerns or questions from the public. The MHRA had already worked with the CHM's Medicines for Women's Health Expert Advisory

Group on consistent messaging, engaged with women's advocacy groups, and communicated data on pregnancy outcomes in women vaccinated prior to pregnancy, to help allay public concerns about potential effects of Covid-19 vaccines on fertility. This is discussed in detail at paragraphs 755 and 758 in the "ADR Chronologies". Therefore, in these instances, the MHRA did not directly respond to the claims in the articles.

431. In contrast, the MHRA continued to respond to any individual concerns received throughout the pandemic. The News Centre is the MHRA team which engages directly with the media. Throughout the pandemic, the MHRA received media enquiries via our News Centre. The MHRA would respond to enquiries about articles or social media posts which typically voiced concerns about the speed of approval of the Covid-19 vaccines and about data from our Yellow Card reporting. The weekly Summary of Coronavirus Yellow Card reporting, which was published to make accurate up-to-date safety data accessible to the public, helped to address false and misleading information, whilst also mitigating against the effects of misinformation/disinformation.

432. We also received a number of requests from media outlets fact-checking claims which were being circulated on the internet and social media. The News Centre worked closely with relevant MHRA experts or managers to carefully consider claims and always sought to provide accurate and timely information in order to provide factual information and reassurance on the benefits and risks of the vaccines.

433. By way of example, in June 2021 the MHRA was made aware of false allegations being shared through social media that pilots had died following Covid-19 vaccines, and the airline was holding "crisis talks" with the government as a result. Our News Centre's response to enquiries from Reuters formed part of the Reuters Fact Check article published on 17 June 2021, debunking these claims [**JR/198 – INQ000494300; JR/199 – INQ000489457**].

434. In September 2022, the MHRA received correspondence from the Royal College of Obstetricians and Gynaecologists about misinformation which may have deterred pregnant and breastfeeding women from taking up their Covid-19 vaccination. The MHRA added clarification to the Public Assessment Report for the Pfizer/BioNTech (Comirnaty) vaccine and our News Centre proactively sent a statement to five fact-checking agencies and other

national news providers [**JR/200 – INQ000494334**]. The BBC referred to our response in its article about the issue dated 1 September 2022 [**JR/201 – INQ000489458**].

435. The cross-Whitehall Health Counter-Disinformation Working Group transitioned into the Health Counter-Disinformation Working Group which was run and chaired by UKHSA. The Working Group sought to understand, research and monitor mis/disinformation and mal/information (MDM) within the anti-vaccine and anti-establishment context, as well as the impact of various mis/disinformation claims on patients and the public. In September 2022, the Working Group prepared "The Health Counter-Disinformation Playbook" about MDM during the pandemic [**JR/202 – INQ000494338**] which it shared with the MHRA before disbanding.

436. The Health Counter-Disinformation Working Group's successor is the Mis/Dis/Mal Analyst Working Group. I exhibit the Terms of Reference for the Mis/Dis/Mal Analyst Working Group dated October 2022 here: [**JR/203 – INQ000494339**]. Although the document bears 'Draft' markings, this is the final version of the Terms of Reference. The MHRA remain active members of this group and attend the fortnightly meetings. Our engagement with the DHSC Covid-19 Vaccine Security Group and the Mis/Dis/Mal Analyst Working Group and its predecessors was valuable because the MHRA does not generally hold or analyse information about the broad impact of MDM. Working in collaboration with others across government enabled us to share good practice in tackling MDM.

437. When the MHRA joined the Health Counter-Disinformation Working Group as described above, these meetings with the DHSC team came to an end. However, efforts to combat misinformation by engaging with reputable media outlets have continued since the pandemic ended. Continuing to address reports of misinformation demonstrates that the MHRA remains committed to providing up to date, trusted scientific advice.

438. During a pandemic, communicating effectively can be challenging due to the rapidly changing landscape and the speed of emerging evidence. The MHRA navigated these challenges with a commitment to new levels of openness and transparency on regulatory decision-making, and proactive communication of safety information. This was essential to maintaining public confidence in the MHRA, to ensure that we can continue to promote better health through access to medicines.

Adverse Drug Reaction Chronologies

439. I have been asked by the Inquiry to provide an overview of the known risks associated with each Covid-19 vaccine and a chronology of when and how each of these risks first came to the attention of the MHRA. The information is presented in ten separate chronologies, one about each known risk. Where appropriate, for completeness the chronologies extend beyond the end of the relevant period (28 June 2022).

440. As already explained in the "Pre-approvals" section of this statement, prior to authorising a vaccine the MHRA considers the data from clinical trials on safety, quality and effectiveness, and in respect of the post-authorisation monitoring of the Covid-19 vaccines has followed the same surveillance strategy that I have outlined above, for each of the vaccines listed in "The MHRA's role in authorising Covid-19 vaccines and medicines". I describe within the section entitled "Post-approval monitoring and surveillance" the need for a robust surveillance strategy given that the size of clinical trials means that rare side effects can only be identified or fully characterised when the vaccines are used in large populations.

441. By 'known risks', I understand the Inquiry to mean adverse reactions where the evidence has shown a plausible causal association with a vaccine and as a result the MHRA has updated the product information for healthcare professionals, the Summary of Product characteristics (or SmPC) and the Patient Information Leaflet (or PIL). Depending on the strength of the evidence and any related risk factors, information on an associated adverse reaction can be added to the SmPC as "undesirable effects", a "special warning and precaution for use" and/or a "contraindication." The ADRs listed whose chronologies I will go on to discuss in detail, are those which relate to "special warnings and precautions for use" and/or "contraindications" as well as "undesirable effects" included in the latest Covid-19 vaccine SmPCs.

442. A special warning or precaution is generally implemented when new conditions for use are introduced for a medicinal product, to minimise the risks associated with a potential or identified adverse reaction. For example, this may be when patients with certain pre-existing medical conditions are at increased risk of an adverse reaction, or when specific clinical or laboratory monitoring should be undertaken during use of the product.

443. A contraindication describes circumstances where a medicinal product must not be given to specific patients for safety reasons, for instance, in the presence of certain concomitant diseases, or where there are clear predisposing factors to an adverse reaction (e.g. genetic susceptibility) or demographic groups where risks outweigh benefits (e.g. by sex or age). For the Covid-19 vaccines for example, a past medical history of thrombosis with thrombocytopenia syndrome or previous capillary leak syndrome were added as contraindications to receiving the AstraZeneca (Vaxzevria) vaccine, as discussed in more detail below. Further information about contraindications can be found here: [**JR/204 - INQ000421322**].

444. It is important to note, where in the chronologies I refer to Yellow Card reports of suspected adverse reactions associated with Covid-19 vaccines, this is not the same as saying that all or any of the events reported were caused by the vaccine. Some events occur frequently in the general population, and when large numbers of individuals are vaccinated over a short period of time, a number of events will coincidentally occur shortly afterwards. To assess whether there may be a 'signal' of an association between an adverse effect and a vaccine it is usual to perform a statistical comparison of the event frequency with that occurring as a background rate in the general population (an 'observed versus expected' analysis).

445. To assess whether there is a causal relationship between a vaccine and an adverse event, it is usual to consider whether there is any pattern in the time to onset of the event, any dose relationship and the biological plausibility for an association. Other evidence may include results of formal epidemiological studies and international safety data from countries using the same vaccine in similar populations. It is a truism in medicines and vaccines vigilance that when an adverse effect is similar to the underlying pathology of the condition to be treated or prevented, it is especially challenging to assess the risk attributable to the medicine or vaccine.

446. In addition to assessing the strength of the evidence for causality, the MHRA's surveillance approach aims to characterise and quantify risks associated with vaccines. If a new risk is confirmed, this will be incorporated in the ongoing continuous evaluation of the balance of benefits of a vaccine versus its risks.

447. As discussed in "Post-approval monitoring and surveillance" in this statement, the MHRA will seek advice from the CHM and its Expert Groups and, if deemed necessary depending on the risk to public health, take regulatory action to communicate and minimise risk and support safe use of a given vaccine (e.g. adding warnings to the product information, sending communications to healthcare professionals and patients, and/or restricting its use). This is a continuous and iterative process. In addition, the associated vaccine risk management plan is continuously reviewed as the effectiveness of risk minimisation action is monitored.

448. I will address the following known associations of the Covid-19 vaccines:

a. Thrombosis with thrombocytopenia syndrome
b. Thrombosis without thrombocytopenia
c. Immune thrombocytopenia
d. Capillary leak syndrome
e. Guillain-Barré syndrome
f. Transverse myelitis
g. Acute disseminated encephalomyelitis
h. Myocarditis or pericarditis
i. Anaphylaxis
j. Menstrual Disorders.

449. Before turning to address those risks, I wish to place on record my profound regret that any person should have suffered adverse effects from a Covid-19 vaccine. I fully recognise the serious suffering and hardship faced by those people now living with long-term injuries and by their families. I wholeheartedly commit to finding out as much as possible about those risks and ensuring that no effort will be spared to prevent similar risks in the future.

450. I believe it is also important to acknowledge the very many deaths that were prevented as a result of the Covid-19 vaccination programme. I am aware that studies have been undertaken examining this issue, and it may well be that the Inquiry receives expert evidence on this point. I note that the UK Health Security Agency has provided regular reports on the effectiveness of the Covid-19 vaccines (see, for example, the report dated 12 October 2023 [**JR/205 - INQ000421333**].

451. It has been estimated that from 1 January to 8 December 2021, Covid-19 vaccines prevented between 14.4 million and 19.8 million deaths from Covid-19 in 185 countries and territories. I have no doubt that the authorisation and subsequent rapid and widescale deployment of the Covid-19 vaccines prevented the loss of many thousands of lives and allowed the UK and indeed the global community to return to normal life more quickly.

Thrombosis with thrombocytopenia syndrome

452. Thrombosis with thrombocytopenia syndrome ("TTS") is a new and very rare (2-3/100,000), specific syndrome which was identified and characterised following the rollout of the Covid-19 vaccination programme. Platelets play an essential role in helping the blood to clot which stops excessive bleeding. It was observed early in the pandemic that Covid-19 infection can be associated with a low blood platelet count.

453. In the thrombosis with thrombocytopenia syndrome, a blood clot or clots (thrombosis) occur together with a low platelet count, below 150 x 10 9/L (thrombocytopenia). In thrombosis with thrombocytopenia syndrome the pattern of blood clotting may particularly affect large veins where blood flow is slower, such as in the brain's cavernous sinuses. Cerebral venous sinus thrombosis (CVST) occurs when the venous sinuses of the brain, or the smaller veins draining into them, are partially or completely blocked by a blood clot. This prevents blood from draining out of the brain and as a result, the oxygen supply to nerve cells may be impaired and blood cells can leak into the brain tissue causing damage to the brain (haemorrhagic infarction). Symptoms of thrombosis with thrombocytopenia can include severe headaches, blurred vision, difficulty breathing, chest pain, drowsiness, and seizures, and unless rapidly diagnosed and treated, thrombosis with thrombocytopenia syndrome may frequently be associated with a fatal outcome.

454. The MHRA first received Yellow Card reports of suspected thrombosis and associated thrombocytopenia associated with the AstraZeneca (Vaxzevria) vaccine in February 2021. At that time the MHRA was monitoring adverse reaction reports of suspected thrombosis and thrombocytopenia separately in preparation for seeking the VBREWG's advice on immune thrombocytopenia (ITP), which was an AESI. It was noted that there were reports of individuals experiencing suspected thrombosis and thrombocytopenia concurrently.

455. On 3, 11 and 18 February 2021, the MHRA identified 3 Yellow Card reports of suspected thrombotic events occurring with thrombocytopenia associated with the AstraZeneca (Vaxzevria) vaccine, the report received on the 11 February being a report with a fatal outcome. Up to 21 February 2021, an estimated 9.4 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine and 8.4 million doses of the AstraZeneca (Vaxzevria) vaccine had been administered in UK [**JR/206 - INQ000421349**].

456. On 25 February 2021, the MHRA sought advice on regulatory action from the VBREWG on an assessment of reports [**JR/207 - INQ000409479**] of suspected ITP associated with administration of the AstraZeneca (Vaxzevria) vaccine, as well as global reports from the manufacturer, and highlighted the 3 reports of suspected thrombosis with concurrent thrombocytopenia [**JR/208 - INQ000409515**]. The VBREWG recommended that these events should be closely monitored, but no immediate regulatory action was advised given the limited reports available in the context of the widespread usage of the vaccine.

457. On 11 March 2021, the Danish Health Authority (which has a role in Denmark equivalent to the JCVI in the UK), announced that it had decided to suspend the deployment of the AstraZeneca (Vaxzevria) vaccine following a report of a 60-year old Danish woman who had an unusual clinical picture with a low number of platelets, blood clots in small and large vessels and bleeding, with a fatal outcome, associated with the AstraZeneca (Vaxzevria) vaccine. The MHRA had not received any further reports of suspected thrombosis with thrombocytopenia associated with the Covid-19 vaccines by this date.

458. On 11 March 2021 the MHRA contacted its equivalent regulatory authority, the Danish Medicines Agency ("DKMA"), to seek further information on the decision by the Danish Health Authority [**JR/209 - INQ000494280**] to suspend the deployment of the AstraZeneca (Vaxzevria) vaccine. The DKMA informed the MHRA that they had the one report of multiple thromboses with fatal outcome in a patient with low platelet count; and that, although causality could not be established, as a precautionary measure the Danish Health Authority was suspending the use of the AstraZeneca (Vaxzevria) vaccine, particularly as, in contrast to the UK, the vaccine was being used in a younger population who were less at risk from Covid-19.

459. Similarly, in early March 2021, a series of European member states (Austria, Norway, Iceland, Italy, Estonia, Latvia, Luxembourg, and Lithuania) suspended use of the AstraZeneca

(Vaxzevria) vaccine based on these reports of a suspected association between the AstraZeneca (Vaxzevria) vaccine and thrombotic events (venous or arterial) which had not been identified at the time of authorisation.

460. As with Denmark, the decision to suspend the use of the AstraZeneca (Vaxzevria) vaccine in these countries was taken by their health authorities and not by the medicines' regulator. For a regulatory authority to restrict the use of a medicinal product, it must restrict, suspend, or revoke the marketing authorisation (product licence). No regulatory restrictions, suspensions, or revocations were implemented by any of the national regulators in relation to the AstraZeneca (Vaxzevria) vaccine. Denmark did not resume the use of the AstraZeneca (Vaxzevria) vaccine as part of their vaccination programme, although it continued to be authorised by the EMA (until May 2024, when it was withdrawn at the request of the marketing authorisation holder) and was therefore approved in all EU countries. Italy, Latvia, Lithuania, and Cyprus resumed the use of the AstraZeneca (Vaxzevria) vaccine from 19 March 2021.

461. On 13 and 15 March 2021, the MHRA received two further Yellow Card reports (making a total of 5 Yellow Card reports) of suspected thrombosis occurring with thrombocytopenia associated with administration of the AstraZeneca (Vaxzevria) vaccine, neither of which had a fatal outcome. In addition, the MHRA was made aware of 3 further reports of suspected thrombotic events occurring in Austria (9 March 2021), Denmark (11 March 2021), and Norway (13 March 2021).

462. On 17 March 2021, the MHRA conducted an initial review of the latest available evidence on thrombosis with thrombocytopenia syndrome from the UK and other countries and sought expert advice from the VBREWG [**JR/210 - INQ000409517**]. The VBREWG considered a range of analyses presented by the MHRA and PHE experts. These included: an epidemiological analysis of thrombosis with thrombocytopenia, peripheral venous thromboembolism, and ITP [**JR/211 - INQ000494282**]; all reports of thrombotic events reported to the MHRA associated with use of both the Pfizer/BioNTech (Comirnaty) vaccine and the AstraZeneca (Vaxzevria) vaccine, one of which had a fatal outcome; observed versus expected analyses; details of the 5 events of suspected thrombocytopenia with associated CVST reported to MHRA, and the reports from Norway (5) and Germany (7) with a similar case definition.

463. The VBREWG advised that while the number of reports of suspected thrombosis with thrombocytopenia associated with administration of the AstraZeneca (Vaxzevria) vaccine was small (5 reports) when considered in the context of 11.7 million doses administered (7 March 2021) [**JR/212** **INQ000421348**], further information should be rapidly gathered with the assistance of expert haematologists, to facilitate further characterisation of the signal.

464. On 18 March 2021, the MHRA provided an update to the Licensing Minister via a submission (dated 17 March 2021), setting out the MHRA's scientific assessments and conveying the advice of the VBREWG, concluding that, while there was considered to be no proven causal link between reports of thrombosis with thrombocytopenia and the AstraZeneca (Vaxzevria) vaccine, this link could not be ruled out and warranted rapid investigation [**JR/213 - INQ000494283**]. As discussed, at this point, the MHRA had received 5 UK reports of suspected thrombosis with associated thrombocytopenia, of which 2 were reports with a fatal outcome.

465. At the same time, the JCVI was informed by the MHRA of the 5 Yellow Card reports. The JCVI advised that the vaccination programme should continue to deploy the AstraZeneca (Vaxzevria) vaccine, as it was considered that the benefits continued to outweigh the risks.

466. This VBREWG advice aligned with the advice published the following day by the EMA, 18 March 2021, based on an analysis of 7 reports of blood clots in multiple blood vessels (disseminated intravascular coagulation (DIC)) and 18 reports of CVST, concluding:

> "*A causal link with the vaccine is not proven, but is possible and deserves further analysis... the vaccine's proven efficacy in preventing hospitalisation and death from COVID-19 outweighs the extremely small likelihood of developing DIC or CVST.*" [**JR/214 - INQ000421332**].

467. On 18 March 2021, at a Number 10 televised press briefing, informed by a summary of the VBREWG minutes from 17 March 2021 [**JR/215 - INQ000494285**; **JR/216 - INQ000494289**]. Alongside the then Prime Minister I gave a full statement as follows:

> *'We have also received 5 reports of a different, rare form of blood clot in the sinuses (Cerebral sinus vein thrombosis or CSVT) occurring with lowered platelets shortly*

after vaccination with Covid-19 vaccine AstraZeneca. This type of blood clot can rarely occur in unvaccinated people as well as in people with Covid-19 disease.

A further review of these events is ongoing, but a causal relationship with the vaccine has not yet been established, and the rate of occurrence of these CSVT events among the 11 million people vaccinated is extremely rare.

While we continue to investigate these cases, as a precautionary measure we would advise anyone with a headache which lasts for more than 4 days after vaccination, or bruising beyond the site of vaccination after a few days, to seek medical attention. We will communicate further on the outcome of the review when complete.

The MHRA assessed this data alongside the benefits of the vaccine in preventing Covid-19, with its associated risk of hospitalisation and death, and determined that the benefits firmly remain to outweigh any risks.

I want to remind everyone that they can and should report all suspected side effects to Covid-19 vaccines through the Coronavirus Yellow Card Scheme.'

468. On 18 March 2021, following the press briefing the MHRA published a statement:

> "*... the available evidence does not suggest that blood clots in veins (venous thromboembolism) are caused by COVID-19 Vaccine AstraZeneca... there is no evidence that that* (sic) *blood clots in veins is occurring more than would be expected in the absence of vaccination, for either vaccine*." [**JR/217 - INQ000408457**].

However, the MHRA informed in the statement that a further, detailed review of the 5 UK reports (as described above in paragraphs 462 and 467) of a suspected very rare and specific type of blood clot in the cerebral veins (sinus vein thrombosis) occurring together with lowered platelets (thrombocytopenia) was ongoing. According to the most recent 'Summary of Yellow Card reporting' (14 March 2021), approximately 13.7 million doses of the AstraZeneca (Vaxzevria) vaccine had been administered in the UK at this time [**JR/218 INQ000421354**].

469. Following the press briefing and published press release issued to the media, there was pick up by other news agencies. The briefing impacted population awareness of reporting side effects. Indeed, following the press briefing and published press release issued to the media, the Coronavirus Yellow Card website requests increased from approximately 500 requests per minute to over 10, 000 requests per minute. This caused a 3 minute down time whilst servers were flooded with requests. Capacity was subsequently upscaled for future announcements [**JR/219** **INQ000507367**. There was also pick up by other news agencies, for example this news article calling the public to contact their GP should headaches persist more than four days after receiving their Covid-19 vaccine [**JR/220** **INQ000507369** Furthermore, the MHRA statement prompted a letter and guidance for expert haematologists regarding the precautionary measures and symptom identification. The MHRA contributed to these documents published on 25 March 2021 [**JR/221** **INQ000507368**, **JR/221(a) - INQ000474508**

470. On 23 March 2021, the MHRA sought advice from the VBREWG on an updated review of thrombotic events reported in conjunction with thrombocytopenia including the above described 5 UK reports [**JR/222 - INQ000494284**]. The evaluation focused on any thrombotic events reported in conjunction with thrombocytopenia, and for completeness this included arterial and venous emboli with a data lock point of 21 March 2021. Reports were considered for inclusion if the reporter considered there to be both a thrombosis and thrombocytopenia.

471. As of 21 March 2021, 28 reports of suspected thrombotic events with thrombocytopenia associated with administration of the AstraZeneca (Vaxzevria) vaccine had been received with 7 of these reporting a fatal outcome. Reports from Norway, Germany, and Denmark were also discussed, as well as global data from AstraZeneca. From the limited available data, the MHRA proposed some initial criteria for a case definition for these cases: any venous or arterial thrombosis and a platelet count less than 150 x 10 9/L.

472. On 26 March 2021, the MHRA convened an independent expert panel to agree the definition of what constitutes a case of thrombosis and thrombocytopenia and to adjudicate each Yellow Card report in light of the varying levels of clinical detail. The MHRA also sought advice from expert haematologists, establishing a rapid timeframe for agreement of a case

definition given the small numbers of reports of suspected CVST with concurrent thrombocytopenia on which to base a case definition.

473. At its meeting on 27 March 2021 [**JR/223 - INQ000409498**], the CHM discussed a potential mechanism for the reports of suspected thrombosis with thrombocytopenia. The CHM noted that a heparin induced thrombocytopenia (HIT)-like mechanism had been proposed by international research groups, whereby thrombocytopenia is caused by the formation of antibodies that activate platelets. This was hypothesized to be related to the presence of platelet factor 4 (PF4) antibodies in some affected patients. These PF4 antibodies promote blood coagulation. It was noted that PF4 can be stimulated by inflammatory responses and that there were likely many conditions that can stimulate PF4, with tuberculosis being one example. The CHM commented that the mechanism for reports suspected of thrombosis with thrombocytopenia could be associated with the PF4 antibodies plus other currently unknown factor(s).

474. The CHM concluded that while there was a temporal association between vaccination and the reported events, the mechanism had not been confirmed and a causal association with the AstraZeneca (Vaxzevria) vaccine could not be established. Furthermore, the CHM advised that better understanding of background rates of these events was required. The CHM advised that communications on the current evidence were required and should align with those from international regulators where possible.

475. At this same meeting on 27 March 2021, the CHM advised that the case definition proposed by the MHRA was appropriate, and the case definition for thrombosis with thrombocytopenia was therefore agreed as follows:

- Confirmed case: Venous / arterial thrombosis + Platelet count < 150 + D-dimer > 4000 + anti-PF4 antibodies +
- Probable case: Venous/ arterial thrombosis + Platelet count < 150 + D-dimer > 4000
- Possible case: Venous/ arterial thrombosis + Platelet count < 150
- Unlikely case: Criteria met for any of the above BUT alternative diagnosis more likely to explain event.
- Criteria not met: only one or none of the criteria met.

476. I am asked why a case definition was not agreed sooner and what steps, if any, could be taken to ensure that case definitions for new adverse events are arrived at sooner. As to this: thrombotic thrombocytopenic syndrome (TTS), also known as vaccine-induced immune thrombocytopenia and thrombosis (VITT), was a new condition with varying presentations. To facilitate agreement of a case definition within as short a timeframe as possible, the MHRA established a panel of expert haematologists to advise, before proposing a case definition that was agreed by the MHRA on 27 March. It is not uncommon for new adverse reactions to take time to characterise (e.g. nephrogenic systemic fibrosis with gadolinium contract agents, progressive multifocal leukoencephalopathy with natalizumab). Ideally there would be an agreed mechanism (preferably internationally) to rapidly convene experts as soon as a novel association of an adverse event with a medicine or vaccine is identified. It was particularly challenging with TTS because of the haematological effects of Covid-19 infection.

477. My attention is drawn to paragraph 2.17 of the minutes of the 27 March 2021 CHM meeting, at which it is recorded: "*The Commission discussed whether risk mitigation was needed due to the presence of an alternative vaccine where these events are not seen at the same level, however it was agreed that risk benefit evaluations should be made without consideration of other vaccines.*"

478. I am asked why benefit risk evaluations were made without consideration of other vaccines. It is not within MHRA's remit to cross-compare the benefit risk evaluations of different vaccine products (or of any products). The MHRA assesses the safety, quality and effectiveness evidence available for a given product as presented by the manufacturer and from all available evidence and evaluates that against the regulatory standards for that medicine, not against the benefit risk of any existing products. There is no comparative safety 'test' in the current medicines legislation. Decisions about vaccine policy, including which of the vaccines to recommend to different patient groups, are made by JCVI. Its decisions may supersede those of the regulator, for example in recommending off-label use.

479. On 1 April 2021, the MHRA sought advice from the CHM on further reports of suspected CVST with concurrent thrombocytopenia. The CHM heard that in the period between the previous discussion at CHM, with a data lock point of 21 March 2021, to the current data lock point of 29 March 2021, the number of reports considered to be "Confirmed", "Probable" or "Possible" according to the agreed case definition had increased to 62, with 19 of these

reporting a fatal outcome, the majority of which were reported retrospectively [**JR/224 - INQ000494287**] Having considered all the evidence in full, the CHM advised that the currently available evidence did not establish a causal association between the AstraZeneca (Vaxzevria) vaccine and TTS, and that further investigations (epidemiological and mechanistic) needed to continue [**JR/225 - INQ000409499**]

480. The MHRA was also made aware, on 1 April 2021, of a letter sent by Professor Wei Shen Lim to the then Secretary of State, Matt Hancock, regarding the growing evidence of the TTS safety signal, as well as discussion on communicating this information. As per this letter, which was circulated to relevant MHRA teams, it was agreed that coordinated communications from JCVI, MHRA, PHE and DHSC are much preferred. However, communication experts had concerns that publishing a statement before the Easter bank holiday weekend could send a confusing message to the public, leading to greater harm than benefit.

481. Indeed, in an email sent by Professor Chris Whitty on 1 April 2021 to Professor Sir Munir Pirmohamed and Profession Wei Shen Lim, in which, I was copied, Professor Whitty explains that "Anything which leads to major policy shifts or changes in public sentiment announced just before the long Easter weekend will get amplified substantially because there will be a 4 day news void, and misunderstandings will be very difficult to combat. There is considerable scope for an accidental miscommunication which is less risky in the working week when misapprehensions can be corrected more easily." [**JR/226 – INQ000507354**].

482. The MHRA is dedicated to openness and transparency when communicating information to the public and agreed that individuals should be fully informed of the benefits and risks of vaccination. In this instance, the agreed communication strategy between government departments and communication experts, was to publish a statement following the bank holiday weekend.

483. For future pandemics, a similar dedication to transparency across the healthcare matrix is vital for maintaining public trust. For example, the MHRA published its weekly summary reports of adverse events, including the one on 25 March 2021, which included a section on thromboembolic events and a link to specialist advice from the British Society for Haematology which was updated daily [**JR/227 - INQ000421354**] Similar transparency of adverse event reporting and linkage with clinical advice should be replicated in the event of a future pandemic.

484. On 4 April 2021, the MHRA updated the CHM on the age-stratified analysis of benefit versus risk of the AstraZeneca (Vaxzevria) vaccine using data collected up to 31 March 2021. Having heard all the evidence, the CHM concluded that the balance of benefits and risk remained favourable for recipients aged 40 years and older. However, given the potential emerging association of the AstraZeneca (Vaxzevria) vaccine with thrombosis with thrombocytopenia, the CHM advised that the balance of benefits and risk was less favourable for recipients aged less than 40 years, except where an individual had risk factors that increased their risk of Covid-19 mortality to a level comparable to the risk for recipients aged 40 years and older, or if another vaccine was not suitable. The CHM recommended that the regulation 174 authorisation should be amended to reflect this assessment of the benefit risk balance in different age groups [**JR/228 - INQ000409500**].

485. Following this advice from the CHM, on the 5 April 2021, I contacted Professor Sir David Spiegelhalter (Chairman of the Winton Centre for Risk and Evidence Communication which was a fixed-term project closed at the end of December 2022 aimed at improving the use of evidence and expertise in public policy) directly to seek his advice on the public communication of risk across different age groups [**JR/229 - INQ000494288**]. In collaboration with the Winton Centre, the MHRA developed slides which were subsequently used by the DCMO as part of the press conference of 7 April 2021 following clearance from DHSC and No 10 [**JR/230 - INQ000421323**].

486. On the 6 April 2021, AstraZeneca provided to the VBREWG an analysis of age-stratified risk of thrombosis with thrombocytopenia associated with the AstraZeneca (Vaxzevria) vaccine [**JR/231 – INQ000409521**] The company analysis considered global cases, the vast majority from the UK and Europe, and analysed these against assumptions of likely mortality from Covid-19 and expected background rates of the cases of concern, using a US database. AstraZeneca concluded that the benefit/risk remained positive for the vaccine, in all age ranges because the current evidence made it difficult to identify a particular age cut-off and that no causal link had been established.

487. However, AstraZeneca acknowledged that their analysis showed that the rates of thromboembolic events and CVST, combined with thrombocytopenia, were observed more

than expected in younger age groups. The company also informed the VBREWG that the trial sponsor had halted recruitment into, and vaccinations of children, in the clinical trial of the use of the vaccine in children. The Company was keen to emphasise their willingness to work further with MHRA and other regulatory authorities.

488. In the light of the AstraZeneca analysis, the CHM re-considered its conclusions of 4 April 2021. This was summarised in a submission to the Secretary of State on 7 April 2021 [**JR/232 - INQ000494385**]. The CHM advised that the further cases and the consistency of the pattern of cases strengthened the evidence of an association with the AstraZeneca (Vaxzevria) vaccine and VBREWG and CHM members were in consensus that there was an association between the AstraZeneca (Vaxzevria) vaccine and thrombosis with thrombocytopenia, but that a causal link had not yet been established. The CHM advised that instead of updates to the regulation 174 temporary authorisation as advised on the 5 April 2021, the product and patient information should be updated to state the risks of these events but should not give a specific "cut-off" age at which the benefit/risk analysis was negative.

489. This advice was in recognition that the numbers of cases of thrombosis with thrombocytopenia at the time were small in the context of usage of the AstraZeneca (Vaxzevria) vaccine and conclusions may change as more data came in, and that it was valid to consider that there was a continuum, rather than a specific age – making it inappropriate at this stage to issue a clear age restriction in the regulatory authorisation. As recorded within the minutes of the meeting, the CHM did consider that the JCVI should consider deployment strategies for different ages, in the light of the data and analyses currently available. The CHM noted that this was the approach taken in other countries where it was the equivalent bodies to the UK's JCVI which had taken deployment decisions, rather than the national regulators putting in place a regulatory restriction.

490. On 7 April 2021, following an expert panel adjudication process (an invited group of independent haematology experts who reviewed and assessed case reports or data to make informed decisions) and review of the suspected reports of thrombosis with thrombocytopenia syndrome against the case definition, the MHRA published updated advice for healthcare professionals and people receiving the Covid-19 vaccines [**JR/233** **INQ000408453**]. This updated advice stated that there was now sufficient evidence of a link between the AstraZeneca (Vaxzevria) vaccine and thrombosis with thrombocytopenia syndrome. The

MHRA's published statement included information on 79 UK reports of suspected thrombotic events received between 11 February and 31 March 2021, which, following the process of medical adjudication, were broken down into 9 confirmed cases, 14 probable cases and 56 possible cases. Nineteen of these reports were associated with a fatal outcome [**JR/234 – INQ000507334**]. The overall estimated incidence of these blood clots with low platelet count was approximately 4 people in a million who had received the AstraZeneca (Vaxzevria) vaccine by that date. The MHRA's published updated advice summarised the evidence of age-related risk, i.e., that the benefit risk of the AstraZeneca (Vaxzevria) vaccine was more finely balanced in younger age groups.

491. In collaboration with the MHRA, the Winton Centre for Risk and Evidence Communication produced a communication outlining this balance of benefit and risk to the public [**JR/235 - INQ000421353**]. In parallel, the JCVI advised that it was preferable for people under 30 years without underlying health conditions that put them at higher risk of severe Covid-19 disease to be offered an alternative Covid-19 vaccine, if available.

492. I am not aware of any correspondence between the MHRA, CHM, JCVI, the DHSC or the Office of the Chief Medical Officer or other relevant individuals or bodies in relation to an advisory as opposed to regulatory approach ahead of the JCVI advice of 7 April 2021.

493. I am asked why the MHRA took longer than other European states/regulators to take action in response to the TTS safety signal and the AstraZeneca (Vaxzevria) vaccine, and whether the UK should have suspended the use of the AstraZeneca (Vaxzevria) vaccine like other countries, in early March 2021. I would firstly say that the judgement on regulatory action in response to a safety signal is always taken in the context of the risk of the disease, the possible severity of that disease, and the availability of other treatments. Over the course of the pandemic over 178,407 people across the UK died within 28 days of a positive test for coronavirus.

494. The benefits of the vaccines in preventing Covid-19 and the serious complications associated with Covid-19, outweighed and continue to outweigh any currently known side effects. As with all vaccines and medicines, the safety of Covid-19 vaccines is continuously monitored, and benefits and possible risks remain under close review. In order to withdraw a vaccine from the market, the risks of being administered with that vaccine would need to outweigh the benefits for the majority of people. Prior to such a step, careful consideration

would be given to the possibility of defining at-risk populations, so as to identify any group in which benefit risk was not favourable.

495. As the regulatory authority, the MHRA assesses benefit risk at a population level, considering the safety, quality and effectiveness of a vaccine and, because of the current legal basis, in isolation from the risks of other vaccines on the market. The JCVI's decision on vaccine use takes into account the burden of disease, evidence of vaccine safety and efficacy comparatively between products, and cost-effectiveness of immunisation strategies. Finally, healthcare professionals, including GPs, and healthcare providers weigh benefit risk factors at the individual, patient level. If the MHRA were to withdraw or restrict products at the point where the evidence showed the benefit of receiving the medicinal product outweighed the risk for the majority of patients, the range of available options for individualised care would be limited.

496. When other European countries did suspend the use of the AstraZeneca (Vaxzevria) vaccine, this action was taken by their respective health authorities and not the medicines regulator. For the UK and devolved administrations, the relevant authority is the JCVI and health authorities of the devolved administrations. The equivalent body for Denmark (the first country to suspend use of the vaccine) was the Danish Health Authority. Health authorities consider the pandemic situation in their territory and vaccine availability when deciding on use of a particular vaccine during vaccination campaigns. The MHRA was aware that the JCVI used a variety of information to make decisions on vaccine use. For example, the MHRA was made aware via email of modelling data which showed that even a small slowing of vaccine rollout would make a large difference, leading to an earlier Covid-19 disease peak, and higher rates of hospitalisation and mortality. (**JR/236 - INQ000507354**.

497. No other regulator de-authorised/ withdrew the AstraZeneca (Vaxzevria) marketing authorisation or restricted its indication. However, the MHRA took regulatory action on 15 April 2021, adding thrombosis with thrombocytopenia to sections 4.3, 4.4 (which detail contraindications, and special warning and precautions for use) and the list of ADRs within the regulation 174 Information for UK healthcare professionals. The EMA similarly updated the AstraZeneca (Vaxzevria) vaccine marketing authorisation on the same day.

498. On 15 April 2021, the product information for vaccine recipients (the PIL) was also updated to include warnings about the symptoms of the thrombosis with thrombocytopenia syndrome [**JR/185 - INQ000507350**], such as:

- *"a severe headache that is not relieved with simple painkillers or is getting worse or feels worse when you lie down or bend over*
- *an unusual headache that may be accompanied by blurred vision, confusion, difficulty with speech, weakness, drowsiness or seizures (fits)*
- *rash that looks like small bruises or bleeding under the skin beyond the injection site*
- *shortness of breath, chest pain, leg swelling or persistent abdominal (tummy) pain".*

Thrombosis with thrombocytopenia was also added to sections 4.3, 4.4 and the list of ADRs within the regulation 174 Information for UK healthcare professionals [**JR/238 - INQ000421343**].

499. The conditions of the temporary authorisation for the Covid-19 vaccines detail specific requirements that must be met for supply of the vaccine in the UK to be permitted. As stated above [**JR/239 - INQ000421325**; **JR/240 - INQ000421324**], the information for healthcare professionals and vaccine recipients were also amended on 15 April 2021 by the MHRA in agreement with AstraZeneca to add information on blood clots with low platelets including:

a. that those who experienced cerebral or other major blood clots occurring with low levels of platelets after their first dose of any Covid-19 vaccine should not receive a second dose of the AstraZeneca (Vaxzevria) vaccine;
b. that those who have a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) should not receive the AstraZeneca (Vaxzevria) vaccine;
c. warnings that cases of serious thromboembolic events with thrombocytopenia have occurred very rarely associated with vaccination with the AstraZeneca (Vaxzevria) vaccine during post-authorisation use (with information on the time to onset and symptoms);
d. a warning that administration of the AstraZeneca (Vaxzevria) vaccine in patients with a history of CVST or antiphospholipid syndrome should only be considered when the benefit outweighs any potential risks.

500. On the same date, [**JR/233 - INQ000408453**], the MHRA advised via the GOV.UK website that:

> "*While the MHRA continues to investigate these cases, as a precautionary measure, anyone who has symptoms four days or more after vaccination is advised to seek prompt medical advice, such as:*
>
> - *a new onset of severe or persistent headache, blurred vision, confusion or seizures*
> - *develop shortness of breath, chest pain, leg swelling or persistent abdominal pain*
> - *unusual skin bruising or pinpoint round spots beyond the injection site.*"

501. On 15 April 2021, on the basis of CHM advice, the MHRA published further updated product information for healthcare professionals and vaccine recipients. [**JR/239 - INQ000421325**; **JR/240 - INQ000421324**]. This advised that patients with a history of heparin-induced thrombocytopenia and thrombosis ("HITT" or HIT type 2) should not receive the AstraZeneca (Vaxzevria) vaccine and those who had experienced major venous and/or arterial thrombosis occurring with thrombocytopenia associated with vaccination with any Covid-19 vaccine should not receive a second dose of the AstraZeneca (Vaxzevria) vaccine. On both 7 and 15 April, the MHRA issued urgent letters to healthcare professionals to advise them of the updated product information for healthcare professionals.

502. On 7 May 2021, the MHRA published an updated statement on the latest data on reports of suspected thrombosis with thrombocytopenia syndrome associated with the Covid-19 vaccines, and the age gradient in risk [**JR/241 - INQ000408455**. By 5 May 2021, 262 reports of suspected thrombosis with thrombocytopenia syndrome had been reported to the MHRA associated with the AstraZeneca (Vaxzevria) vaccine. While the balance of benefits and risks was favourable for older people it was more finely balanced for younger people and the MHRA advised that this evolving evidence should be taken into account when considering the use of the vaccine. The JCVI in parallel updated its advice [**JR/242 - INQ000390090**:

> "*in addition to those aged under 30, unvaccinated adults aged 30 to 39 years who are not in a clinical priority group at higher risk of severe COVID-19 disease, should be preferentially offered an alternative to the AstraZeneca COVID-19 (AZD1222) vaccine…*".

503. On 4 May 2021, 3 days before the release of this updated advice, the JCVI contacted relevant bodies, including the MHRA, for any comments on the wording of the updated advice [**JR/242 - INQ000390090**]. This was discussed internally within the MHRA to provide appropriate feedback on wording. For example, the MHRA added detail on reporting rates of TTS, and how reporting rates may be influenced by various factors including stimulated reporting or changes in use of the vaccine. The MHRA also provided feedback on the use of regulatory terminology to ensure correct interpretation of content. The MHRA sent feedback and advice on wording to the JCVI that same day, as well as further feedback on the 6 May 2021, both of which can be found here [**JR/243 INQ000503583 JR/244 INQ000503582 JR/245 - INQ000503577**].

504. Close monitoring and analysis of reports of suspected thrombosis with thrombocytopenia by the MHRA continued throughout 2021 and into 2022. Professor Sir Munir Pirmohamed, in his role as an independent clinical researcher and scientist, convened a specialist working group to analyse the UK and international evidence, established as the "Thrombosis and thrombocytopenia in COVID-19 Consortium" comprising researchers from multiple specialties (epidemiology, immunology, neurology, and haematology), with the purpose of coordinating further investigative work. Specific research areas included background rates of thrombosis with thrombocytopenia events in the general population, and the evaluation of the association between SARS-CoV-2 infection and thrombotic disorders, and between Covid-19 vaccination and these events. The Consortium has published papers and held a scientific symposium on 1 June 2023 which included the perspectives of patients and families.

505. The conditions of the temporary authorisation for the Covid-19 vaccines detail specific requirements that must be met for supply of the vaccine in the UK to be permitted. As stated above [**JR/239 – INQ000421325**; **JR/240 – INQ000421324**], the information for healthcare professionals and vaccine recipients was amended on 15 April 2021 by the MHRA in agreement with AstraZeneca to add information on blood clots with low platelets including:

i. that those who experienced cerebral or other major blood clots occurring with low levels of platelets after their first dose of any Covid-19 vaccine should not receive a second dose of the AstraZeneca (Vaxzevria) vaccine;

ii. that those who have a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) should not receive the AstraZeneca (Vaxzevria) vaccine;

iii. warnings that cases of serious thromboembolic events with thrombocytopenia have occurred very rarely associated with vaccination with the AstraZeneca (Vaxzevria) vaccine during post-authorisation use (with information on the time to onset and symptoms);

iv. a warning that administration of the AstraZeneca (Vaxzevria) vaccine in patients with a history of CVST or antiphospholipid syndrome should only be considered when the benefit outweighs any potential risks.

506. On 5 January 2022, the information for healthcare professionals and vaccine recipients was amended by the MHRA (in agreement with AstraZeneca) to include a warning about CVST without thrombocytopenia.

507. The MHRA advice remains that anyone who experienced cerebral or other major blood clots occurring with low levels of platelets after a vaccine dose of the AstraZeneca (Vaxzevria) vaccine should not have a further dose. The MHRA continued to publish the latest analysis of all suspected reports of these extremely rare side effects on the MHRA webpages; this was weekly until June 2022 then every 2 weeks and then monthly from August 2022.

508. The last published 'Summary of Yellow Card reporting' provided the latest incidence rate figures as of 23 November 2022 for "thrombosis with thrombocytopenia syndrome". The overall incidence after first or unknown doses was 15.9 per million doses, with a higher reported incidence rate in the younger adult age groups following the first dose compared to the older groups (21.8 per million doses in those aged 18-49 years compared to 11.3 per million doses in those aged 50 years and over) [**JR/246 - INQ000421360**].

509. The JCVI has not recommended the use of the AstraZeneca (Vaxzevria) vaccine in any Covid-19 vaccine booster campaign since Autumn 2021 and there are no further supplies available in the UK. The JCVI stopped recommending the AstraZeneca (Vaxzevria) vaccine due to concerns about rare cases of thrombosis with thrombocytopenia syndrome (TTS) following vaccination. Furthermore, since May 2024, the marketing authorisation for AstraZeneca (Vaxzevria) has been withdrawn at the request of the marketing authorisation holder. Since the product information updates and press statements on 7 April 2021 and 7 May 2021, where vaccination dates were provided, the MHRA received 2 further reports of suspected thrombosis with thrombocytopenia associated with the AstraZeneca (Vaxzevria)

vaccine in patients under 40 years of age, one of which had a fatal outcome. These were discussed at the VBREWG on 21 June 2021 JR/337 - INQ000409529. However, the MHRA does continue to receive reports of suspected thrombosis with thrombocytopenia syndrome from AstraZeneca originating from legal cases and from publications in the literature, which appear to be duplicate reports.

510. I am asked about utilisation of the four 'pillars' of the MHRA's Covid-19 vaccine vigilance strategy, as described earlier in my statement from paragraph 328], in relation to the TTS safety signal. For TTS the MHRA primarily used the first pillar, which involved assessing spontaneous data with rapid/active follow up, individual case assessment and expert opinion.

511. The MHRA could not have used the second pillar (rapid cycle analysis) because this approach relied upon primary care data and there were delays in the capture of events diagnosed in secondary care using these sources and missing data, particularly on thrombocytopenia. In addition, rapid cycle analysis is primarily a signal detection tool and while the MHRA was actively monitoring individual AESIs (including a number of thrombotic and thrombocytopenic conditions independently), TTS was not a pre-specified AESI.

512. We could not have used the third pillar (Yellow Card Vaccine Monitor ("YCVM") data) for TTS because TTS occurs too rarely in the general population for the cohort of patients recruited in the YCVM to be sufficient to identify any cases. The YCVM was a targeted proactive monitoring tool, the objective of which was not necessarily to detect very rare risks. Rather the objective was to further characterise the safety profile of the vaccines by recruiting the number of people that are generally included in a clinical trial (i.e. in the thousands), in order to compare the frequency and severity of side effects in the general population to groups that were included in trials. The YCVM strategy also sought and facilitated the collection of data on groups excluded from clinical trials, such as pregnant women. The MHRA is no longer recruiting to the YCVM (as above, the YCVM has not been discontinued), but is still receiving and monitoring follow-up information through YCVM.

513. In terms of the fourth pillar (formal epidemiological studies), through the coordination of Professor Cathie Sudlow, the MHRA engaged with a network of leading epidemiologists with access to multiple large linked electronic healthcare record databases who were conducting vaccine safety studies in order to better understand the strengths and limitations of the data

with regards to this specific issue, advise on evidence needs, and support the rapid availability of epidemiological studies. For more commonly occurring conditions, all pillars of the strategy were used. For example, all strands were used for the assessment of Guillain-Barré Syndrome in association with the AstraZeneca (Vaxzevria) vaccine.

Thrombosis (without thrombocytopenia)

514. Thrombosis is the term referring to the formation of a blood clot in a blood vessel. Thrombosis **without** thrombocytopenia (discussed here) is a condition which is not specific to the Covid-19 vaccines.

515. Thrombotic events were not identified as adverse reactions during clinical trials for the Covid-19 vaccines. Further details on clinical trials, including numbers of participants, were discussed within the "Pre-approvals" section. Thrombosis is known to be a potential side effect of a number of vaccines and was included in the list of Adverse Events of Special Interest ("AESIs") for all the Covid-19 vaccines. It was therefore subject to enhanced monitoring by the MHRA from the start of the vaccination rollout.

516. As an AESI, reports of suspected thrombosis were kept under close review by the MHRA, and the advice of the VBREWG was sought on thrombosis as part of general vaccine safety reviews. The MHRA first sought expert advice from the VBREWG on 19 August 2021 on a specific review of thrombotic (blood clotting) events without concurrent thrombocytopenia associated with administration of the Covid-19 vaccines. This followed recent publications of observational studies reporting an increased risk of thrombotic events in vaccinated cohorts. It is important to note that a number of studies had also been published around this time which suggested an association between Covid-19 infection and haematological (blood related) abnormalities, including thrombosis [**JR/248 – INQ000494351**].

517. The advice of the VBREWG was sought on scientific publications characterising background rates of thrombosis prior to the Covid-19 pandemic, rates of thrombosis in those with Covid-19 infection and comparative analysis of thrombosis rates between the general population, those with Covid-19 and/ or those vaccinated [**JR/248 – INQ000494351**]. From the start of the vaccination programme up until 11 August 2021 (the most recent data available at this time), an estimated 21 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine,

24.7 million first doses of the AstraZeneca (Vaxzevria) vaccine and 1.4 million first doses of Moderna (Spikevax) vaccine had been administered [**JR/249 – INQ000413038**].

518. A search of all UK spontaneous Yellow Card reports and Yellow Card Vaccine Monitor (YCVM) suspected adverse reaction (ADR) reports within the Embolic and Thrombotic Events Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query without concurrent thrombocytopenia, received up to and including 31 July 2021, was conducted for the three vaccines under review. The following results were obtained: AstraZeneca (Vaxzevria) vaccine – 6,589 reports, Pfizer/BioNTech (Comirnaty) vaccine – 1,627 reports, and Moderna (Spikevax) vaccine – 70 reports [**JR/250 - INQ000494310**].

519. The VBREWG noted that the review of the post-authorisation data and MHRA's epidemiological analyses (ecological and rapid cycle analysis) showed trends in the incidence of thrombotic events (myocardial infarction, stroke, venous thromboembolism) but rapid cycle analysis using CPRD data did not indicate any signals for thrombotic events compared to pre-pandemic levels, although the VBREWG emphasised that the available evidence suggested a clinically substantial risk of thrombosis following COVID-19 infection, increasing the background rates of thrombosis.

520. The VBREWG advised that whilst the observational studies provided evidence of a potential association between Covid-19 vaccines and thrombotic events, the findings were not replicated across studies or populations enough to consistently associate specific vaccines with events of interest (deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, CVST) and/or increased risk in specific age and gender groups. The VBREWG advised that further research was required to corroborate the findings to date and requested that this topic be brought back for further discussion and advice once the MHRA had completed additional epidemiological analyses.

521. On 31 August 2021, further advice was sought from the VBREWG [**JR/251 - INQ000494352**], when the MHRA outlined new information received from the European Medicines Agency ("EMA") following a review of reports of suspected thrombosis without thrombocytopenia associated with the adenovirus-based vaccines (the AstraZeneca (Vaxzevria) vaccine and the Janssen vaccine) within the monthly summary safety reports submitted by the manufacturers.

522. The VBREWG also noted the EMA's new age-stratified observed versus expected analyses for suspected thrombosis for both vaccines and EEA (European Economic Area) reports reported to EudraVigilance, which was the EMA's system for managing ADRs until 31 July 2021. A marked imbalance in the observed versus expected ratio for CVST was observed for AstraZeneca (Vaxzevria) vaccine across all age groups, indicating a potential signal.

523. The MHRA also presented to the VBREWG the results of an observed versus expected analysis of CVST without thrombocytopenia for the Pfizer/BioNTech (Comirnaty) vaccine and the AstraZeneca (Vaxzevria) vaccine which suggested a signal for an overall increase in risk within 42 days following a first dose of the AstraZeneca (Vaxzevria) vaccine using the maximum background rate. This signal was not reflected across all age groups [**JR/252 - INQ000494312**].

524. The VBREWG advised that no immediate regulatory action was required such as updating product information or risk communication to the public or healthcare professionals and requested an update once additional evidence from the manufacturers of the adenovirus-based vaccines had been reviewed by the EMA.

525. At a VBREWG meeting on 24 September 2021 [**JR/253 – INQ000494353**], the MHRA sought advice on a further observed versus expected analysis of Yellow Card data, examining venous thromboembolism and arterial embolic events [**JR/252 – INQ000494312**]. The MHRA's observed versus expected analyses suggested no signal for an overall risk of venous thromboembolism or arterial embolic events within 42 days following a Covid-19 vaccination. In an age-stratified analysis, a signal of increased risk of pulmonary embolism was raised associated with the first dose of AstraZeneca (Vaxzevria) vaccine in the under 20 years age group as well as a signal of an increased risk of myocardial infarction with the second dose of AstraZeneca (Vaxzevria) vaccine in the same age group. However, it was noted each signal was based on only one report.

526. The VBREWG advised that the observed versus expected analysis for venous thromboembolism and arterial embolic events presented for the Pfizer/BioNTech (Comirnaty) vaccine, Moderna (Spikevax) vaccine and the AstraZeneca (Vaxzevria) vaccine did not raise

a signal of concern with respect to the risk of thrombosis (without concurrent thrombocytopenia).

527. On 19 November 2021, advice was sought from the VBREWG [**JR/254 – INQ000409537**] on the results of the analysis from AstraZeneca of thrombosis associated with the AstraZeneca (Vaxzevria) vaccine [**JR/252 – INQ000494312**], together with an EMA Pharmacovigilance Risk Assessment Committee ("PRAC") review of this submission [**JR/255 - INQ000494318**]. The EMA's PRAC review considered that there was sufficient data to indicate "a reasonable possibility of a causal association between CVST without thrombocytopenia" and the AstraZeneca (Vaxzevria) vaccine.

528. The VBREWG noted the EMA proposal to update the European product information to list thrombosis without thrombocytopenia as a recognised ADR. The VBREWG reached a similar view as the EMA and noted that the new data for the AstraZeneca (Vaxzevria) vaccine added to the existing evidence and could be considered a weak signal that supported an update of the product information for the AstraZeneca (Vaxzevria) vaccine on thrombosis without thrombocytopenia. The VBREWG advised that an update to the UK product information should follow, in alignment with the European product information changes.

529. At its meeting on 16 and 17 December 2021, on reviewing the discussion and advice of the previous VBREWG meetings, the CHM endorsed several safety updates to the AstraZeneca (Vaxzevria) vaccine product information including CVST without thrombocytopenia with a frequency unknown. The product information for the AstraZeneca (Vaxzevria) vaccine was updated on 4 January 2022 [**JR/256 - INQ000421330**] to add the following warning:

> *"Cerebrovascular venous and sinus thrombosis: Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been observed very rarely following vaccination with Vaxzevria. Some cases had a fatal outcome. The majority of these cases occurred within the first four weeks following vaccination. This information should be considered for individuals at increased risk for cerebrovascular venous and sinus thrombosis. These events may require different treatment approaches than TTS and healthcare professionals should consult applicable guidance."*

530. On 6 January 2022, the MHRA's regular publication 'Summary of Yellow Card reporting' was updated, presenting Yellow Card data up to 22 December 2021 [**JR/257** - **INQ000421335** and informing that a thorough review of events of CVST without concurrent low platelet levels associated with vaccination with the AstraZeneca (Vaxzevria) vaccine had concluded that there was a possible link between thrombosis without low platelets and the AstraZeneca (Vaxzevria) vaccine. It also advised that the product information for the AstraZeneca (Vaxzevria) vaccine would be updated to include the information that thrombotic events not associated with low levels of blood platelets occurred extremely rarely. The product information for the AstraZeneca (Vaxzevria) vaccine was updated to include the risk of CVST without thrombocytopenia and to provide advice to healthcare professionals and patients. The MHRA also confirmed that the evidence to date did not suggest that the AstraZeneca (Vaxzevria) vaccine increased the risk of venous thromboembolism (i.e. deep vein thrombosis and/or pulmonary embolism) in the absence of a low platelet count.

531. 'Thrombosis with thrombocytopenia' and 'venous thrombosis' were also added to the SmPC of the only other adenoviral Covid-19 vaccine Janssen (Jcovden) approved in the UK. This vaccine was never supplied or deployed in the UK.

Immune Thrombocytopenia

532. Immune thrombocytopenia, also known as idiopathic thrombocytopenic purpura (ITP) is an autoimmune blood disorder characterised by abnormally low levels of platelets, the blood components which are important for blood clotting. This disorder can therefore lead to bruising and bleeding. In cases where platelet counts are extremely low, serious and even fatal bleeding complications can occur.

533. Immune thrombocytopenia or ITP is an AESI for the Covid-19 vaccines because thrombocytopenia is a known rare adverse effect of certain vaccines, and coagulation disorders including thrombotic events have also been previously associated with vaccines and were therefore subject to enhanced monitoring from the start of the vaccine rollout. There were no reports of ITP in the clinical trials for any of the Covid-19 vaccines (the numbers of

patients in the clinical trials for the 3 main Covid-19 vaccines used in UK are provided at paragraphs 199, 222, 239 above).

534. On 25 February 2021, the MHRA sought advice from the VBREWG on Yellow Card reports of suspected ITP and the globally available data on the potential risk of ITP in association with the Covid-19 vaccines, including an observed versus expected analysis conducted by Pfizer/BioNTech [**JR/258** - **INQ000409515**].

535. As set out in the EWG's paper [**JR/207** - **INQ000409479**]: from the start of the vaccination program in December 2020, up to and including 22 February 2021, the MHRA had received 5 Yellow Card reports of suspected ITP associated with use of the Pfizer/BioNTech (Comirnaty) vaccine, none of which was fatal. The MHRA had additionally received 17 reports of suspected ITP with use of the AstraZeneca (Vaxzevria) vaccine, in the context of an estimated 8.4 million vaccine administrations up to and including 21 February 2021. This included one report with a fatal outcome, however case features supporting causality had not been confirmed. No doses of the Moderna (Spikevax) vaccine had been administered in the UK at this time and Moderna reported to the MHRA that, globally, they had received no reports of suspected autoimmune responses including ITP.

536. The VBREWG advised that it was plausible that ITP could potentially be associated with each of the three Covid-19 vaccines in use. A clear signal was not detected, although the VBREWG noted the number of ITP cases likely represented "a borderline signal with the Pfizer/BioNTech (Comirnaty) and the Moderna (Spikevax) vaccine, and perhaps a more likely signal for the [AstraZeneca (Vaxzevria)] vaccine." The VBREWG advised that robust judgements on causality could not be made at that time and therefore further data were required.

537. On 23 April 2021, the MHRA sought further advice from the VBREWG on reports of suspected ITP associated with the Covid-19 vaccines [**JR/259** - **INQ000409523**]. The VBREWG heard that from the start of the vaccination programme up to and including 20 April 2021, there had been 36 reports of suspected ITP, none of which was fatal but 13 required hospitalisation, reported to the MHRA through Yellow Cards associated with administration of the Pfizer/BioNTech (Comirnaty) vaccine, and 121 reports of suspected ITP (8 with fatal outcomes) associated with the AstraZeneca (Vaxzevria) vaccine [**JR/260** - **INQ000494290**].

There were no reports of suspected ITP associated with administration of the Moderna (Spikevax) vaccine.

538. At this time, around 41 million first and second doses of the Covid-19 vaccines had been administered. Ongoing analysis by Pfizer suggested that observed reports of ITP did not exceed that normally expected in the general population, and therefore a signal was not detected.

539. The MHRA's epidemiological analysis did not show a signal of ITP with the Pfizer/BioNTech (Comirnaty) vaccine from the observed versus expected analyses. Similarly, analysis conducted by Pfizer did not demonstrate a signal for ITP in the global observed versus expected analysis. There was stronger evidence of an ITP signal with the AstraZeneca (Vaxzevria) vaccine in the MHRA's observed versus expected analysis as well as a signal observed in the rapid cycle analysis. The VBREWG noted that stimulated reporting may be impacting on the AstraZeneca (Vaxzevria) vaccine signal. Stimulated reporting can occur when spontaneous reporting is encouraged by, for example, enhanced post-marketing vigilance information and communications.

540. The VBREWG highlighted the complexities of the diagnosis of ITP and the range of different thrombocytopenic disorders which have been recognised, with varying mechanisms. The VBREWG recommended that an expert haematology panel be formed to support the MHRA in reviewing reports of suspected thrombocytopenic events following Covid-19 vaccination to underpin further review of the signal.

541. The MHRA sought advice from the CHM on the risk of ITP associated with the Covid-19 vaccines at its meeting on 6 - 7 May 2021 [**JR/261 - INQ000409503**]. The CHM considered the lack of confirmatory diagnosis in all the reports of suspected ITP and concurred with the VBREWG that advice should be sought from an expert panel of haematologists for further investigation of this topic. The MHRA sought advice from a consultant haematologist to develop case classification criteria for ITP reports and, following a process of medical adjudication of the Yellow Card reports received from the start of the vaccination programme, on 29 October 2021 the MHRA sought the advice of the VBREWG on an analysis of the available confirmed spontaneous reports of ITP [**JR/262 - INQ000494317**].

542. At the 29 October 2021 VBREWG meeting [**JR/263 - INQ000494355**], there were 76 confirmed Yellow Card reports of ITP associated with the AstraZeneca (Vaxzevria) vaccine (including 2 reports with a fatal outcome), 40 associated with the Pfizer/BioNTech (Comirnaty) vaccine, 2 associated with the Moderna (Spikevax) vaccine and 12 associated with the Janssen vaccine. Approximately 10-20% of Yellow Card reports involved patients with prior primary ITP or medical conditions associated with secondary ITP. Further detail on these reports is set out within the paper 'COVID-19 Vaccines and Risk of Immune Thrombocytopenia' [**JR/262 - INQ000494317**].

543. Observed versus expected analyses of the Yellow Card reports did not provide strong evidence of a signal for ITP without thrombosis with any dose of a Covid-19 vaccine. However, in the sensitivity analyses, which took into account an assumption of under-reporting, there was strengthening of the signal raised previously with the AstraZeneca (Vaxzevria) vaccine. In addition to spontaneous reports, the assessment considered PHE Snap Survey data, epidemiological data, and the published literature. The PHE snap survey was established by PHE to enable UK healthcare professionals to submit detailed information on patients who experienced ITP in association with Covid-19 vaccines. It allowed cases to be submitted via the survey if they met inclusion criteria for the diagnosis of ITP and temporal association with administration of a Covid-19 vaccine.

544. At the 29 October 2021, the VBREWG advised that the available evidence warranted the addition of ITP to the product information for the AstraZeneca (Vaxzevria) vaccine but not for the other Covid-19 vaccines [**JR/263 - INQ000494355**]. The VBREWG also advised that the AstraZeneca (Vaxzevria) vaccine product information should include risk minimisation advice to monitor platelet count following vaccination for patients with a history of primary ITP or risk factors for secondary ITP because these patients may be at particular risk of this reaction. The wording on ITP recommended by the PRAC on 30 September 2021 and implemented in the EU product information for the AstraZeneca (Vaxzevria) vaccine was considered appropriate for the UK product information. The VBREWG advised that the updated UK product information update for the AstraZeneca (Vaxzevria) vaccine should be communicated in the MHRA's 'Summary of Yellow Card reporting' for the Covid-19 vaccines. Finally, VBREWG advised that reports of ITP should continue to be closely monitored.

545. At its meeting on 17 November 2021 [**JR/264 - INQ000409511**], the CHM endorsed the addition of ITP as an adverse reaction to the UK product information for the AstraZeneca (Vaxzevria) vaccine, with no changes recommended to the product information for the other Covid-19 vaccines.

546. Following discussions with the marketing authorisation holder to agree wording, and preparing Ministerial submissions, the product information for the AstraZeneca (Vaxzevria) vaccine was accordingly updated on 4 January 2022 to include the following warning about ITP [**JR/256 INQ000421330**]:

> "Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving Vaxzevria, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels (<20,000 per µL) and/or were associated with bleeding. Cases with fatal outcome have been reported. Some cases occurred in individuals with a history of immune thrombocytopenia. If an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination."

Immune thrombocytopenic purpura was also added to the product information for the AstraZeneca (Vaxzevria) vaccine as a possible side effect (frequency not known).

547. On 6 January 2022, the MHRA's 'Summary of Yellow Card reporting' was updated with the published report covering the period from 9 December 2020 to 22 December 2021 [**JR/265 INQ000421341**] The MHRA advised that reports of suspected ITP associated with Covid-19 vaccines had been closely monitored and that a recent review confirmed that this adverse event was reported extremely rarely for the AstraZeneca (Vaxzevria) vaccine in the UK, at approximately four reports per million doses. In approximately 10-20% of the reports, patients had a history of ITP or an underlying condition known to be associated with ITP. The summary stated that the product information for the AstraZeneca (Vaxzevria) vaccine had been updated following the most recent review of data which suggested a possible link between the AstraZeneca (Vaxzevria) vaccine and ITP.

Capillary leak syndrome

548. Capillary leak syndrome (CLS) is a rare condition causing fluid leakage from small blood vessels, which leads to a fall in blood pressure. It is a recurring condition, with the severity and frequency of attacks varying between individuals. Symptoms may include nasal congestion, cough, feeling faint and swelling of the extremities. If untreated, it can lead to organ failure and death.

549. Capillary leak syndrome has been reported in patients with viral infections including patients with Covid-19 infection, potentially resulting from the overproduction of pro-inflammatory cytokines. Largely however, the factors predisposing to the development of CLS, and its pathophysiological mechanism are unknown.

550. There were no reports of CLS in clinical trials for the Covid-19 vaccines, and CLS was not identified as an AESI for the Covid-19 vaccines prior to vaccination roll out. However, as with all suspected ADRs, once reported, CLS was kept under close review by the MHRA.

551. On 12 April 2021, the MHRA sought the advice of the VBREWG on 3 reports of suspected CLS associated with the AstraZeneca (Vaxzevria) vaccine submitted through the Yellow Card scheme [**JR/266 - INQ000507345**] The VBREWG was informed that on 9 April 2021, the EMA PRAC had started a review of a safety signal of reports of suspected CLS in people who had received the AstraZeneca (Vaxzevria) vaccine [**JR/267 - INQ000494294**] As part of the PRAC review, the manufacturer was asked to undertake and submit a cumulative review of suspected CLS reports associated with the vaccine. The VBREWG noted that two of the Yellow Card patient reporters had a history of CLS prior to vaccination making any causality assessment difficult. The VBREWG advised that the signal should be closely monitored, with no regulatory action at that time.

552. The MHRA's 'Summary of Yellow Card reporting' was updated on 15 April 2021 [**JR/268 - INQ000421357**] to include information that, as of 5 April 2021, the MHRA had received three reports of suspected CLS in the context of more than 20 million doses of the AstraZeneca (Vaxzevria) vaccine administered [**JR/268 - INQ000421357**]. The update also advised that the evidence did not suggest that CLS was caused by the AstraZeneca (Vaxzevria) vaccine, but that the MHRA would continue to monitor this issue closely.

553. As of 7 May 2021, the MHRA had received 7 reports of suspected CLS associated with the AstraZeneca (Vaxzevria) vaccine and no reports of CLS associated with the Pfizer/BioNTech (Comirnaty) vaccine or the Moderna (Spikevax) vaccine. None of these reports had a fatal outcome. The manufacturer review concluded that given the overall post-marketing exposure to the AstraZeneca (Vaxzevria) vaccine, the number of reports of suspected CLS in the population having received the AstraZeneca (Vaxzevria) vaccine was considered small [**JR/267 - INQ000494294**].

554. On 14 May 2021, the MHRA sought the advice of the VBREWG on an update of the CLS signal associated with the AstraZeneca (Vaxzevria) vaccine including Yellow Card data, an assessment of a cumulative review of worldwide clinical study and post-authorisation reports, and a literature review submitted by the manufacturer [**JR/261 - INQ000409503**]. However, a causality assessment was difficult due the prior medical history of CLS in 2 of the 7 reports, and in some of the reports causality was considered unlikely given that the time of the onset of CLS was over a month after vaccination and therefore inconsistent with a vaccine-related effect [**JR/267 – INQ000494294**].

555. The VBREWG advised that the currently available data did not suggest an association between the AstraZeneca (Vaxzevria) vaccine and CLS and that based on the data presented no updates to the product information or the risk management plan of the vaccine were warranted. The VBREWG supported the proposal to keep the issue under close review.

556. On 4 June 2021, the MHRA sought the advice of the VBREWG on a further update on reports of suspected CLS. As of 2 June 2021, the EMA review of suspected CLS following the AstraZeneca (Vaxzevria) vaccine had included one EU report with a fatal outcome, which was reviewed by the MHRA [**JR/269 – INQ000494297**]. The VBREWG was informed that the EMA had made a preliminary recommendation to incorporate warnings in the AstraZeneca (Vaxzevria) vaccine product information to contraindicate use in people who had previously experienced CLS and to warn of a risk of recurrence of CLS in patients with a history of the syndrome [**JR/270 - INQ000409527**].

557. Since the last data lock point of 7 May 2021, the MHRA had received 3 further UK reports of suspected CLS associated with the AstraZeneca (Vaxzevria) vaccine. A review of the 10 available reports excluded unlikely and mis-coded reports and concluded that the UK had

received 5 reports of suspected CLS in patients associated with the AstraZeneca (Vaxzevria) vaccine, of which 2 had a prior medical history of CLS. None of the reports had a fatal outcome [**JR/269 - INQ000494297**]. This number remained small in the context of more than 40 million doses of the AstraZeneca (Vaxzevria) vaccine, considering that CLS generally occurs in < 1 per million, and the VBREWG considered that there remained some uncertainty within the evidence and that it was difficult to confirm a signal [**JR/271 - INQ000421356**].

558. However, the VBREWG advised that a precautionary statement should be included in the product information, given the serious and potentially fatal nature of the condition, though it advised that there was insufficient evidence to include a contraindication in people with a past history of CLS.

559. On 14 June 2021, the MHRA sought the advice of the VBREWG regarding the EU PRAC's recommendation that the product information for the AstraZeneca (Vaxzevria) vaccine should be updated to include a contraindication to the vaccine in people with a past history of capillary leak syndrome, a warning regarding rare cases of CLS potentially associated with the vaccine, and to include CLS as a possible adverse reaction with a note of the fatal outcome from CLS that had been reported in the EU [**JR/272 - INQ000409528**].

560. As of 9 June 2021, the MHRA had received no further reports of suspected CLS associated with Covid-19 vaccines. The VBREWG considered the latest available data and advised that warnings should be included in the product information for the AstraZeneca (Vaxzevria) vaccine, maintaining alignment between the product information in GB and Northern Ireland. The VBREWG did note that given the very small numbers and extreme rarity of the reported events, inclusion of these warnings was a precautionary step and should not set a precedent for including warnings where data are limited.

561. Following the VBREWG's recommendation on 14 June, on 16 June 2021 the MHRA submitted to the Licensing Minister the advice of the VBREWG to add a contraindication to the product information of the AstraZeneca (Vaxzevria) vaccine regarding use in patients with a past history of CLS and recommended that this advice should be accepted [**JR/273 - INQ000494299**]. The Minister accepted this advice.

562. On 17 June 2021, the MHRA's 'Summary of Yellow Card reporting' (the published report covering the period 9 December 2020 to 9 June 2021) was updated [**JR/274 - INQ000421340**] to state that as of 9 June 2021, as a precautionary measure, the MHRA advised that the AstraZeneca (Vaxzevria) vaccine should not be used in people who have previously experienced episodes of CLS and advised that the product information was being updated to reflect this advice.

563. On 9 July 2021, the marketing authorisation holder submitted a variation to update the product information (the corresponding EU variation had been approved on 30 June 2021) [**JR/275 - INQ000494374**].

564. On 19 July 2021, the Summary of Product Characteristics for the AstraZeneca (Vaxzevria) vaccine was updated [**JR/276 - INQ000421334**] to add the following contraindication:

> '*Individuals who have previously experienced episodes of capillary leak syndrome (see also section 4.4)*'.

565. The following warning about CLS was also added, noting the report of a case of CLS with a fatal outcome in the EU:

> "*Very rare cases of capillary leak syndrome (CLS) have been reported in the first days after vaccination with Vaxzevria. A history of CLS was apparent in some of the cases. Fatal outcome has been reported. CLS is a rare disorder characterised by acute episodes of oedema mainly affecting the limbs, hypotension, haemoconcentration and hypoalbuminaemia. Patients with an acute episode of CLS following vaccination require prompt recognition and treatment. Intensive supportive therapy is usually warranted. Individuals with a known history of CLS should not be vaccinated with this vaccine. See also section 4.3.*"

566. Finally, CLS was added to the product in formation of the AstraZeneca (Vaxzevria) vaccine as a possible side effect (with a frequency 'not known').

567. The MHRA has kept reports of suspected CLS associated with the Moderna (Spikevax) vaccine and Pfizer/BioNTech (Comirnaty) vaccine under close review. For the Moderna (Spikevax) vaccine, while no association with new onset of CLS was found, a potential risk of flare-up of existing CLS was identified following vaccination. On 29 March 2022, the

VBREWG's advice was sought on the differing levels of evidence for flare-up of suspected CLS for the Moderna (Spikevax) vaccine and the Pfizer/BioNTech (Comirnaty) vaccine, with 3 Moderna (Spikevax) vaccine reports meeting WHO 'probable' criteria, while only one Pfizer/BioNTech (Comirnaty) vaccine report met the WHO 'possible' criteria.

568. The VBREWG noted that this was a very small number of reports in the context of the total doses administered. The VBREWG was also informed that the PRAC had concluded that a warning regarding flare-up of CLS should be added to the Moderna (Spikevax) vaccine product information, although no update was required for the Pfizer/BioNTech (Comirnaty) vaccine. The VBREWG advised that the available data supported the inclusion of a warning in the Moderna (Spikevax) vaccine product information, and that Prizer/BioNTech should continue to monitor reports of suspected CLS as part of their bi-monthly safety reports [**JR/277 - INQ000409540**].

569. On 15 June 2022, the product information for the Moderna (Spikevax) vaccine was updated to highlight the potential risk of a flare-up of CLS to healthcare professionals and patients. For the Pfizer/BioNTech (Comirnaty) vaccine, no association between new-onset or flare-up of CLS has been identified to date.

Guillain-Barré Syndrome

570. Guillain-Barré syndrome (GBS) is a neurological disorder characterised by muscle weakness, sensory abnormalities, and autonomic dysfunction due to damage to peripheral nerves and nerve roots. The severity of GBS can range from mild, transient weakness to complete paralysis. These symptoms are a result of damage to peripheral nerves and nerve roots. While the underlying causes of GBS are not completely understood, it is considered to be caused by a problem with the immune system, which mistakenly attacks and damages nerves, leading to demyelination or axonal damage or both.

571. There are reports in the literature of suspected GBS associated with Covid-19 infection. However, a UK cohort study [**JR/278 - INQ000408391**] comparing cases of GBS with or without Covid-19 infection and to previous background rates of GBS found no increased risk of GBS in association with Covid-19 infection. The annual incidence of GBS has been estimated at between 0.4 and 4.0 cases per 100,000 population per year, with most well-

designed prospective studies in developed countries suggesting an incidence of 1–2 per 100,000 population per year.

572. Guillain-Barré syndrome has been linked to other vaccines, most notably a swine flu inactivated monovalent and bivalent vaccine used in 1976 in the USA. The increased risk of GBS was estimated to be approximately one additional case of GBS for every 100,000 people who received the swine flu vaccine. A variety of mechanisms are proposed for a causal link between a vaccine and GBS, including molecular mimicry, destruction of the axonal myelin membranes directly by vaccine virus or vaccine associated products, or host factors and genetic polymorphisms which may result in a predisposition to GBS in some individuals. One postulated mechanism is that the vaccine virus can infect a peripheral neuron, use an active retrograde transport mechanism across the synapse onto the cell body and reach the brain. Others include direct damage through receptors, cytokine-related injury, and hypoxia-related sequela.

573. As Guillain-Barré Syndrome is an AESI for all vaccines, it was included in the Covid-19 AESIs list as described at paragraph 317 of the "Post-approval" section of this statement and was therefore under enhanced monitoring from the start of the vaccines rollout.

574. During global clinical trials for the AstraZeneca (Vaxzevria) vaccine, a small number of neurological events were observed in the vaccine group (including one report of suspected multiple sclerosis ("MS"), one report of suspected transverse myelitis and six reports of suspected facial paralysis). In the manufacturer's clinical trials, there was one report of suspected mild sensory GBS in the AstraZeneca (Vaxzevria) vaccine arm of US trials. No reports were seen in the control arm.

575. Accordingly, at the time of authorisation, a warning was included in the product information that "very rare events of neuroinflammatory disorders have been reported following vaccination with Covid-19 vaccine AstraZeneca (Vaxzevria). A causal relationship has not been established" [**JR/279 - INQ000421350**].

576. Additionally, as a result of the clinical trial findings, when the AstraZeneca (Vaxzevria) vaccine was deployed in the UK from January 2021 (noting that the UK was the first country to start using this vaccine), spontaneous reports of suspected GBS were targeted for

individual assessment by the MHRA. The manufacturer AstraZeneca also closely monitored reports of suspected GBS and submitted observed versus expected studies for signal monitoring in its monthly summary safety reports to the MHRA.

577. On 9 March 2021, the MHRA sought the advice of the VBREWG on reports received via the Yellow Card scheme of suspected GBS in association with Covid-19 vaccines. The MHRA presented an overview of safety data relating to suspected GBS associated with the AstraZeneca (Vaxzevria) vaccine, the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine [**JR/280 - INQ000494279**].

578. This overview showed that from the start of the vaccination programme in December 2020, up to and including 3 March 2021, the MHRA had received a total of 24 reports (1 with fatal outcome) of suspected GBS associated with the AstraZeneca (Vaxzevria) vaccine and 8 reports (2 with fatal outcome) associated with the Pfizer/BioNTech (Comirnaty) vaccine. The Moderna (Spikevax) vaccine had not yet been supplied to the UK at the time but 8 reports from outside the UK of suspected GBS associated with Spikevax were also considered. Up to 7 March 2021, an estimated 10.9 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine and 11.7 million doses of the AstraZeneca (Vaxzevria) vaccine had been administered in the UK [**JR/281 - INQ000421348**].

579. The VBREWG advised that there was the potential of an increased signal of GBS, particularly associated with the AstraZeneca (Vaxzevria) vaccine and that reports of suspected GBS should be closely monitored, but that the signal was not yet sufficiently strong enough to support a formal epidemiological study [**JR/282 - INQ000494346**].

580. On 23 April 2021, the MHRA sought the advice of the VBREWG on all the available Yellow Card reports of suspected GBS, epidemiological analyses, clinical trial data and manufacturer's data from their Summary Monthly Safety Review [**JR/259 INQ000409523**]. Numbers of reports of suspected GBS were increasing, with a total of 118 Yellow Card reports received by the MHRA by 11 April 2021, in the context of rapidly increasing numbers of individuals being vaccinated. The VBREWG commented that there was difficulty in assessing reports due to a lack of information. However, 24 reports met the Brighton Collaboration criteria for diagnosis of GBS, including one report of GBS with a fatal outcome associated with

the AstraZeneca (Vaxzevria) vaccine, and these could support an association of GBS with the vaccine [**JR/283 - INQ000494291**].

581. On 7 May 2021, the MHRA sought further advice from the VBREWG [**JR/284 - INQ000494348**]. Up until 29 April 2021, there had been 194 reports of suspected GBS (6 with fatal outcome, however 5 of those cases did not meet the Brighton Collaboration criteria) associated with the AstraZeneca (Vaxzevria) vaccine, 29 reports (3 with fatal outcome) associated with the Pfizer/BioNTech (Comirnaty) vaccine, and no UK reports associated with the Moderna (Spikevax) vaccine. Again, there were around 85% of reports which did not meet the diagnostic criteria [**JR/285 - INQ000494292**]. Up to 12 May 2021, an estimated 11.7 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine, 23.9 million first doses of the AstraZeneca (Vaxzevria) vaccine, and 0.2 million first doses of Moderna (Spikevax) vaccine had been administered in the UK.

582. The VBREWG considered that there could be a suggestion of a signal for GBS for the AstraZeneca (Vaxzevria) vaccine. The evidence was not considered alarming, and the VBREWG advised that a more formal epidemiological study should be undertaken. As I will go on to discuss at paragraph 585, this was completed and presented to the CHM on 5 August 2021.

583. On 23 July 2021, the MHRA sought the advice of the VBREWG on further updates on GBS for the AstraZeneca (Vaxzevria) vaccine, Pfizer/BioNTech (Comirnaty) vaccine and Janssen vaccine [**JR/286 - INQ000409532**]. Up until 18 July 2021, the MHRA had received 391 reports (5 with fatal outcome) of suspected GBS associated with the AstraZeneca (Vaxzevria) vaccine, 40 reports (2 with fatal outcomes) associated with the Pfizer/BioNTech (Comirnaty) vaccine, and 2 reports (none with fatal outcomes) associated with the Moderna (Spikevax) vaccine [**JR/287 - INQ000494306**]. Up to 14/15 July 2021, an estimated 20 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine, 24.6 million first doses of the AstraZeneca (Vaxzevria) vaccine, and 1.4 million first doses of Moderna (Spikevax) vaccine had been administered in the UK.

584. The VBREWG considered there was growing evidence to suggest a potential causal relationship between the AstraZeneca (Vaxzevria) vaccine and GBS, although the mechanism remained unclear. Although causality had not been fully established, the VBREWG

recommended updating the AstraZeneca (Vaxzevria) vaccine product information to include GBS as an adverse reaction. Similarly, in their meeting on 5-8 July 2021 the PRAC had recommended the inclusion of a statement in the product information to alert healthcare professionals and people receiving the AstraZeneca (Vaxzevria) vaccine to GBS as a potential risk [**JR/288 - INQ000421326**].

585. On 5 August 2021, the MHRA sought the advice of the CHM on proposed wording regarding GBS in the product information for the AstraZeneca (Vaxzevria) vaccine, the Pfizer/BioNTech (Comirnaty) vaccine, the Moderna (Spikevax) vaccine and the Janssen vaccine [**JR/289 - INQ000494309**; **JR/290 - INQ000409505**]. The information presented by MHRA to the VBREWG included vaccine usage, Yellow Card data, clinical trial data, data from manufacturer monthly summary update reports and epidemiological analyses. Observed versus expected analyses of reports showed a significantly increased observed number of reports over that which would be expected in patients 50-59 years old association with the AstraZeneca (Vaxzevria) vaccine, indicating a potential signal. No statistically significant signals were raised for the Pfizer/BioNTech (Comirnaty) vaccine or the Moderna (Spikevax) vaccine. Overall, the epidemiological analyses showed some evidence of an increased risk of GBS associated with the first dose of the AstraZeneca (Vaxzevria) vaccine.

586. The MHRA also sought the CHM's advice on whether additional recommendations should be made regarding whether the second dose of Covid-19 vaccine should be offered to patients who had developed GBS following the first dose. The Yellow Card data did not show evidence of an increased risk of GBS associated with the second dose of any Covid-19 vaccine, and there was no evidence of GBS recurrence in patients who were re-exposed to the same Covid-19 vaccine. There was not enough evidence to conclude on the severity of GBS following the first dose versus severity following the second dose. As with all vigilance data, the CHM advised the MHRA to provide all relevant data to public health bodies to support their decisions and any advice issued.

587. The CHM supported the proposed wording in relation to GBS as detailed in Annex 4 of the paper presented by MHRA to the CHM [**JR/289 - INQ000494309**] to be included in the GB SmPC for the AstraZeneca (Vaxzevria) vaccine. The CHM advised that the product information for the AstraZeneca (Vaxzevria) vaccine should be updated to include a precautionary statement detailing the symptoms of GBS which vaccine recipients should be

aware of and when to seek medical advice about GBS following receipt of the vaccine, in section 4.8 of the UK SmPC and section 4 of the UK Patient Information Leaflet.

588. On 20 August 2021, these updates to the product information for the AstraZeneca (Vaxzevria) vaccine were implemented by the MHRA [**JR/291 - INQ000421345**]. The updated PIL wording [**JR/292 - INQ000421327**] advised vaccine recipients to:

> "*seek immediate medical attention if you develop weakness and paralysis in the extremities that are persistent and can affect both sides of the body at the same time and can progress to the chest and face (Guillain-Barré Syndrome). This has been reported very rarely after vaccination with Covid19 vaccine AstraZeneca (Vaxzevria).*"

589. On 10 September 2021, following a company review of reports of suspected GBS, the MHRA sought the VBREWG's advice on further data for suspected GBS associated with the AstraZeneca (Vaxzevria) vaccine [**JR/293 - INQ000494313**]. Data for suspected GBS associated with the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine were not presented as no signal had been detected for these vaccines. At its meeting held between 30 August to 2 September 2021 the EMA PRAC had recommended updates to the AstraZeneca (Vaxzevria) vaccine product information including GBS as a side effect and adding pain in the legs, arms or stomach and influenza-like symptoms to the list of side effects [**JR/294 - INQ000421328**].

590. The VBREWG endorsed amendments to the GB product information for the AstraZeneca (Vaxzevria) vaccine with regard to GBS warnings, including a recommendation for patients to speak to their doctor, pharmacist, or nurse if they previously had GBS after being given a first dose of the AstraZeneca (Vaxzevria) vaccine [**JR/295 -** **INQ000409534**]. On 21 October 2021 these amendments were implemented in the product information of the AstraZeneca (Vaxzevria) vaccine (see paragraph 596), following further meetings with the VBREWG and CHM below.

591. On 17 September 2021, the VBREWG's advice was sought on a presentation from an invited expert on the results of a study to explore the risk of GBS associated with Covid-19 vaccines conducted using linked data from the NHS England intravenous immunoglobulin

database and the national immunisation management system [**JR/296 - INQ000409535**]. The study showed a higher rate of GBS in the 6 weeks following a first dose of the AstraZeneca (Vaxzevria) vaccine compared to the Pfizer/BioNTech (Comirnaty) vaccine.

592. The VBREWG agreed that the study strengthened the evidence of an association between GBS and the AstraZeneca (Vaxzevria) vaccine and recommended a further review of the product information. Following previous consideration of this issue in paragraph 586, the VBREWG also recommended that patients experiencing GBS following a first dose of the AstraZeneca (Vaxzevria) vaccine, should be offered an alternative vaccine for their second dose.

593. On 30 September 2021, the MHRA sought further advice from the CHM on the available evidence on the risk of GBS associated with the AstraZeneca (Vaxzevria) vaccine [**JR/297 - INQ000494336**]. The evidence considered by the CHM included the study results reviewed by the VBREWG on 17 September 2021. The CHM noted that while less severe cases of GBS were not captured in the study, the overall risk of developing GBS was very low.

594. The CHM noted the actions recommended by the PRAC which included updates to section 4.8 of the EU SmPC and to sections 2 and 4 of the PIL. The CHM advised that the previous precautionary statement on GBS in the UK product information for the AstraZeneca (Vaxzevria) vaccine should be updated both in section 4.8 of the SmPC and section 4 of the Patient Information Leaflet.

595. The CHM also supported including a statement in the PIL to advise patients who developed GBS following their first AstraZeneca (Vaxzevria) vaccine dose to speak to their GP prior to receiving their second vaccine dose. The CHM stated that there should be a preference for a different vaccine for the second dose in individuals who had developed GBS after the first dose of the AstraZeneca (Vaxzevria) vaccine and that the MHRA should work with Public Health England and other health bodies to communicate this advice.

596. Subsequently, on 21 October 2021, the product information for the AstraZeneca (Vaxzevria) vaccine for healthcare professionals and vaccine recipients, was revised accordingly. [**JR/298 - INQ000421351**); **JR/299 - INQ000421352**; **JR/300 - INQ000421329**].

597. The following wordings were added to the information for healthcare professionals:

> "***4.4 Special warnings and precautions for use***
>
> ***Neurological events***
>
> *Guillain-Barré Syndrome (GBS) has been reported very rarely following vaccination with COVID-19 Vaccine AstraZeneca. Healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes."*
>
> The following wordings were added to the PIL:
>
> "***2. What you need to know before you are given COVID-19 Vaccine AstraZeneca***
>
> ***Warnings and Precautions***
>
> *If you previously had Guillain-Barré syndrome (temporary loss of feeling and movement) after being given Vaxzevria.*
>
> *…*
>
> ***4. Possible side effects***
>
> ***Very rare (may affect up to 1 in 10,000 people***
>
> *serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome [GBS]).*"

These changes were widely communicated via a Drug Safety Update on 4 November 2021 [**JR/421(a) - INQ000494327**].

598. Reports of suspected GBS associated with Covid-19 vaccines have continued to be closely monitored by the MHRA.

Transverse myelitis

599. Transverse myelitis (TM) is a rare acute neurological disorder causing inflammation of a particular level of the spinal cord, the part of the central nervous system that sends impulses from the brain to nerves in the body. Common symptoms include back or neck pain, weakness or sensation changes in the arms or legs, or loss of bladder or bowel control. Although it is possible to fully recover from TM, the healing process can take months to years, and most people are left with residual symptoms or permanent impairments that affect daily living.

600. Covid-19 infection has been associated with neurological manifestations and several cases of TM have been reported in temporal relationship with Covid-19 infection. However, 60% of cases remain idiopathic, meaning that the cause is unknown, and the mechanism through which Covid-19 may be linked to TM is still unclear.

601. In the pooled clinical trials for the AstraZeneca (Vaxzevria) vaccine, there were two reports of demyelinating disorders in the treatment arm, including one of TM, and one of multiple sclerosis ("MS") in a participant with pre-existing but previously undiagnosed MS. The phase I UK trial was suspended after the SUSAR report of TM in a female participant was received. At its meetings on 10 and 11 September 2020, the CHM concluded that there was still uncertainty in the underlying diagnosis, and there was insufficient evidence from this SUSAR to indicate a causal association with the AstraZeneca (Vaxzevria) vaccine. The advice of the CHM was therefore that the trial could be restarted [**JR/72 - INQ000400208**].

602. Transverse Myelitis was an AESI for the Covid-19 vaccines as it has previously been reported rarely in association with certain vaccines, and because of the possible cases during clinical trials. Transverse myelitis was therefore under enhanced monitoring from the start of the Covid-19 vaccines deployment.

603. On 4 February 2021, the MHRA sought the advice of the VBREWG on a general safety update for the AstraZeneca (Vaxzevria) vaccine [**JR/301 - INQ000409513**]. The VBREWG was informed that by 28 January 2021, a report of suspected TM had been received in association with the AstraZeneca (Vaxzevria) vaccine. At this point, over 3 million doses of the AstraZeneca (Vaxzevria) vaccine had been administered in the UK [**JR/302 - INQ000421355**]. The advice of the VBREWG was sought regarding an association between Covid-19 vaccines and TM. It was noted that observed versus expected analyses and rapid cycle analyses were being performed for TM as part of the enhanced monitoring strategy [**JR/303 - INQ000494272**]. No signals were identified from the data available using these methods and no regulatory action was advised by the VBREWG at this time.

604. As of 19 February 2021, the MHRA had received a total of 6 Yellow Card reports of suspected TM in association with the AstraZeneca (Vaxzevria) vaccine. On 25 February 2021, the MHRA sought the advice of the VBREWG on their review of TM considering these reports, and their previous advice that the observed versus expected analyses did not provide a signal

of an increased risk. Rapid cycle analyses of individual reports showed the observed recorded number of events was consistent with the expected number of events [**JR/304 - INQ000409478** The VBREWG again advised that no regulatory action was justified at that time but further detailed information on the reports was required to support detailed individual case assessment. [**JR/305 INQ000409515**

605. On 14 May 2021, the advice of the VBREWG was sought on the possible increased risk of neurological and autoimmune conditions associated with Covid-19 vaccines including a further assessment of reports of suspected TM associated with Covid-19 vaccines [**JR/261 - INQ000409503; JR/306 - INQ000494295**]. As of 5 May 2021, an estimated 20 million doses of the Pfizer/BioNTech (Comirnaty) vaccine, including over 8 million second doses had been administered. Over 30 million doses of the AstraZeneca (Vaxzevria) vaccine had been administered, including over 7 million second doses. Under 200,000 doses of the Moderna (Spikevax) vaccine had also been administered.

606. By 12 May 2021, 57 Yellow Card reports of suspected TM had been reported to the MHRA in association with the AstraZeneca (Vaxzevria) vaccine, none of which were reports with a fatal outcome, and 18 reports in association with the Pfizer/BioNTech (Comirnaty) vaccine, none of which were reports of a fatal outcome. By 31 March 2021, there had been no Yellow Card reports in association with the Moderna (Spikevax) vaccine.

607. The observed versus expected analyses conducted by the manufacturers with data cumulative to 31 March 2021 concluded that the number of events did not exceed what was to be expected within the general population. The MHRA's observed versus expected analysis identified a signal of TM for the AstraZeneca (Vaxzevria) vaccine assuming 100% reporting for all age groups, and for the Pfizer/BioNTech (Comirnaty) vaccine assuming 50% reporting in the under 50 years age group, and 25% reporting in the 50-64 years age group. It was noted that well over half of the reports of suspected TM for each vaccine (39 out of 57 for AstraZeneca (Vaxzevria) vaccine and 5 out of 18 for Pfizer/BioNTech (Comirnaty) vaccine either had a reported onset time of 7 days or less or had reaction onset reported as 'unknown', and as such inclusion of these reports in the MHRA's analyses reflected a highly conservative approach. In addition, there was uncertainty on how many of these reports met the case definition criteria for TM.

608. The MHRA rapid cycle analysis did not identify a signal of TM associated with either the Pfizer/BioNTech (Comirnaty) vaccine or AstraZeneca (Vaxzevria) vaccine. The VBREWG considered that reports of suspected TM should continue to be closely monitored and noted that epidemiological studies would be investigating this potential association. The VBREWG advised that the available evidence did not support any updates to the product information for any of the Covid-19 vaccines.

609. On 29 October 2021, the advice of the VBREWG was sought on a review of the latest available data from clinical trials, published literature, and spontaneous case reports regarding an association of suspected TM with the Covid-19 vaccines [**JR/263 INQ000494355**]. At the data lock point of 12 October 2021, the MHRA had received 111 Yellow Card reports (none with fatal outcome) of suspected TM associated with the AstraZeneca (Vaxzevria) vaccine, 27 Yellow Card reports (none with a fatal outcome) associated with the Pfizer (Comirnaty) vaccine, and one report (not with a fatal outcome) associated with the Moderna (Spikevax) vaccine [**JR/307 - INQ000494316**].

610. The VBREWG was generally reassured by the low level of reporting of TM given the wide exposure to the vaccines and advised that the number of vaccine related events may be overestimated due to a high background rate of TM in multiple sclerosis patients (estimated to be up to 5,000 new cases per year in the UK). It was anticipated that many patients presenting with TM may subsequently be diagnosed with multiple sclerosis, with TM being secondary to multiple sclerosis.

611. To improve the identification of cases, it was recommended that information should be obtained as part of case follow up on whether longitudinally extensive lesions had been identified on MRI scanning. The VBREWG heard that the evidence for the AstraZeneca (Vaxzevria) vaccine included a report of TM in the treatment arm of the clinical trials, as well as a limited number of Yellow Card reports in the context of usage (an estimated 4 reports per million vaccine recipients). The VBREWG also heard that a signal for TM had been detected in the observed versus expected analysis of the Yellow Card data in all age groups, with the exception of the under 18-year age group in which use of the AstraZeneca (Vaxzevria) vaccine was very limited.

612. It was noted that a conservative approach had been taken in the observed versus expected analysis to include all reported cases, which may overestimate the signal if cases were not meeting a case definition criterion. The VBREWG agreed that the observed versus analysis of TM was associated with a number of limitations but was reassured that this event was being studied as part of the ongoing epidemiological study 'OpenSafely'.'

613. The VBREWG advised that the overall evidence presented for the AstraZeneca (Vaxzevria) vaccine was sufficient to warrant an update to the product information to include TM. It also advised that a second dose of the AstraZeneca (Vaxzevria) vaccine should not be given to anyone who developed TM after receiving a first dose of this vaccine. The VBREWG further recommended that this information should be communicated via the MHRA's weekly 'Summary of Yellow Card reporting'. The VBREWG advised, based on the evidence available, that no action was justified at the current time for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine, but that reports of suspected TM associated with these vaccines should continue to be closely monitored.

614. On 17 November 2021, the advice of the CHM was sought on the current evidence on the potential risk of TM associated with the AstraZeneca (Vaxzevria) vaccine and the Janssen Covid-19 vaccine [**JR/308 - INQ000409511**]. The CHM agreed that the data may show an emerging signal and advised the MHRA on the updates to the AstraZeneca (Vaxzevria) vaccine UK product information for healthcare professionals and patients which were to be implemented.

615. In line with the CHM's advice and proposed wording agreed during their 17 November 2021 meeting, and following discussions with manufacturers, the AstraZeneca (Vaxzevria) vaccine product information was updated on 26 January 2022 and published on 26 January 2022 [**JR/309 - INQ000421331**] to add the following warning:

> *"Extremely rare cases of transverse myelitis have been reported following Vaxzevria. A further dose of Vaxzevria should not be given to those who have experienced symptoms of transverse myelitis after a previous dose of this vaccine."*

616. Very rare events of neuroinflammatory disorders were also added to the possible Undesirable Effects / ADRs list [**JR/310 - INQ000421336**].

617. The MHRA's 'Summary of Yellow Card reporting' was updated on 27 January 2022 (published report covering the period 9 December 2020 to 19 January 2022) [**JR/311 - INQ000421346**] to advise that the MHRA had continually monitored reports of suspected TM associated with Covid-19 vaccines since the start of the vaccination programme. The report also advised that whilst the incidence rate of this adverse event with any of the Covid-19 vaccines used in the UK remained extremely rare (less than 1 report per 100,000 doses of each vaccine), the available evidence reviewed by the MHRA suggested that an association between TM and the AstraZeneca (Vaxzevria) vaccine was possible. The report also set out the updates that had been added to the product information of the AstraZeneca (Vaxzevria) vaccine.

Acute Disseminated Encephalomyelitis

618. Acute Disseminated Encephalomyelitis (ADEM) is a neurological disorder characterised by short-lasting but widespread attacks of inflammation in the brain and spinal cord that damage myelin. Myelin is the protective coating over nerves that helps with electrical nerve signalling. The symptoms of ADEM may include loss of vision, weakness, difficulty in coordination, fever and unconsciousness. The most serious cases of ADEM can result in lifelong neurological sequelae or death.

619. Acute Disseminated Encephalomyelitis may be triggered by a viral infection, and there have been a number of case reports in the literature of ADEM associated with Covid-19 infection. Direct viral effects upon the nervous system, endothelial injury and the consequential effects of inflammation have all been suggested as the potential cause of neurologic involvement in Covid-19. It has also very rarely been seen in association with some vaccines, notably those for smallpox and rabies. However, vaccine-associated ADEM is considered rare and accounts for fewer than 5% of all cases. In these cases, it is thought that ADEM can occur as a result of an immune response to a vaccine component. There may be some commonality with the pathophysiology of other central nervous system disorders associated with nerve damage associated with some vaccines. Host factors and genetic polymorphisms may also predispose an individual to being more susceptible to ADEM (see MHRA's 'COVID-19 Vaccine AstraZeneca and risk of Acute disseminated encephalomyelitis' paper for the VBREWG of August 2022: [**JR/312 - INQ000494333**].

620. No cases of suspected ADEM were reported during clinical trials for the Covid-19 vaccines, however because of experience linking ADEM with some other vaccines, ADEM is an AESI for the Covid-19 vaccines and has been closely monitored since the first deployment of the vaccines in the UK.

621. Following deployment, the MHRA received company monthly safety update reports for the AstraZeneca (Vaxzevria) vaccine which were reviewed in MHRA's internal Covid-19 vaccine signal detection meetings. The company's periodic safety update report covering the time period between December 2020 and June 2021 received by the MHRA on 6 September 2021 was also discussed [**JR/313 - INQ000494381**]. As of 28 June 2021, AstraZeneca had received 26 reports of suspected ADEM associated with the AstraZeneca (Vaxzevria) vaccine world-wide, of which 9 reports originated from the UK. There were no reports with a fatal outcome.

622. The AstraZeneca monthly safety update reports showed a very small, but increasing, number of reports of suspected ADEM received globally in association with the AstraZeneca (Vaxzevria) vaccine. Cumulative observed versus expected analyses did not identify a statistical signal for ADEM. In the summary report covering the status as of June 2021, AstraZeneca provided a more detailed analysis and stratified the reports by region, with the EU and UK treated as one entity. Again, cumulative observed versus expected analyses did not identify a statistically significant increase in the incidence of ADEM associated with vaccines, either globally or in the EU/UK. The MHRA agreed with the company's conclusions that the available data did not support a signal for ADEM or encephalitis associated with the AstraZeneca (Vaxzevria) vaccine.

623. The PSUR (of June 2021) concluded that there was insufficient evidence of a safety concern with ADEM to warrant an update to product information, and that ADEM should continue to be monitored as part of ongoing surveillance.

624. On 10 November 2021, the EMA's PRAC reviewed the PSUR and noted the absence of statistically significant signals for suspected ADEM or encephalitis in the spontaneous adverse reaction reports [**JR/314 - INQ000507347**]. The PRAC commented in its assessment that:

"ADEM should continue to be closely monitored and discussed in the next PSUR, including an updated observed versus expected analysis and a discussion of cases from the literature".

625. In February 2022, the MHRA reviewed the second PSUR for the AstraZeneca (Vaxzevria) vaccine for the period 29 June 2021 to 28 December 2021 [**JR/315 - INQ000494371**]. This report contained an updated analysis of reports of suspected ADEM which, as discussed above, had been requested by the EMA following the PRAC review of the first PSUR. The search identified 34 spontaneous reports of suspected ADEM associated with the AstraZeneca (Vaxzevria) vaccine and 1 report from the published literature. Of these reports, 4 had a fatal outcome.

626. In its assessment of the PSUR in December 2021, the PRAC concluded that there was insufficient evidence to support an association between the AstraZeneca (Vaxzevria) vaccine and ADEM and requested continued close monitoring by the manufacturer [**JR/316 - INQ000507353**]. The PRAC also noted that more information was expected from a Post-Authorisation Safety Study using secondary user services databases which would examine the incidence of encephalitis and ADEM associated with vaccines. Noting that the Therapeutic Goods Administration in Australia was considering regulatory action to add a warning about ADEM to the product information of the AstraZeneca (Vaxzevria) vaccine, as discussed further in paragraph 636, the MHRA brought a report on this issue to its internal signal management meeting on 14 July 2022 as discussed in paragraph 628.

627. On 21 June 2022, as a member of the International Coalition of Medicines Regulatory Authorities ("ICMRA"), the MHRA co-chaired an ICMRA Vaccine Pharmacovigilance Network (ICMRA VPN) meeting. The MHRA was informed during the meeting that the Therapeutic Goods Administration in Australia had recently received a report of ADEM with a fatal outcome associated with administration of the AstraZeneca (Vaxzevria) vaccine. The ICMRA VPN was informed that the TGA had commenced discussions with the manufacturer to add information on ADEM to the product information for the AstraZeneca (Vaxzevria) vaccine.

628. On 14 July 2022, the strength of the evidence for an association between a potential signal of ADEM and the AstraZeneca (Vaxzevria) vaccine and the need for further action was reviewed at the MHRA's regular internal Covid-19 vaccine and therapeutics signal meeting

[**JR/317 - INQ000494376; JR/318 - INQ000494377**]. During the meeting, the seriousness, morbidity and potential mortality associated with ADEM, and the challenges around correctly identifying and diagnosing such cases, were discussed. It was agreed that it would be beneficial to obtain specialist neurological advice on the detailed characteristics of the reports to date of suspected ADEM and the advice of the VBREWG would be sought.

629. On 25 August 2022, the MHRA sought the advice of the VBREWG on the available evidence on a potential signal of ADEM associated with the AstraZeneca (Vaxzevria) vaccine [**JR/312 - INQ000494333; JR/319 -** **INQ000409543**. The VBREWG considered data from clinical trials, published literature case reports, spontaneous sources including Yellow Card reports received up to 27 July 2022 and internal observed versus expected analyses. The VBREWG also considered the 6-monthly PSUR reviews undertaken by the manufacturer and data identified from other regulatory authorities.

630. The reporting rate for ADEM was considered low in the context of both the usage of these vaccines and the background incidence of ADEM, with 14 Yellow Card reports of suspected ADEM (1 report with a fatal outcome) arising from nearly 25 million first doses, 24 million second doses and 58,000 booster doses of the AstraZeneca (Vaxzevria) vaccine administered in the UK. In the UK the background incidence rate of ADEM is 1-2.4 cases per 100,000 patient years. This was not exceeded by the Yellow Card reporting rate for suspected ADEM associated with the AstraZeneca (Vaxzevria) vaccine, and so a signal was not identified. The VBREWG also noted the diagnostic complexity of ADEM in adult populations, which may contribute to under-reporting.

631. The attention of the VBREWG was drawn to a review by the EMA's PRAC of the signal of ADEM with the AstraZeneca (Vaxzevria) vaccine as presented in the 6-monthly PSURs. The PRAC had concluded that the available evidence did not support a causal association, and that this signal should continue to be monitored closely.

632. The VBREWG and invited neurological experts considered that, given the link between the AstraZeneca (Vaxzevria) vaccine and other neurological events such as Guillain-Barré syndrome and transverse myelitis, an association could not be excluded based on the limited available data, and that more information should be sought. The VBREWG advised that MHRA should work with the UK Health Security Agency (UKHSA) to investigate the feasibility

of a self-controlled case series study to investigate the risk further, which is discussed at paragraph 670. The VBREWG noted that the epidemiology of the condition was not clear-cut and advised that the totality of the evidence currently available did not indicate a causal association. The VBREWG recommended that no immediate regulatory action was justified, with the understanding that this would continue to be closely monitored by the marketing authorisation holder and by MHRA and further evaluated with additional data sources.

633. On 21 December 2022, following the VBREWG advice, the MHRA circulated a series of questions to other regulatory agencies to obtain more information about the signal of ADEM in foreign adverse reaction reporting data. Of the six agencies that responded (Australia, USA, Switzerland, Singapore, New Zealand and Canada), only the Australian regulator had taken action to list ADEM in its product information for the AstraZeneca (Vaxzevria) vaccine. For all other responding territories, the number of reports of suspected ADEM received across all vaccines was small and not considered to represent a signal. Only the US had additional pharmacovigilance measures in place to investigate ADEM for the mRNA vaccines (the AstraZeneca (Vaxzevria) vaccine was not authorised in the US).

634. On 5 May 2023, the MHRA sought the advice of the VBREWG on a further review of suspected ADEM with the AstraZeneca (Vaxzevria) vaccine [**JR/320 - INQ000494364**; **JR/321 - INQ000409573**]. The VBREWG considered Yellow Card data, statistical analyses using secondary user services data provided by UKHSA, published literature and data identified from other regulatory authorities. The MHRA sought the advice of the VBREWG considering how the risk of ADEM was reflected in the product information within other regulatory jurisdictions.

635. Since the previous review on 25 August 2022, one additional suspected ADEM report with a fatal outcome had been received, bringing the total number of spontaneous UK reports of suspected ADEM associated with the AstraZeneca (Vaxzevria) vaccine to 15 reports. The reporting rate remained below the expected background incidence rate for the UK population. Additional analyses had been performed to address the diagnostic complexity of ADEM in adult populations and the potential under-reporting of such cases, and the UKHSA had undertaken an additional epidemiological review to further investigate this potential signal. Data for the mRNA vaccines did not indicate a signal.

636. The advice of the VBREWG was sought regarding the acknowledgment by the TGA in Australia that the evidence did not support a clear increase in risk, however, based on biological plausibility and case assessment, as a precautionary measure the TGA had added ADEM to the warnings and precautions for use section of the product information for the AstraZeneca (Vaxzevria) vaccine. No other international regulators had acted regarding ADEM for any of their Covid-19 vaccines.

637. The VBREWG and invited neurology experts considered that, given the link between the AstraZeneca (Vaxzevria) vaccine and other neurological events such as Guillain-Barré syndrome and transverse myelitis, an association could not be excluded based on the limited available data. The VBREWG noted the strength of the evidence was marginal, and that additional evidence of this association was unlikely to become available.

638. The VBREWG concluded that a precautionary approach should be pursued given the seriousness of ADEM and advised that updates to the product information should be implemented to reflect the potential risk of ADEM in a similar manner to that presented by the TGA. Following the advice of the VBREWG, the MHRA discussed the matter with the EMA, and with the manufacturer. The MHRA contacted the manufacturer on 24 May 2023, and correspondence and meetings took place to ensure an appropriate understanding of the strengths and weaknesses of the evidence, and to ensure the wording for the updates to the product information reflected this [**JR/322 - INQ000494372**]. This led to a variation application being submitted on 6 November 2023 by the manufacturer to update the product information [**JR/323 - INQ000494386**], which was approved by the MHRA on 21 November 2023 [**JR/324 - INQ000494387**].

639. On 22 November 2023, the UK SmPC for the AstraZeneca (Vaxzevria) vaccine was updated to include the following wording (under the heading "Special warnings and precautions for use") [**JR/325 – INQ000468853**]:

> **"Neurological events**
>
> …
>
> Extremely rare cases of acute disseminated encephalomyelitis (ADEM) have been reported following Vaxzevria, although a causal relationship has not been established. Cases with fatal outcome have been reported. Healthcare

professionals should be alert to signs and symptoms of brain and spinal cord inflammation (uni- or bi-lateral weakness in the extremities, numbness or tingling, changes in mental state or level of consciousness, visual impairment, or seizures)."

640. On 22 November 2023, the PIL for the AstraZeneca (Vaxzevria) vaccine was updated to include the following [**JR/326 - INQ000468854**]:

> **"2. What you need to know before you are given Vaxzevria**
>
> ...
>
> **Warnings and precautions**
>
> ...
>
> **Neurological events**
>
> ...
>
> Extremely rare cases of acute disseminated encephalomyelitis (inflammation in the brain and spinal cord) have been reported following vaccination with Vaxzevria. However, it has not been determined whether these events were due to the vaccine. Seek urgent medical attention if you develop weakness, numbness or tingling in the extremities, changes to your state of awareness, alertness or wakefulness, changes to your eyesight, or seizures."

641. The EMA decided not to take regulatory action to change the product information [**JR/327 INQ000494384; JR/ 328 – INQ000494383**].

Myocarditis / pericarditis

642. Myocarditis is inflammation of the heart muscle. Pericarditis is inflammation of the exterior membrane covering the heart. These conditions commonly co-exist and were investigated by the MHRA together. Both conditions can often fully resolve with non-invasive interventions such as rest and painkillers. Rarely, myocarditis can cause damage to the heart and be fatal. I use the umbrella term 'myo/pericarditis' here as this was the term used in the VBREWG papers.

643. It is important to note that viral infections, including Covid-19 are a leading cause of myo/pericarditis worldwide. A number of epidemiological studies have concluded that Covid-19 increased the incidence of myo/pericarditis at least 15 times over pre-Covid levels although

the condition remains rare. The incidence of myo/pericarditis pre-Covid was reported at 1 to 10 cases/100,000 individuals and since Covid-19, ranging from 150 to 4,000 cases/100,000 individuals.

644. Myo/pericarditis has been reported in association with vaccines (such as live smallpox and influenza vaccines) and consequently these reactions were included in the AESIs for the Covid-19 vaccines in the UK. From the first deployment of the Covid-19 vaccines, myo/pericarditis cases were closely monitored by the MHRA. No cases of myo/pericarditis were reported during clinical trials on the Covid-19 vaccines.

645. On 4 February 2021, the MHRA sought the advice of the VBREWG for the first time on reports of suspected myo/pericarditis associated with vaccines [**JR/329 – INQ000409513**]. Up to and including 27 January 2021, the MHRA had received 2 Yellow Card reports of suspected pericarditis and 5 reports of suspected myocarditis associated with the Pfizer/BioNTech (Comirnaty) vaccine and 1 report of suspected pericarditis with no reports of suspected myocarditis associated with the AstraZeneca (Vaxzevria) vaccine. There were no reports of suspected myocarditis or pericarditis with a fatal outcome. The Moderna (Spikevax) vaccine had not yet been deployed in the UK. An MHRA assessment report summarising the most recent epidemiological analyses of suspected myo/pericarditis associated with Covid-19 vaccines was also presented (the paper also discussed Bell's Palsy) [**JR/330 - INQ000494273**]. This provided updates on the observed versus expected analyses of Yellow Card reports of suspected myocarditis and/or pericarditis together with results from a Rapid Cycle Analysis study conducted in the Clinical Practice Research Datalink ("CPRD").

646. The VBREWG was informed that in combined analyses no signals were raised, however a signal was raised in patients aged <50 years where 5 cases had been identified compared to an expected 1.1. This resulted in an estimated relative risk of 4.5 in the 42 days after the first dose of the Pfizer/BioNTech (Comirnaty) vaccine. The 42-day risk window was recommended by the Brighton Collaboration and the Safety Platform for Emergency Vaccines in the data analysis recommendations for myocarditis, as well as the other AESIs [**JR/331(a) - INQ000468830**]. The estimated risk was based on a small number of reports, with suspected myocarditis more frequently diagnosed in younger adults.

647. Ecological analysis showed that the incidence of myo/pericarditis, particularly when restricted to older patients, was highly variable due to the rarity of the event, so it would not have been surprising to see short-lived outliers in incidence rates compared to the background average [**JR/330 – INQ000494273**]. The VBREWG considered that this was likely to be a chance finding given the body of evidence. It was recommended that monitoring of myocarditis should continue given the overlap with myocarditis occurring as part of Multisystem Inflammatory Syndrome, a rare but serious condition causing diffuse inflammation, seen predominantly in paediatric patients with a Covid-19 infection.

648. By 5 May 2021, the MHRA had received 19 Yellow Card reports of suspected myocarditis and 16 reports of suspected pericarditis associated with the Pfizer/BioNTech (Comirnaty) vaccine, 21 reports of suspected myocarditis and 41 reports of suspected pericarditis (including 2 reports with fatal outcomes) associated with the AstraZeneca (Vaxzevria) vaccine and 1 report of suspected myocarditis and none of pericarditis associated with the Moderna (Spikevax) vaccine **JR/331(b) - INQ000421511**. This was in the context of the administration of an estimated 11.4 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine and 23.3 million first doses of AstraZeneca (Vaxzevria) vaccine, and around 8.7 million and 7.5 million second doses of the Pfizer/BioNTech (Comirnaty) and AstraZeneca (Vaxzevria) vaccines, respectively. An approximate 0.1 million first doses of Moderna (Spikevax) vaccine had also been administered **JR/332(a) - INQ000468857**.

649. On 7 May 2021, the MHRA sought the advice of the VBREWG on reports of suspected myocarditis in both the US and Israel associated with the Pfizer/BioNTech (Comirnaty) vaccine, particularly in young male recipients and after the second dose [**JR/331(b) - INQ000421511**; **JR/284 - INQ000494348**]. The Centers for Disease Control and Prevention ("CDC") in the US, with a data lock point of 26 April 2021, had indicated that there was no signal in observed versus expected analyses for either mRNA vaccine. The MHRA also did not identify a strong signal for an increased risk of myocarditis with the Pfizer/BioNTech (Comirnaty) vaccine in either the observed versus expected or the rapid cycle analyses. The VBREWG requested more information on reports of suspected myo/pericarditis in the US, to determine what other factors may be contributing to the events as well as to seek further information about exposed populations. The VBREWG advised the MHRA to continue the ongoing Yellow Card analysis and epidemiological monitoring.

650. On 4 June 2021, the MHRA sought the advice of the VBREWG on the latest data on the risk of myo/pericarditis associated with the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine **JR/332(b) - INQ000409527**. The MHRA presented data from Yellow Card reports, observed versus expected analysis, UKHSA Secondary User Service ("SUS") data, manufacturers' data and international data from the US and Israel. From the beginning of the vaccination programme up until 2 June 2021, the Yellow Card scheme had received 34 reports of suspected myocarditis and 26 reports of suspected pericarditis associated with the Pfizer/BioNTech (Comirnaty) vaccine, 31 reports of suspected myocarditis and 55 reports of suspected pericarditis associated with the AstraZeneca (Vaxzevria) vaccine, two reports of suspected myocarditis and no reports of suspected pericarditis associated with the Moderna (Spikevax) vaccine. [**JR/333 - INQ000421356**].

651. Up until 2 June 2021, an estimated 14.7 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine and 24.5 million first doses of AstraZeneca (Vaxzevria) vaccine had been administered, and around 10.7 million and 15.7 million second doses of Pfizer/BioNTech (Comirnaty) vaccine and AstraZeneca (Vaxzevria) vaccine had been administered, respectively. An approximate 0.46 million first doses of the Moderna (Spikevax) vaccine had also been administered [**JR/334 - INQ000421356**].

652. The VBREWG considered that the data from the deployment of the second Pfizer/BioNTech (Comirnaty) vaccine dose in Israel suggested a possible signal of myo/pericarditis but noted that the same increased risk associated with the second dose had not been seen in the UK and European data. The VBREWG also noted that the second dose of the Pfizer/BioNTech (Comirnaty) vaccine was being administered with a 21-day interval from the first dose in the US and Israel while longer dose intervals were used elsewhere. The VBREWG advised that no regulatory action was required at this time but reports of suspected myo/pericarditis should be closely monitored, particularly with the deployment of second doses starting in younger age groups [**JR/335 - INQ000468866**]. Data gathered later on myocarditis showed a lower risk associated with a second dose with a longer dose interval, such as was recommended in the UK. The longer dose interval in the UK has therefore been postulated as mitigating myocarditis risk.

653. On 10 June 2021, the MHRA incorporated comments on specific reports of suspected myo/pericarditis associated with Covid-19 vaccines into its weekly summary publication

[**JR/333 - INQ000421356**]. The comments stated that the number of reports of suspected myo/pericarditis associated with the vaccines in the UK remained similar to or below the expected background rate in different age groups within the general population and did not indicate an increased risk associated with Covid-19 vaccines. The MHRA committed to continuing close monitoring of these events in the UK and internationally.

654. On 21 June 2021, the MHRA sought the advice of the VBREWG on 20 further Yellow Card reports describing suspected myo/pericarditis with generally mild symptoms such as chest pain and fatigue, received between 1 and 13 June 2021 associated with the Pfizer/BioNTech (Comirnaty) vaccine [**JR/336 – INQ000494302**; **JR/337 – INQ000409529**]. Data from Pfizer/BioNTech, Moderna and AstraZeneca's observed versus expected analyses of myo/pericarditis were presented, which continued not to show a signal.

655. However, since the last update to the VBREWG, data from the UKHSA, the EMA and the US CDC indicated an increased risk of myocarditis in younger age groups, in particular associated with the Pfizer/BioNTech (Comirnaty) vaccine and Moderna (Spikevax) vaccine, with some data suggesting an increased risk associated with the AstraZeneca (Vaxzevria) vaccine. Furthermore, data from Israel had shown via observed versus expected analysis a signal associated with the Pfizer/BioNTech (Comirnaty) vaccine in young males, strongest in the 16-19-year-old age group.

656. The VBREWG advised that the product information for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine should be updated to include a warning on the risk of myo/pericarditis. However, the VBREWG concluded that the available data for the AstraZeneca (Vaxzevria) vaccine did not indicate a risk and therefore did not support an update to the product information for this vaccine.

657. On 23 June 2021, the MHRA sought the advice of the CHM on the recommendations of the VBREWG [**JR/338 INQ000409504**]. The CHM endorsed the VBREWG advice, concluding that there was sufficient evidence to support the inclusion of a warning that suspected myocarditis and pericarditis had been reported in association with the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine and also to highlight the symptoms of myocarditis and pericarditis of which healthcare professionals and vaccine recipients should be aware [**JR/339 - INQ000468826**]. The CHM endorsed the

circulation of a healthcare professional letter from the MHRA on this risk (which was published on 7 July 2021 and is discussed at paragraph 660 [**JR/340 - INQ000468855**]. The CHM advised that the overall benefit risk remained positive for the authorised Covid-19 vaccines.

658. On 25 June 2021, the Licensing Minister accepted in full the CHM's advice that a warning about the risk of myo/pericarditis associated with the Pfizer/BioNTech (Comirnaty) vaccine and with the Moderna (Spikevax) vaccine be added to the product information [**JR/341(a) - INQ000494303**]. The product information for the Moderna (Spikevax) and the Pfizer/BioNTech (Comirnaty) vaccines were updated on 25 June 2021 [**JR/342(a) - INQ000468849**; **JR/343(a) INQ000468850**].

659. On 5 July 2021, the MHRA sought the advice of the VBREWG on further international regulatory updates on myocarditis and pericarditis in association with Covid-19 vaccines. The US Food and Drug Administration ("FDA") had updated the product information for mRNA Covid-19 vaccines to include similar warnings on the risk of myocarditis and pericarditis to those advised by the CHM. Other regulators including the EMA, Health Canada and the Israeli regulator were continuing to investigate the signal of myocarditis and pericarditis. The VBREWG advised the inclusion of myocarditis and pericarditis as important identified risks in the risk management plans for the mRNA vaccines, with investigation of these risks in post-authorisation safety studies and ongoing close monitoring [**JR/344(a) - INQ000409530**]

660. On 7 July 2021, the MHRA published a Drug Safety Update article which described the MHRA review of reports of suspected myocarditis/pericarditis associated with Covid-19 vaccines and the CHM advice [**JR/340 - INQ000468855**]. The article outlined the revisions made to the product information on 25 June 2021 and recorded that a notification had been sent to the NHS and healthcare stakeholders with advice for healthcare professionals on the signs and symptoms of myocarditis, the higher incidence in younger men shortly after receiving a second dose of the vaccine, and information on incidence and severity of myocarditis after Covid-19 vaccination.

661. On 19 July 2021, the MHRA sought the advice of the VBREWG on further reports of suspected myo/pericarditis [**JR/341(b) INQ000409531**; **JR/342(b) INQ000468859**]. Up to and including 14 July 2021, the Yellow Card scheme had received 112 reports of suspected myocarditis and 103 reports of suspected pericarditis associated with the Pfizer/BioNTech (Comirnaty)

vaccine; 76 reports of suspected myocarditis and 126 reports of suspected pericarditis associated with the AstraZeneca (Vaxzevria) vaccine, and 17 reports of suspected myocarditis and 20 reports of suspected pericarditis associated with the Moderna (Spikevax) vaccine. There were no reports with a fatal outcome. The VBREWG noted that there were ongoing clinical and epidemiological studies in the UK and highlighted the need for studies into potential mechanisms for an increased risk of myo/pericarditis.

662. The VBREWG discussed the risk of myo/pericarditis after adenovirus-based Covid-19 vaccines, noting the signal of a possible increased risk after the first dose of the AstraZeneca (Vaxzevria) vaccine in UK hospital data as well as the reporting rates of suspected myo/pericarditis for adenovirus-based vaccines in the EU/EEA data. The MHRA highlighted that the VBREWG would be asked in August to advise on a review of Yellow Card data on suspected myo/pericarditis associated with the AstraZeneca (Vaxzevria) vaccine and that additional data requested by the EMA from AstraZeneca and Janssen on suspected myocarditis and pericarditis would be presented to the VBREWG when available.

663. It is worth noting that new epidemiological evidence looking at risk of myocarditis and pericarditis in younger age groups was published around this time and showed that myocarditis and pericarditis from primary Covid-19 infection occurred at a rate as high as 450 per million in young males. Young males infected with the virus are up to 6 times more likely to develop myocarditis as those who have received the vaccine JR/343(b) - INQ000507352

664. At its meetings on 19 August 2021 and 31 August 2021 [JR/344(b) **INQ000494351; JR/251 - INQ000494352**], the VBREWG was provided with updates, and advised that further data and studies were required to determine the long-term outcomes following suspected myo/pericarditis associated with Covid-19 vaccines and supported a planned PHE study of long-term cardiac outcomes in the UK.

665. In September 2021, the MHRA took the initiative to develop an internal case adjudication process for Yellow Card reports of suspected myo/pericarditis in patients 12- 18 years of age. With myo/pericarditis having been added to the Product Information in June, the need for a systematic approach to case adjudication was recognised in line with other major regulators. Additionally, a significant number of reports of suspected myo/pericarditis lacked clinical detail to aid the confirmation of cases and many Yellow Card reports were not submitted by medical

professionals (as described earlier in my statement, patients may self-report suspected adverse reactions via the Yellow Card system).

666. The adjudication process consisted of the MHRA working together with two external cardiology experts on the process and all reports in under 18-year-olds up to 29 September 2021 were reviewed. The published, pre-existing CDC criteria defining acute myocarditis, acute pericarditis and myopericarditis were used; these utilise a combination of clinical symptoms with laboratory investigations and cardiac imaging to classify reports as 'probable' or 'confirmed'. Reports which were judged not to meet the criteria for 'probable' or 'confirmed' were further classified as 'unlikely' or 'case criteria not met'. Of 12 reports reviewed by the experts, 6 were classified as 'probable' myo/pericarditis and 6 were deemed 'case criteria not met', highlighting the challenge in confirming cases of myo/pericarditis from information provided in Yellow Cards.

667. On 13 October 2021, the MHRA sought the advice of the VBREWG on the adjudication process and its plan to apply the process to reports of suspected myo/pericarditis in older age groups [**JR/345 - INQ000494315**; **JR/346 -** **INQ000409566** The MHRA also made further changes to the Coronavirus Yellow Card reporting form to include specific questions to increase the level of detail provided by reporters about cases of suspected myo/pericarditis. For these cases, an additional reporting page introduced new data fields to capture detailed clinical information including details of hospital admissions(s), severity of symptoms (such as chest pain and shortness of breath), diagnostic tests and results (e.g. troponin levels, electrocardiogram, X-ray, computed tomography scan, magnetic resonance imaging scan), treatment administered and patient response, and relevant medical history (such as previous cardiac issues, vaccination status). The MHRA also added a structured reporting format (including drop-down menus) for consistent data entry, utilised conditional reporting (for example, if a reporter indicated that symptoms of myo/pericarditis were present, specific follow-up questions about diagnostic tests and treatments would be displayed), and added enhanced user guidance and automated validation checks. The MHRA proceeded to use the adjudication process for internal signal assessment and for identifying individual cases for follow up.

668. On 19 October 2021, the MHRA sought the advice of the VBREWG on an updated review of national and international data concerning myo/pericarditis in different age groups

associated with the Pfizer/BioNTech (Comirnaty), the Moderna (Spikevax) and the AstraZeneca (Vaxzevria) vaccines [**JR/347** INQ000507336 **JR/348 - INQ000494354**]. The MHRA review included assessment of Yellow Card reports, company data, MHRA's epidemiological analyses, international data and literature articles.

669. Analysis of Yellow Card reporting rates showed that the rates of suspected myo/pericarditis remained similar between the first and second doses of Pfizer/BioNTech (Comirnaty) while Moderna (Spikevax) had a higher reporting rate after the second dose in younger age groups and higher overall reporting rates when compared with the Pfizer/BioNTech (Comirnaty) vaccine. The vast majority of suspected reports of myo/pericarditis were non-serious and there was no difference in severity in suspected reports between the vaccines. Additionally, fewer than one third of cases met the criteria for myocarditis and pericarditis diagnosis following medical adjudication. For AstraZeneca (Vaxzevria) the reporting rates were lower overall than for the mRNA vaccines. Yellow Card reports continued to show more reporting in young males than females with 74% of reports being in males versus 18% for females, with a median age of 28.

670. A self-controlled case series conducted by Edinburgh Scottish Carbon Capture Storage showed an increased risk of myocarditis associated with both the first and second doses of the mRNA vaccines as well as for the first dose of the AstraZeneca (Vaxzevria) vaccine. When the UK adverse reaction data were stratified to patients under 40 years of age, the incidence rate ratio was higher for the Moderna (Spikevax) vaccine than either the Pfizer/BioNTech (Comirnaty) or AstraZeneca (Vaxzevria) vaccines.

671. New data from international regulators (US, Israel) followed a similar pattern of higher reporting in males and younger age groups and associated with the second dose, with higher reporting for Moderna (Spikevax) than Pfizer/BioNTech (Comirnaty). Reporting rates tended to be higher in the US and Israel than in the UK, with a stronger signal emerging for the second dose of the Moderna (Spikevax) vaccine. In the UK, by 21 October 2021, there were 18 reports per million doses of Pfizer/BioNTech (Comirnaty) vaccine in 18–49 year-olds, 44 reports per million doses of Moderna (Spikevax) vaccine in 18–49 year-olds, and 8 reports per million doses of AstraZeneca (Vaxzevria) vaccine in 18–49 year-olds.

672. The VBREWG considered that, while international and UK data may show a slightly higher risk with the Moderna (Spikevax) vaccine in the younger population compared to the Pfizer/BioNTech (Comirnaty) vaccine, the UK comparative risk was not considered significant between the mRNA vaccines regarding the risk of myocarditis in any age group. There was therefore not enough evidence to advise that the benefit risk was negative for Moderna (Spikevax) vaccine in any particular age group. The VBREWG advised that further regulatory action should be considered if analysis of emerging data indicated a change in the benefit risk for a specific vaccine or in specific subgroups.

673. On 29 October 2021, the advice of the VBREWG was sought regarding the US FDA's update to the healthcare professional factsheet for the Janssen (JCovden) Covid-19 vaccine. This update added myo/pericarditis as a post-marketing adverse reaction [**JR/263 - INQ000494355**]. This appeared to be a precautionary update as the warnings included for the mRNA vaccines had not previously been included for the Janssen (JCovden) vaccine.

674. On 9 November 2021, advice was sought from the VBREWG concerning the need for further regulatory action on the risk of myo/pericarditis with the mRNA vaccines or the AstraZeneca (Vaxzevria) vaccine [**JR/349** **INQ000409536** The latest UK findings were consistent with the previous presentation to the VBREWG in October. Yellow Card reporting rates remained similar for the first and second doses of the Pfizer/BioNTech (Comirnaty) vaccine, and the Moderna (Spikevax) vaccine showed higher reporting rates after the second dose in the younger age groups compared to the first dose and higher reporting rates overall compared to the Pfizer/BioNTech (Comirnaty) vaccine. Reporting rates for AstraZeneca (Vaxzevria) continued to be lower than for the mRNA vaccines with little difference between doses, except for the 18-29 year-old group where rates were slightly higher with the second dose. This vaccine was no longer recommended by the JCVI in patients under 40, so this finding may have reflected the atypical nature of this subgroup. Yellow Card data continued to show higher reporting in males versus females and in younger ages.

675. The VBREWG noted the consistent pattern of higher reporting rates of suspected myo/pericarditis for Moderna (Spikevax) compared with Pfizer/BioNTech (Comirnaty) in international and UK spontaneous data and discussed whether the extended dose interval used in the UK may explain the weaker signal with dose 2 in the UK compared with the other countries. The VBREWG also considered whether the half dose of Moderna (Spikevax) being

used as a booster in the UK might be associated with lower rates of myo/pericarditis than with primary immunisation.

676. Based on this information, the VBREWG asked for mechanistic work (looking at the potential biological mechanism of the vaccine to cause myo/pericarditis) to be undertaken by the manufacturers and was informed by the MHRA that this would be pursued through the RMP update which had recently been submitted. The VBREWG advised that no further regulatory action was required based on the data presented.

677. On 15 November 2021, the JCVI announced that the Covid-19 vaccination booster campaign would be extended to 40–49-year-olds and that 16-17-year-olds were recommended to receive a second dose of the Pfizer/BioNTech (Comirnaty) vaccine [**JR/350 - INQ000468864**; **JR/351 - INQ000468838**]. An MHRA press release communicated that the VBREWG had advised that:

> "*reports of suspected myocarditis (heart inflammation) following the COVID-19 vaccines are extremely rare and that the balance of risks and benefits overall remains favourable.*"

678. On 3 December 2021 [**JR/352 - INQ000494356**], the MHRA sought the advice of the VBREWG about planned updates by the EMA to the product information for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine to include data from recent observational studies on the rate of myocarditis being reported with the vaccines. The VBREWG advised that further updates to the GB product information should align with the EMA wording.

679. On 24 December 2021, following the agreed update from 3 December 2021, the Summary of Product Characteristics [**JR/353 - INQ000468865**] (section 4.4, special warnings and precautions for use) for the Pfizer/BioNTech (Comirnaty) vaccine was updated as follows:

> ***"Myocarditis and pericarditis***
>
> *There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8).*

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised."

680. On 13 January 2022, the MHRA sought advice from the VBREWG on the need for regulatory action in light of updated data for myo/pericarditis. The MHRA presented an updated review comprising Yellow Card analysis, international data and recent literature articles. In the UK, by 5 January 2022, in the 18-29 year-old age group there were 23 and 27 reports of myo/pericarditis per million doses of Pfizer/BioNTech (Comirnaty) vaccine associated with the first and second dose respectively, 54 and 71 reports per million doses of Moderna (Spikevax) vaccine, associated with the first and second dose respectively and 9 and 15 reports per million doses of AstraZeneca (Vaxzevria) vaccine associated with the first and second dose respectively. In the 20-39 year-old age group there were 20 and 23 reports per million doses of Pfizer/BioNTech (Comirnaty) vaccine associated with the first and second dose respectively, 48 and 55 reports per million doses of Moderna (Spikevax) vaccine, associated with the first and second dose respectively and 12 and 11 reports per million doses of AstraZeneca (Vaxzevria) vaccine associated with the first and second dose respectively.

681. Trends in Yellow Card reporting rates for suspected myo/pericarditis had not changed for the mRNA vaccines or the AstraZeneca (Vaxzevria) vaccine. For the Pfizer/BioNTech (Comirnaty) vaccine, reporting rates of suspected myo/pericarditis in the UK were similar for homologous and heterologous boosters [**JR/354 – INQ000507361**]. Analysis of US spontaneous reports indicated that reporting rates of suspected myo/pericarditis were lower for booster doses than for the primary schedule.

682. The VBREWG advised that no regulatory action was required and that future updates from the MHRA should focus on reports of suspected myo/pericarditis associated with booster doses and reports in the under 18 age group, following the expansion of second doses to 12–15-year-olds and potential roll-out to 5–11-year-olds of the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine. It was agreed that future MHRA reviews would also include data on long term outcomes of myocarditis and pericarditis [**JR/355 – INQ000507337** **JR/356 - INQ000494357**].

683. On 18 January 2022, following the product information updates on 24 December which were agreed at the meeting on 3 December 2021, an MHRA Drug Safety Update article was issued to highlight the new wording on the risk of myo/pericarditis in the product information for the Moderna (Spikevax) vaccine [**JR/357 - INQ000468839**]. The updated wording in the Summary of Product Characteristics [**JR/358 - INQ000468863**] (section 4.4, special warnings and precautions for use) was as follows:

> "**Myocarditis and pericarditis**
>
> *There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8).*
>
> *Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.*
>
> *Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute or persisting) chest pain, shortness of breath or palpitations following vaccination.*
>
> *Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.*
>
> *The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised."*

684. On 4 February 2022, the MHRA sought the advice of the VBREWG on the latest data regarding the risk of myocarditis. This included Yellow Card reports as well as international

data and literature [**JR/359 - INQ000494325**]. The VBREWG was presented with reporting rates for suspected myocarditis for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine third/ booster doses. For these vaccines, the reporting rate was lower associated with the third dose than associated with primary doses. The VBREWG advised that the benefits continued to exceed the risks for all vaccines for all authorised populations and therefore no further regulatory action was required based on the latest available data [**JR/360 - INQ000494358**].

685. On 18 February 2022, the MHRA sought the advice of the VBREWG on a pre-print publication regarding two reports of cardiomyopathy with a fatal outcome from the USA associated with a second dose of the Pfizer/BioNTech (Comirnaty) vaccine [**JR/361 - INQ000494359**]. The VBREWG requested that the MHRA seek further data on these reports from the FDA and the authors. The MHRA did so and on 24 June 2022 received information concerning the two reports of cardiomyopathy with fatal outcomes from the manufacturer [**JR/362 - INQ000494388**]. The VBREWG reconsidered this data on 22 July 2022, as discussed at paragraph 696. The VBREWG was also presented with long-term follow-up information received for Yellow Card reports of suspected myo/pericarditis.

686. The VBREWG was informed that at 3 months post-diagnosis of myo/pericarditis, the majority of patients had recovered or were recovering and that patients who had further diagnostic tests including cardiac MRI and ECG were not showing long-term complications associated with severe outcomes. Updated long-term follow-up data from the US CDC also continued to show that the majority of patients had recovered with no signs of serious long-term harm. The VBREWG was reassured by the follow-up data but agreed that this should continue to be monitored.

687. At a meeting on 8 June 2022 the advice of the VBREWG was sought regarding the case reported to MHRA in May 2022, a previously well 36-year-old female from the UK who had died suddenly at home in June 2021, 11 days after receiving a first dose of the Pfizer/BioNTech (Comirnaty) vaccine. A Coroner's Inquest had been conducted in May 2022. A Yellow Card Report had not been submitted. The MHRA had not been invited to give evidence at the Inquest but obtained follow-up information from the Coroner and from the clinician involved. The Inquest recorded the cause of death as 1a. Acute Myocarditis and 1b. Recent Covid-19 immunisation.

688. The MHRA sought the advice of the VBREWG on this case and invited cardiology experts to advise on the strength of the evidence for a causal relationship between Covid-19 vaccines and the sudden death from acute myocarditis, what information should additionally be sought and whether it had any other comments or recommendations. [**JR/363 - INQ000494365**].

689. The VBREWG noted that cardiac pathology is a highly specialised field requiring expert analysis, which had not been undertaken in this case and should be sought. Full genetic, antimicrobial and molecular testing was recommended, including screening of the patient's family for possible inherited cardiac disorders. Overall, the VBREWG could not give definitive advice about causality due to the absence of key information. Follow-up information sought by the MHRA from an expert cardiac histopathologist, who examined retained samples, excluded the presence of myocarditis and recommended family screening for inherited cardiac disorders.

690. Further to this, on 23 June 2022, the MHRA sought the advice of the VBREWG [**JR/364 - INQ000409567**] on a Yellow Card report received from a healthcare professional describing a previously well adolescent male who had suffered a cardiac arrest while playing sport, five days after receiving a second dose of the Pfizer/BioNTech (Comirnaty) vaccine. The patient suffered a hypoxic brain injury due to the cardiac arrest and later died in hospital. All the available information was presented to the VBREWG.

691. The VBREWG, including invited cardiology experts, noted that the post-mortem examination and histopathology results were awaited and would be critical to understanding the cause of the cardiac arrest. It was important to collect clinical infection history, such as a history of diarrhoea, vomiting and fever. Overall, the VBREWG could give no definitive advice about causality given the lack of key information. Follow-up information later received from the Coroner indicated that the underlying cause of collapse was likely an inherited arrhythmia leading to out-of-hospital cardiac arrest. The Pfizer/BioNTech (Comirnaty) vaccine was not considered by the Coroner to have been the cause of death.

692. During the same meeting on 23 June 2022, the MHRA sought the advice of the VBREWG about Yellow Card reports, new literature and international data which had become available on the risk of myo/pericarditis associated with Covid-19 vaccines. The VBREWG noted that

reports of suspected myo/pericarditis remained very rare with all three Covid-19 vaccines deployed in the UK, although the conditions were more frequently reported with the mRNA vaccines. The advice of the VBREWG was sought on the stabilisation of reporting rates, and the similarity of rates between first and second doses with consistently lower rates seen after the third/booster dose.

693. In the UK on 23 June 2022, in the 18-29 year-old age group there were 26, 29 and 17 reports per million doses of Pfizer/BioNTech (Comirnaty) vaccine associated with the first, second and third doses respectively, 61, 69 and 21 reports per million doses of Moderna (Spikevax) vaccine, associated with the first, second and third doses respectively; and 10 and 16 reports per million doses of AstraZeneca (Vaxzevria) vaccine associated with the first and second dose respectively. In the 20-39 year-old age group there were 23, 24 and 16 reports per million doses of Pfizer/BioNTech (Comirnaty) vaccine associated with the first, second and third doses respectively; 59, 54 and 21 reports per million doses of Moderna (Spikevax) vaccine, associated with the first, second and third doses respectively; and 14 and 12 reports per million doses of AstraZeneca (Vaxzevria) vaccine associated with the first and second dose respectively. International data suggested a similar pattern [**JR/365 – INQ000507362**]. The VBREWG noted that the limited available data on long-term outcomes in the Yellow Card reports had not indicated any long-term consequences from myo/pericarditis, however the MHRA would keep long-term outcomes under review.

694. At this same meeting on 23 June 2022, the MHRA also sought advice from the VBREWG on new international data regarding the Novavax (Nuvaxovid) vaccine including post-marketing reports of suspected myo/pericarditis associated with the vaccine. Novavax (Nuvaxovid) had been approved on 3 February 2022, but it had not yet been deployed in the UK at the time of the VBREWG meeting. The signal had been first raised in Australia and pericarditis had been added to the Australian Novavax (Nuvaxovid) Covid-19 product information as a possible adverse reaction. The advice of the VBREWG was also sought regarding the EU PRAC's commencement of a review of myo/pericarditis associated with the Novavax (Nuvaxovid) vaccine and the fact that the US FDA had also identified myo/pericarditis as a potential risk.

695. The VBREWG was informed that the MHRA had requested a review of myo/pericarditis associated with the Novavax (Nuvaxovid) vaccine from the manufacturer and that this issue

would be brought to the VBREWG for advice once the data became available. During this meeting it was agreed that routine updates to the VBREWG on myocarditis and pericarditis associated with Covid-19 vaccines were no longer required. There would instead be a focused assessment of reports of interest and any significant new data would be presented to the group.

696. On 22 July 2022, the VBREWG's advice was sought on a new pre-print article authored by the US CDC [**JR/366** - INQ000409568], which provided comments on the article previously presented to the VBREWG on 18 February 2022. The original article had described the clinical and autopsy investigations of two teenage boys in the USA who died shortly after receiving the second dose of the Pfizer/BioNTech (Comirnaty) vaccine (discussed at paragraph 685). The authors had concluded that both patients had myocardial injury considered to be a post-vaccine reaction resembling a catecholamine-mediated stress or toxic cardiomyopathy. At its meeting in February 2022 the VBREWG had considered that the article contained limited detail on some aspects and seemed to lack expert cardiac histopathology input, recommending that further information should be sought from the FDA and authors.

697. The later article described the CDC's involvement in post-mortem testing in the two cases and highlighted test results not included in the original article. The CDC concluded that one of the patients had evidence of parvovirus B-19 infection in the heart tissue, stopping short of identifying this as the cause of death but highlighting its relevance in the differential diagnosis, while the second patient died from Clostridium septicum sepsis. The VBREWG was asked to comment on the latest article and offer any additional observations. The VBREWG expressed concerns that the original article omitted key data. Overall, the VBREWG advised that there were alternative causes for cardiac pathology in both the US cases and that no further regulatory action was warranted.

698. In the same meeting on 22 July 2022, the MHRA sought the advice of the VBREWG on a review of suspected myo/pericarditis reported in association with the Novavax (Nuvaxovid) vaccine, including the EU PRAC's assessment. The manufacturer's review and their observed versus expected analysis were also considered. The VBREWG advised that there was insufficient evidence to take regulatory action regarding the potential risk of myo/pericarditis in association with the Novavax (Nuvaxovid) vaccine; however, the issue should continue to be kept under close review.

699. On 25 August 2022, the advice of the VBREWG was again sought on suspected myocarditis and pericarditis associated with the Novavax (Nuvaxovid) vaccine [**JR/367** - **INQ000409543**]. The Novavax (Nuvaxovid) vaccine has been used very little in the UK (only 26 first doses had been administered by September 2022) and therefore no characterisation of the risk of suspected myocarditis per dose (i.e. first, second or booster) was undertaken. However, the advice of the VBREWG was sought on an updated review including the EU PRAC's updated assessment of the issue.

700. The EU PRAC had recommended that EU product information for the Novavax (Nuvaxovid) vaccine should be updated to include a warning about myocarditis and/or pericarditis and to list myocarditis and pericarditis as undesirable effects associated with Novavax (Nuvaxovid). The VBREWG also noted that a warning about myo/pericarditis was already included in the US product information for Novavax (Nuvaxovid) vaccine and that pericarditis was listed as an adverse reaction from post-marketing experience in the product information for the Novavax (Nuvaxovid) vaccine in Australia and New Zealand.

701. The VBREWG considered the evidence on whether to align the GB product information for Novavax (Nuvaxovid) with the EU and other regulators. At that time, Novavax (Nuvaxovid) was not being deployed in the UK. The VBREWG advised that currently there was no evidence on the risk of myo/pericarditis associated with a booster dose of Novavax (Nuvaxovid) vaccines in patients who had previously experienced myo/pericarditis associated with an mRNA Covid-19 vaccine. The VBREWG also advised that Novavax should also be asked what procedures or analyses they were undertaking in relation to investigating potential mechanisms for myo/pericarditis with their vaccine.

702. Taking all the evidence into account, the VBREWG advised that the available data supported updating the Novavax (Nuvaxovid) vaccine product information, in line with the EU PRAC's proposed update to EU product information, to include a warning about the risk of myocarditis and pericarditis and to list myocarditis and pericarditis as adverse reactions. The VBREWG also agreed that the benefit risk balance of Novavax (Nuvaxovid) vaccine remained positive.

703. On 20 September 2022, the MHRA sought the advice of the VBREWG about an EU variation to update the Pfizer/BioNTech (Comirnaty) product information concerning myo/pericarditis [**JR/368** - **INQ000409544**]. The EU variation had been submitted to the MHRA via the EC decision reliance procedure. The VBREWG heard that, to reflect the current state of the evidence with regards to the known adverse events 'myocarditis' and 'pericarditis', several updates had been made to the EU product information. In particular, the sentence: "*The risk of myocarditis after a third dose of Comirnaty has not yet been characterised*" had been removed from the Summary of Product Characteristics as this was no longer the case. This change was supported by the company's analysis of US spontaneous reports, showing a lower rate of myo/pericarditis associated with booster doses than primary doses, and of US electronic health records, showing that the reporting rate was lower associated with booster versus primary doses in homologous regimens (heterologous Comirnaty regimens had not been widely used in the US) [**JR/369** **INQ000507342**] [**JR/370** - **INQ000507341**]

704. The company Pfizer/BioNTech also reviewed spontaneous data from Israel and the Netherlands and found a lower risk of myo/pericarditis with booster doses than with the primary vaccination. In addition to the removal of the statement on booster doses, the following sentence had been included in section 4.8 (undesirable effects) of the Summary of Product Characteristics: 'Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years. This change was supported by published CDC analyses of spontaneous and electronic health record data and by US literature articles. No concerns were raised by the VBREWG, and it was agreed that the reliance procedure variation was approvable.

705. During the same meeting on 20 September 2022, the VBREWG advised on a variation submitted via the EC decision reliance procedure to introduce a homologous and heterologous booster dose in individuals aged 18 years and older for the Novavax (Nuvaxovid) vaccine. The VBREWG was advised that a study on booster doses reported that adverse reactions occurred at higher frequencies after a booster dose of Novavax (Nuvaxovid) compared with after the primary vaccination. This reactogenicity profile remained within that seen with other Covid-19 vaccines and was reflected in the updated SmPC. The VBREWG was informed that a variation had been submitted to update the product information for the Novavax (Nuvaxovid) vaccine and the Novavax (Nuvaxovid) RMP to include a warning about

the risk of myocarditis and pericarditis and include these as adverse reactions in the product information.

706. The VBREWG advised that in light of the increased reactogenicity seen with a third dose of Novavax (Nuvaxovid) the RMP updates should consider the need to characterise whether there was any increased risk of myocarditis/pericarditis with a third dose. The RMP was updated via the reliance route to reclassify the risk of myocarditis/ pericarditis from an important potential risk to an important identified risk, and state that risk characterisation of myo/pericarditis will continue to be evaluated in PSURs as post-marketing data are received, including observed versus expected analyses of suspected myo/pericarditis associated with the Novavax (Nuvaxovid) vaccine by dose.

707. Between November 2022 and October 2023, the MHRA published information for the Pfizer/BioNTech (Comirnaty) vaccine, the Moderna (Spikevax) vaccine and the Novavax (Nuvaxovid) vaccine in relation to myocarditis and pericarditis via the GOV.UK website as follows:

a. 9 November 2022 - Pfizer/BioNTech (Comirnaty) vaccine: product information updated on myocarditis and pericarditis after a third dose and in the age group 5-11 years **[JR/371- INQ000507343**.
b. 29 November 2022 - Pfizer/BioNTech (Comirnaty) vaccine: Drug Safety Update bulletin highlighting the above changes to product information having been made to reflect the most up-to-date information about these known side effects [**JR/189-INQ000468831**].
c. 9 November 2022 - Novavax (Nuvaxovid) vaccine: warning for myo/pericarditis in the product information [**JR/372 - INQ000507360**.
d. 9 December 2022 – Moderna (Spikevax) vaccine: amendment to text for the SmPC on myocarditis/pericarditis [**JR/373 - INQ000507344**.
e. 15 September 2023 – Moderna (Spikevax) vaccine: updates to product information on myocarditis and pericarditis [**JR/374 - INQ000408426**.

708. I am asked about utilisation of the four 'pillars' of the MHRA's Covid-19 vaccine vigilance/surveillance strategy, as described earlier, in relation to the myo/pericarditis safety signal. Enhanced passive surveillance, rapid cycle analysis and ecological analysis and formal epidemiological studies were utilised in combination in respect of the myo/pericarditis

signal (the first, second and fourth pillars). There was minimal use of Yellow Card Vaccine Monitor data in respect of the myo/pericarditis safety signal because the YCVM dataset was not suited to study this type of rare adverse reaction for the same reasons set out at paragraph 510-513 in relation to TTS.

Anaphylaxis

709. Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset. Severe anaphylaxis is characterised by potentially life-threatening failure of the circulation and breathing which may result in death if not treated as a medical emergency. In the Covid-19 vaccine clinical trials, no signals for anaphylaxis were identified. Nevertheless, due to anaphylaxis being a known but very rare side effect with any vaccine, the product information for all four vaccines included warnings for healthcare professionals and vaccine recipients about the potential risk of anaphylactic events and the actions to be taken if anaphylaxis was suspected.

710. On 8 December 2020, the first day of the Covid-19 vaccination campaign, the MHRA received two reports of suspected anaphylaxis and one of a suspected allergic reaction associated with administration of the Pfizer/BioNTech (Comirnaty) vaccine [**JR/375 - INQ000494268**].

711. On 9 December 2020, an urgent meeting of the VBREWG was convened to review the available evidence of the risk of anaphylaxis associated with the Pfizer/BioNTech (Comirnaty) vaccine and the appropriate risk management advice [**JR/376 - INQ000494378**]. In attendance were MHRA representatives, experts in allergy and clinical immunology and the medical directors from the hospitals where the cases had occurred. Having reviewed the 3 cases, it was concluded there was a causal association between the events and the Pfizer/BioNTech (Comirnaty) vaccine. Drawing a causal relationship in the case of anaphylaxis is in most cases more straightforward than other suspected ADRs due to the proximity in time of the vaccine and nature of the reaction.

712. As a result of the 3 cases of anaphylaxis in association with the Pfizer/BioNTech (Comirnaty) vaccine, an updated warning was sent to the NHS and a press release was issued by the MHRA to advise that vaccine recipients should be monitored for 15 minutes after

vaccination, with a longer observation period when indicated by clinical assessment [**JR/377 - INQ000494266**].

713. The VBREWG suggested that the cases of anaphylaxis may have been caused by a pre-existing allergy to polyethylene glycol (PEG), which is an excipient of the Pfizer/BioNTech (Comirnaty) vaccine. The VBREWG advised that healthcare professionals may be unaware of PEG allergies and may not be able to recognise PEG from the list in the product information as it was currently published. Therefore, the VBREWG advised that the product information for the Pfizer/BioNTech (Comirnaty) vaccine should be strengthened to ensure that the description of the PEG content was simplified and clarified to enable healthcare professionals to recognise it more easily as an ingredient of the vaccine. Further, the VBREWG advised that use of the Pfizer/BioNTech (Comirnaty) vaccine should be avoided in people with a known PEG allergy.

714. Following the provision of this advice, on 9 December 2020, the MHRA published a press release on GOV.UK to warn of the risk of anaphylaxis and to advise against the use of the vaccine in any person with a history of anaphylaxis to a vaccine, medicine or food, or who had experienced anaphylaxis associated with administration of the first dose of the vaccine, and setting out the reports of suspected anaphylaxis and the guidance issued to vaccination centres on managing allergic reactions associated with vaccination with the Pfizer/BioNTech (Comirnaty) vaccine [**JR/378 -** INQ000469446

715. On 10 December 2020, the GB product information for healthcare professionals and for recipients of the Pfizer/BioNTech (Comirnaty) vaccine was updated to include a contraindication for those with hypersensitivity to the active substance or to any of the excipients (including PEG). Special warnings and precautions for use were also added for individuals with a history of immediate-onset anaphylaxis to a vaccine, medicine, or food and those who had experienced anaphylaxis to the first dose of a Covid-19 mRNA vaccine [**JR/379 - INQ000468833**; **JR/380 - INQ000468834**].

716. On 17 December 2020, the MHRA sought the advice of the VBREWG on the latest reports of suspected anaphylactic reactions associated with the Pfizer/BioNTech (Comirnaty) vaccine, taking into account the incidence of suspected anaphylactic reactions reported in association with flu vaccines [**JR/381 -** INQ000400234. The VBREWG advised that

individuals who had only mild adverse reactions associated with their first dose should still receive their second dose and that the post-dose monitoring for these individuals should be increased to half an hour.

717. On 22 December 2020 [**JR/382 -** INQ000400235 , the MHRA sought advice from the VBREWG on the previous warning which had been issued on 9 December against use of the Pfizer/BioNTech (Comirnaty) vaccine in patients with food allergies. The VBREWG noted that there was little evidence for increased susceptibility to anaphylactic adverse reactions in this population, and that advising against the use of the vaccine in those with food allergies may have an adverse impact on vaccine uptake. The VBREWG therefore advised that patients with food allergies should not be excluded from taking the vaccine. In contrast patients with a history of allergy to PEG must avoid the vaccine. The VBREWG noted that the available data did not indicate an increased risk in those with a history of allergies to other vaccines, foods, or medicines and therefore, advice could be updated.

718. On 31 December 2020, the MHRA updated the regulation 174 information for the Pfizer/BioNTech (Comirnaty) vaccine for UK healthcare professionals [**JR/383 - INQ000468835**] and UK recipients [**JR/384 - INQ000468836**] to the below:

> "***4.4 Special warnings and precautions for use***
>
> ***Hypersensitivity and anaphylaxis***
> *Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.*
>
> *Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of the COVID-19 mRNA Vaccine BNT162b2.*"

719. The information for recipients of the Pfizer/BioNTech (Comirnaty) vaccine was revised to include:

> "***2. What you need to know before you receive COVID-19 mRNA Vaccine BNT162b2***

COVID-19 mRNA Vaccine BNT162b2 should not be given

- *if you are allergic to the active substance or any of the other ingredients of this medicine, listed in section 6. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue. Contact your doctor or healthcare professional immediately or go to the nearest hospital emergency room right away if you have an allergic reaction. It can be life-threatening.*

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if you have:

- *ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given COVID-19 mRNA Vaccine BNT162b2 in the past.*"

720. The MHRA's Drug Safety Update monthly electronic bulletin for healthcare professionals of 6 January 2021 included a summary of the current advice for the Pfizer/BioNTech (Comirnaty) vaccine relevant to anaphylaxis (referred to as allergies/allergic reactions) [**JR/187 - INQ000468825**]. On 7 January 2021, the MHRA also published on the GOV.UK website the summary of current advice relevant to anaphylaxis for the Pfizer/BioNTech (Comirnaty) vaccine and the AstraZeneca (Vaxzevria) vaccine.

721. The information for recipients of the AstraZeneca (Vaxzevria) vaccine, relevant to anaphylaxis, at this time was as follows:

"***2. What you need to know before you receive COVID-19 Vaccine AstraZeneca***

Do not have the vaccine:

If you have ever had a severe allergic reaction to any of the active substances or any of the other ingredients listed in section 6.

Warnings and precautions

Tell your doctor, pharmacist or nurse before vaccination:

- *If you have ever had a severe allergic reaction (anaphylaxis) after any other vaccine injection*"

722. On 13 January 2021, the MHRA sought the advice of the VBREWG on a further review of the risk of anaphylaxis associated with the Pfizer/BioNTech (Comirnaty) vaccine and Moderna (Spikevax) vaccine [**JR/375 - INQ000494268**; **JR/385 - INQ000494344**]. As of 7 January 2021, the MHRA had received a total of 29 reports of suspected anaphylaxis associated with the administration of the Pfizer/BioNTech (Comirnaty) vaccine, none of which had a fatal outcome. The VBREWG was reassured that the incidence of suspected anaphylaxis associated with the Pfizer/BioNTech (Comirnaty) vaccine remained similar to that previously reported and agreed that the 15-minute observation period should be maintained.

723. There had been no post-approval use of the Moderna (Spikevax) vaccine in the UK at this point, and clinical trial data did not indicate evidence of anaphylaxis occurring with the vaccine.

724. As a precaution, similar warnings to the Pfizer/BioNTech (Comirnaty) vaccine were included in the product information for Moderna (Spikevax) vaccine, given that these were both vaccines from a similar mRNA platform.

725. On 29 January 2021, the advice of the VBREWG was sought again on the risk of anaphylaxis associated with the Covid-19 vaccines [**JR/386 - INQ000494345**]. A total of 14 reports of suspected anaphylactic reactions associated with the AstraZeneca (Vaxzevria) vaccine had been reported to the MHRA, most of lesser severity than reactions associated with the Pfizer/BioNTech (Comirnaty) vaccine. Only a small proportion of the suspected anaphylaxis reports associated with the AstraZeneca (Vaxzevria) vaccine were of immediate onset associated with vaccination. Up to 31 January 2021, an estimated 6.6 million first doses of the Pfizer/BioNTech (Comirnaty) vaccine and 3 million doses of the AstraZeneca (Vaxzevria) vaccine had been administered [**JR/302 - INQ000421355**].

726. During the same meeting, the advice of the VBREWG was sought on Yellow Card reports of suspected anaphylaxis associated with the Pfizer/BioNTech (Comirnaty) vaccine [**JR/387 - INQ000494271**]. The MHRA informed the VBREWG that up to 25 January 2021, there was a reporting rate of 1.8 suspected adverse reactions with symptoms related to anaphylaxis or hypersensitivity per 100,000 doses administered, and that none of the adverse reactions for any of the vaccines had fatal outcomes. The Moderna (Spikevax) vaccine was still not yet

being used in the UK, but US CDC data suggested an estimate of 2.5 cases of anaphylaxis per million doses.

727. The VBREWG was informed that the UK Risk Management Plan (RMP) for the Pfizer/BioNTech (Comirnaty) vaccine did not currently include anaphylaxis as an important identified risk, but that this was included in the EU RMP, which had been authorised after the UK's authorisation of this vaccine. The VBREWG advised that the UK RMP for Pfizer/BioNTech (Comirnaty) vaccine should be updated to include anaphylaxis as an important identified risk, bringing the information in line with the warnings in the EU SmPC and with the EU RMP. This was updated on 29 April 2021 by the MHRA, and the documents are exhibited as: [**JR/388 - INQ000494298**].

728. On 23 February 2021, regulation 174 information for UK healthcare professionals and information for UK recipients for the AstraZeneca (Vaxzevria) vaccine was also updated to list anaphylaxis as an ADR (frequency not known) [**JR/389 - INQ000468845**; **JR/390 - INQ000468846**].

729. On 31 March and 5 July 2021, the advice of the VBREWG was sought regarding the latest available data on anaphylaxis and in particular, the review of the 15-minute observation time following administration of mRNA vaccines [**JR/391 - INQ000494286**; **JR/392 - INQ000409520**]. The VBREWG considered advice including an assessment by NHS England of their perspective of the 15-minute observation period including infection control concerns and concomitant administration of Covid-19 vaccine with flu vaccine [**JR/393 - INQ000494305**; **JR/344(a) - INQ000409530**]

730. The VBREWG considered that NHS England should collect further data to support an evidence-based review of the 15-minute observation period requirement and advised that the MHRA should continue to review reports of suspected anaphylaxis for all the Covid-19 vaccines. The VBREWG advised that in the meantime, no changes to the SmPC advice on the observation period should be made.

731. On 17 September 2021, the advice of the VBREWG was sought on the PHE's proposal to update Green Book advice to remove the requirement for the 15-minute observation time for homologous booster doses of the Pfizer/BioNTech (Comirnaty) vaccine and Moderna

(Spikevax) vaccine for patients who had not experienced any suspected allergic reactions associated with the first and second doses [**JR/394 - INQ000409535**]. The Green Book has the latest information on vaccines and vaccination procedures in the UK for vaccine preventable infectious diseases. It was noted that suspending the observation period would speed up the delivery of third doses of Covid-19 vaccines and of flu vaccines.

732. The MHRA presented Yellow Card data and data available from Israel on the reporting rates of suspected anaphylaxis associated with first, second and third/booster doses [**JR/395 - INQ000494314**]. The VBREWG concluded that for those receiving a homologous booster dose of an mRNA vaccine who had not experienced an allergic reaction or anaphylaxis with the primary doses, the requirements for the 15-minute observation period could be removed, including for third doses for immunocompromised patients. However, for those receiving a heterologous third or booster dose of an mRNA vaccine (which effectively meant that they were receiving an mRNA vaccine for the first time), the requirement for a 15-minute observation should be retained.

733. On 13 December 2021, the MHRA sought advice from the CHM on the benefits of suspending the observation period for all Covid-19 vaccines in light of the rapid spread of the Omicron variant [**JR/396 – INQ000507340**]. The CHM also heard from NHSE on the impact of the 15-minute observation period on operational aspects of the Covid-19 vaccination programme in England [**JR/397 - INQ000494320**]. The NHSE analysis showed that removing the 15-minute observation time could result in a 23% improvement of the throughput of vaccinations for hospital hubs, pharmacies and vaccine centres, which increased to 42-65% in Primary Care Networks (PCNs), such as small surgeries and pharmacies. The NHSE also highlighted that the suspension of the 15-minute observation time would increase efficiency in housebound vaccinations, freeing up resources for elsewhere in PCNs, and increased accessibility of vaccination to other vulnerable patients.

734. The CHM recognised the public health importance of rapidly increasing the number of booster vaccinations in the context of the rapid spread of the Omicron variant and advised temporarily suspending the 15-minute observation period for all the Covid-19 vaccines, but that the MHRA should keep reports of suspected anaphylaxis under close review. The CHM advised that the temporary suspension would be best implemented by changes to vaccination policy rather than through changes to product information. The CHM also highlighted that

robust data would need to be collected to inform future decisions on the 15-minute observation period for subsequent doses in the Covid-19 vaccination programme.

735. As a result of the CHM's advice, on 14 December 2021 the MHRA issued a press release stating that during the emergency response to the Omicron variant, the 15-minute observation period would be waived for the Pfizer/BioNTech (Comirnaty) vaccine and for the Moderna (Spikevax) vaccine for most people (excluding those with a history of allergies), because the benefits of vaccinating people as efficiently as possible outweighed the very small risks of anaphylaxis [**JR/398 - INQ000468847**]. The MHRA also updated its website on the same date with a prominent statement that the 15-minute observation period following vaccination with the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine would be temporarily suspended [**JR/399 - INQ000468848**; **JR/400 - INQ000468851**]. There was also an article explaining the advice in the MHRA's Drug Safety Update bulletin on 6 January 2022 [**JR/401 - INQ000468827**].

736. On 13 January 2022, further advice from the VBREWG was sought on national and international data on reports of suspected anaphylaxis associated with Covid-19 vaccines [**JR/402 - INQ000494322**; **JR/356 - INQ000494357**]. The VBREWG was informed that Ireland had taken similar action in suspending the 15-minute observation period to enable a quicker rollout of the vaccines in response to the Omicron variant, while retaining the 15-minute observation period for primary doses and those with a history of anaphylaxis. The VBREWG was informed by NHS England that the ambulance service had not seen an increase in callouts for anaphylaxis following vaccination and that the temporary suspension of the observation time had allowed increased throughput at vaccination centres resulting in more people receiving their booster vaccine. The VBREWG advised that the temporary suspension of the 15-minute observation period should be maintained. During the same meeting, the VBREWG considered that while children were not expected to be at an increased risk of anaphylaxis compared to adults, a further review should be undertaken before a decision to suspend the observation period for 5–11-year-olds was made.

737. Following this advice, on 19 January 2022, the MHRA sought the advice of the VBREWG on the available Yellow Card and international data on suspected anaphylaxis in 5-11-year-olds associated with the Pfizer/BioNTech (Comirnaty) vaccine [**JR/403 - INQ000494323**; **JR/404 - INQ000409538**]. There had been extremely limited exposure in this age group in the

UK, with only 250 exposures for the Pfizer/BioNTech (Comirnaty) vaccine in 5–11-year-olds by 19 January 2022, and only 16 Yellow Card reports in this age group had been received in total, none of which reported anaphylaxis. International data indicated that anaphylaxis was very rare in this age group, with lower reporting rates compared to the overall population. The VBREWG advised that, as the risk of anaphylaxis in 5-11-year-olds associated with the Pfizer/BioNTech (Comirnaty) vaccine was very small, the suspension of the 15-minute observation period could also apply to this age group. The VBREWG highlighted that this suspension should remain under close review.

738. On 4 February 2022, the MHRA sought the advice of the VBREWG on a 'Summary of Yellow Card reporting' update on suspected anaphylaxis since the introduction of the temporary suspension of the observation period [**JR/405 - INQ000494324**; **JR/360 - INQ000494358**]. The VBREWG considered this summary alongside international data and other data presented by UKHSA and NHS England. The VBREWG considered the data to be reassuring and supported permanently suspending the 15-minute observation period and the risk-based approach detailed in the Green Book for those 12 years and older for all authorised Covid-19 vaccines and for all doses including primary vaccination. It was recommended that the advice in the Green Book could be clarified accordingly. The UKHSA agreed to consider this clarification. The VBREWG noted that this would remain a public health policy decision rather than a regulatory change in the product information for the Covid-19 vaccines.

739. On 5 May 2022, the MHRA communicated via its website the permanent suspension of the 15-minute observation period for those aged 12 years and older and who had no history of a severe allergic reaction for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine. These changes were also published in an MHRA Drug Safety Update bulletin on 10 May 2022: [**JR/406 - INQ000468828**]. The MHRA reiterated that the temporary suspension of the 15-minute observation period for 5-11-year-olds remained in place and would be reviewed on a regular basis.

740. On 20 September 2022, the MHRA sought the advice of the VBREWG on suspected anaphylaxis reports in 5–11-year-olds following the temporary suspension of the 15-minute observation period [**JR/407 - INQ000494337**; **JR/408 - INQ000409544**]. The VBREWG reviewed the data available and concluded that the incidence of anaphylaxis in 5-11-year-olds was low and that the temporary suspension of the 15-minute observation period had not led

to an increased risk. The VBREWG advised that the temporary suspension of the 15-minute observation period in 5-11-year-olds should become a permanent suspension, as previously advised for those aged 12 years and older. This change was communicated through the Green Book and remains reflected in the 20 February 2024 publication [**JR/178 - INQ000468861**].

Menstrual Disorders

741. Menstrual disorders can be categorised as unexpected vaginal bleeding including symptoms such as heavier than usual periods, heavy and/or painful periods, delayed periods or post-menopausal bleeding. Menstrual disorders are extremely common, and stressful life events can disrupt menstrual periods. As such, there is no specific record of the expected background rate of menstrual disorders in the general population. Changes to the menstrual cycle have been reported associated with infection with Covid-19 and in people affected by long-Covid.

742. Menstrual disorders, as an umbrella term for the above symptoms, was not included in the list of AESIs prepared by the MHRA to inform the creation of initial RMPs for the Covid-19 vaccines. As with all suspected ADRs associated with Covid-19 vaccines, menstrual disorders, once reported, were kept under review by the MHRA. However, given the lack of available background rate data, observed versus expected analysis was not possible.

743. In January 2021, reports of irregular menstrual bleeding soon after receiving the Pfizer/BioNTech (Comirnaty) vaccine triggered an MHRA review of Yellow Card reports related to any abnormal menstrual bleeding in association with the Pfizer/BioNTech (Comirnaty) vaccine [**JR/409 - INQ000494380**]. As of 20 January 2021, 243 reports of bleeding were identified, including 58 reports of irregular bleeding related to menstrual bleeding. On 27 January 2021, this review was discussed at an MHRA signal detection meeting, where it was agreed to continue to monitor for further reports and to follow up some of the menstrual bleeding reports to determine how long it had taken for the abnormal bleeding to settle. [**JR/410 - INQ000494379**].

744. On 4 June 2021, the advice of the VBREWG was sought on the evidence related to menstrual disorders and the Covid-19 vaccines [**JR/270 - INQ000409527**]. Since January

2021, the number of Yellow Card reports of menstrual disorders received associated with the Covid-19 vaccines had increased alongside the usage of the vaccines. Recent media reports reported unusually heavy periods associated with the Moderna (Spikevax) vaccine. The MHRA presented an assessment of clinical trial data and UK Yellow Card data for the AstraZeneca (Vaxzevria) vaccine, Pfizer/BioNTech (Comirnaty) vaccine and Moderna (Spikevax) vaccine alongside written comments received from members of the CHM's Medicines for Women's Health Expert Advisory Group (MWHEAG). The MHRA also presented relevant media reports reporting menstrual disorders associated with the Covid-19 vaccines published in May and April 2021 [**JR/411 - INQ000494296**].

745. By 17 May 2021, the MHRA had received 2,734 Yellow Card reports of menstrual disorders associated with the AstraZeneca (Vaxzevria) vaccine, 1,158 reports associated with the Pfizer/BioNTech (Comirnaty) vaccine, and 66 reports associated with the Moderna (Spikevax) vaccine. The most frequent condition reported was heavy menstrual bleeding (making up 808 of the Yellow Card reports associated with the AstraZeneca (Vaxzevria) vaccine, 259 associated with the Pfizer/BioNTech (Comirnaty) vaccine, and 22 associated with the Moderna (Spikevax) vaccine). The number of reports received was considered low in relation to the usage of these vaccines in females: over 18 million total doses of AstraZeneca (Vaxzevria) vaccine, over 13 million total doses of the Pfizer/BioNTech (Comirnaty) vaccine and almost 124,000 doses of the Moderna (Spikevax) vaccine.

746. The types of adverse menstrual events most frequently reported were similar across the 3 vaccines and included heavy menstrual bleeding, vaginal haemorrhage, and menstrual disorders such as early, delayed, prolonged, missed, or irregular menstruation. Such disorders are commonly experienced in the population, although there were some reports of extremely heavy bleeding, accompanied by severe cramping and unusual clotting which were considered by the reporters as being highly unusual for them. It should be noted that few patients reported that they required hospitalisation or medical intervention for the reported events and therefore; while distressing and potentially disruptive to daily life, the majority of events appear not to have been serious.

747. In many Yellow Card reports, patients mentioned that they knew other women who had experienced similar issues, or they referred to articles in the mainstream media or on social media concerning the Covid-19 vaccine-related effects on menstruation. The VBREWG was

informed that the heightened media coverage was likely to have increased general awareness of the potential issue and stimulated increased reporting to the Yellow Card System. For example, the number of reports received for the Pfizer/BioNTech (Comirnaty) vaccine increased three-fold on the day the BBC published an article on this issue [**JR/411 - INQ000494296**].

748. The VBREWG advised that the then currently available evidence did not appear to support an association between menstrual disorders, postmenopausal haemorrhage and/or vaginal/uterine haemorrhage with the three vaccines reviewed. The VBREWG supported communicating the findings of this review in the MHRA coronavirus vaccine 'Summary of Yellow Card reporting' and advised that any communications should make it clear that the current evidence did not suggest that menstrual disorders are caused by the Covid-19 vaccines and that women should not delay seeking medical attention for menstrual disorders, when appropriate. The VBREWG advised that no regulatory action was required; however, reports of menstrual disorders associated with the Covid-19 vaccines should continue to be kept under close review.

749. On 10 June 2021, in line with the VBREWG advice, the MHRA published safety monitoring information about menstrual disorders in the 'Summary of Yellow Card reporting' [**JR/412 - INQ000421356**]. It stated that the current evidence did not suggest an increased risk of either menstrual disorders or unexpected vaginal bleeding in association with Covid-19 vaccines, but that the MHRA would continue to closely monitor reports of menstrual disorders and vaginal bleeding.

750. On 28 June 2021, the MHRA again sought the advice of the VBREWG on a review of menstrual disorders associated with the Covid-19 vaccines [**JR/413 - INQ000494304**]. It was noted by the VBREWG [**JR/414 - INQ000494350**] that there had been a large increase in the number of spontaneous reports of menstrual disorders received for all three of the Covid-19 vaccines deployed in the UK (the Pfizer/BioNTech (Comirnaty) vaccine, the AstraZeneca (Vaxzevria) vaccine and the Moderna (Spikevax) vaccine), since the meeting of 4 June 2021.

751. The VBREWG noted that the increase in the number of reports continued to correspond with publication of media reports of menstrual disorders associated with Covid-19 vaccines, which was considered possibly to represent stimulated reporting. It had been noted by the

MHRA that there were few reports of hospitalisation or medication intervention to stop bleeding. The VBREWG found that a causal association had not been established and advised that no regulatory action was required based on the available data.

752. The VBREWG requested that this issue should be brought back to a VBREWG meeting and that experts from the CHM's MWHEAG should be invited to contribute their expertise to the discussion. The VBREWG supported a planned MHRA review of CPRD data to try to determine background rates of reporting of menstrual disorders, particularly in younger women, while acknowledging that many women manage menstrual changes themselves rather than seeking advice from healthcare professionals and such cases would not be captured in any CPRD analysis.

753. On 9 July 2021, the MHRA published the coronavirus vaccine 'Summary of Yellow Card reporting' [**JR/415 - INQ000468841**]. This recorded 20,680 reports of varied menstrual disorders having been received following approximately 41 million Covid-19 vaccines administered. Advice was given in the report that anyone experiencing menstrual disorders and/or unexpected vaginal bleeding should seek medical advice.

754. On 19 July 2021, the MHRA sought the advice of the VBREWG on its proposed strategy for capturing further data on the incidence and nature of menstrual disorders associated with Covid-19 vaccines [**JR/247 -** INQ000409531 **]**. The VBREWG supported the MHRA's strategy and advised that it would be challenging to identify robust data and undertake analyses that could support a conclusion on whether a causal association between menstrual disorders and Covid-19 vaccines existed or not. However, the VBREWG agreed that there was a clear need to look at other data sources to better understand the absolute risk and the duration and severity of menstrual changes.

755. On 23 July 2021, the MHRA sought the advice of the VBREWG on a further review of the data on menstrual disorders associated with Covid-19 vaccines with invited experts and written expert comments [**JR/286 -** INQ000409532 . The VBREWG agreed that the latest available evidence did not support a causal association between the Covid-19 vaccines and menstrual disorders. The group noted that there are many reasons for menstrual irregularities, including stress and illness. Both Covid-19 infection and long Covid have also been reported to be associated with menstrual disorders. Possible mechanisms for the Covid-19 vaccines

affecting the menstrual cycle have been proposed, however the MHRA was not aware of specific studies carried out to investigate mechanisms and there was no evidence to confirm or refute a causal relationship.

756. The VBREWG highlighted the need for clear communication to emphasise the absence of evidence of a causal association with the vaccines, which is further discussed at paragraph 763 and that the menstrual changes being reported were usually short-lived and there was no evidence that these would affect a woman's fertility. The VBREWG requested a further update on the available data once the younger age groups had received a second dose of the vaccines.

757. On 26 July 2021, the CHM's MWHEAG was consulted on the available data on menstrual disorders associated with Covid-19 vaccines and was informed of the MHRA's previous reviews and the advice from the VBREWG [**JR/416 - INQ000494326**]. The MWHEAG agreed with the VBREWG position that the available evidence did not support a causal association between the Covid-19 vaccines and menstrual disorders and that there was no evidence for any negative effects on fertility. The MWHEAG advised that it was important to continue to investigate menstrual disorders and/or unexpected bleeding associated with Covid-19 vaccines. The MWHEAG agreed that the increase in reporting may relate in part to the media interest leading women to report pre-existing or previously dismissed menstrual problems.

758. The MWHEAG also advised on the importance of consistent messaging, which is discussed further at paragraphs 763 to 766 and recommended that the MHRA engage with women's advocacy groups such as the Women's Health Taskforce, the British Fertility Society and the British Society for Gynaecological Endoscopy. The MWHEAG suggested that information could also be cascaded through the Women's Voices Involvement Panel of the Royal College of Obstetricians and Gynaecologists. It agreed to review the data in a further 6 weeks.

759. On 1 August 2021, the MHRA's Drug Safety Update bulletin was published [**JR/417 - INQ000468844**]. The newsletter summarised information about the MHRA's review of reports of menstrual disorders and unexpected vaginal bleeding associated with Covid-19 vaccines. Healthcare professionals were asked to continue to report suspected side effects through the Yellow Card scheme and to encourage their patients to do the same.

760. On 31 August 2021, the MHRA sought the advice of the VBREWG on a paper outlining the latest data on menstrual disorders associated with Covid-19 vaccines [**JR418-INQ000494311**; **JR/419 - INQ000494352**]. As of 23 August 2021, the MHRA had received 11,918 Yellow Card reports of menstrual disorders associated with the AstraZeneca (Vaxzevria) vaccine, 12,426 Yellow Card reports associated with the Pfizer/BioNTech (Comirnaty) vaccine, and 1,685 Yellow Card reports associated with the Moderna (Spikevax) vaccine. These reporting rates remained low in the context of over 49.5 million doses of AstraZeneca (Vaxzevria) vaccine, 37 million doses of the Pfizer/BioNTech (Comirnaty) vaccine and 2.1 million doses of the Moderna (Spikevax) vaccine. Data were also presented regarding international reports of menstrual disorders associated with the Janssen (JCovden) vaccine, although this vaccine was not deployed in the UK.

761. The most frequently reported menstrual disorder remained heavy menstrual bleeding. The severity of cases received up to the data lock point of 23 August 2021 remained unchanged. No cases reported a fatal outcome, and across the categories of reported menstrual disorders, the outcome at the time of reporting was reported as recovered/recovering in 38% vaccine recipients overall.

762. The VBREWG considered written comments received from members of the CHM's MWHEAG. The VBREWG was also informed about recent MHRA communications which had aimed to provide clear and reassuring messages on menstrual disorders for the UK public and healthcare professionals. The VBREWG agreed that the updated review did not identify any new signals regarding menstrual disorders and unexpected vaginal bleeding associated with Covid-19 vaccines.

763. The VBREWG advised that it remained the case that a causal relationship between menstrual disorders and the four vaccines had not been established to date, and that no regulatory action was justified at that time based on the available evidence. The VBREWG advised that the MHRA should continue to keep this issue under close monitoring and that the issue should be brought back to future VBREWG meetings on an ad hoc basis as needed. The VBREWG supported the recent MHRA communications on menstrual disorders and Covid-19 vaccines, and on Covid-19 vaccines in relation to fertility. The VBREWG advised that reassuring messages should continue to be communicated and that current advice should

be reiterated to healthcare professionals such as GPs and midwives to help ensure that key messages were communicated to vaccine recipients.

764. On 24 September 2021, the MHRA sought the advice of the VBREWG about ongoing and planned epidemiological studies and also on an increase in reporting of menstrual disorders associated with Covid-19 vaccines after a British Medical Journal editorial published on 16 September 2021 was followed by widespread media coverage [**JR/253 - INQ000494353**]. The VBREWG agreed that the increase in Yellow Card reporting was likely to have been stimulated by the BMJ article and media coverage and did not raise any new concerns. Additionally, as recommended by the VBREWG, the MHRA had continued to work on reassuring messaging regarding menstrual disorders associated with Covid-19 vaccines on social media.

765. Specifically, the MHRA had created a set of key messages for the UK public and healthcare professionals outlining the latest evidence and advice on menstrual disorders, pregnancy and Covid-19 vaccines [**JR/418 - INQ000494311**]. The MHRA had also engaged with specific individuals and organisations that could cascade the information to target audiences including media medical professionals, leading fact-checking sites, and the Royal College of Obstetricians and Gynaecologists. The VBREWG advised that communicating data on pregnancy outcomes in women who were vaccinated prior to pregnancy would be helpful to allay public concerns about potential effects of Covid-19 vaccines on fertility. The VBREWG was reassured that data sources that may capture these data were being explored by the MHRA.

766. On 18 March 2022, the MHRA sought the advice of the VBREWG on the available evidence from UK Yellow Card reporting, spontaneous data from the Netherlands, new published and pre-print studies on menstrual disorders and a new study on fertility associated with Covid-19 vaccines [**JR/420 -** **INQ000409539** An exploratory analysis using linked Secondary Users Service/CPRD data in England was presented. The VBREWG also considered written comments from members of the CHM's MWHEAG. The VBREWG noted various factors and concluded that there were no consistent trends in the study data, for example, both heavy menstrual bleeding and delayed or light bleeding associated with the Covid-19 vaccines were reported. The VBREWG concluded that the available evidence

continued not to support a causal link between menstrual disorders and unexpected vaginal bleeding and Covid-19 vaccines, and therefore no regulatory action was advised.

767. On 18 November 2022, the attention of the VBREWG was drawn to the EU PRAC's recommendation that heavy menstrual bleeding should be added to the product information for Pfizer/BioNTech (Comirnaty) vaccine and Moderna (Spikevax) vaccine as an undesirable effect of unknown frequency JR/421(b) - INQ000409545 This was based on the PRAC conclusion following their most recent review of this issue that there was at least a reasonable possibility that the occurrence of heavy menstrual bleeding was causally associated with these Covid-19 vaccines.

768. The MHRA presented to the VBREWG an updated review of Yellow Card data for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine including UK usage and data in the PRAC assessment reports which had not previously been considered by the VBREWG: new published literature, manufacturer observed versus expected analyses (performed with background incidence rates 9.3 per 1,000 person years for females aged 10-59 years old based on a study in the Netherlands that included females who consulted their general practitioner for heavy menstrual bleeding between 2004 and 2013) and updated reviews of clinical trial data and serious reports of heavy menstrual bleeding) JR/422(a) **INQ000494341**].

769. The VBREWG maintained its advice that the available evidence did not support a causal relationship between the Covid-19 vaccines and menstrual disorders. The VBREWG noted that the PRAC agreed product information wording for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine included a descriptive statement that most cases appeared to be non-serious and temporary in nature. The VBREWG advised that the MHRA should consider adding heavy menstrual bleeding to GB product information, and if possible, to include a statement in the patient leaflet that there is no evidence of any negative impact of the Covid-19 vaccines on fertility.

770. The VBREWG also suggested that the MHRA should consider whether there was a need for an updated review of reports of heavy menstrual bleeding in association with the AstraZeneca (Vaxzevria) vaccine. The MHRA concluded that an updated review of heavy menstrual bleeding and AstraZeneca (Vaxzevria) vaccine was not justified at the present time,

as the latest review had not identified any new concerns. This was in line with the EMA which also had not identified a signal for heavy menstrual bleeding in association with the AstraZeneca (Vaxzevria) vaccine [**JR/423 - INQ000494362**; **JR/424 – INQ000494361**].

771. On 24 and 25 November 2022, the MHRA sought the advice of the CHM on the available evidence regarding the Covid-19 vaccines and association with heavy menstrual bleeding [**JR/425 -** INQ000494342]; **JR/426 -** INQ000409563]. The CHM was reassured that the data indicated that heavy menstrual bleeding associated with the Covid-19 vaccines was mainly non-serious and temporary in nature. It advised that while the evidence for a causal association was not conclusive, the data may suggest a possible link between the Moderna (Spikevax) vaccine and the Pfizer/BioNTech (Comirnaty) vaccine and heavy menstrual bleeding. The CHM agreed that heavy menstrual bleeding should be added as an undesirable effect to the product information for the Pfizer/BioNTech (Comirnaty) vaccine and the Moderna (Spikevax) vaccine and endorsed aligning with the PRAC agreed wording. The CHM cautioned that the update should be clear in its communication that it was a warning regarding heavy menstrual bleeding and not on adverse effects on fertility.

772. On 9 December 2022, the SmPC for the Pfizer/BioNTech (Comirnaty) vaccine was updated [**JR/427 - INQ000468842**] to include: "heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)" as an adverse reaction (frequency not known). At the time of the addition of this information to the SmPC, fewer younger women of menstruating age were being vaccinated due to changes in JCVI advice on who should receive the vaccine.

773. On 14 December 2022, the SmPC for the Moderna (Spikevax) vaccine was updated [**JR/428 - INQ000468843**] to include: "heavy menstrual bleeding" as an adverse reaction (frequency not known).

Alleged risks

774. The Inquiry has asked about alleged risks associated with the Covid-19 vaccines which have been positively disproved by clinical research or otherwise. It should be noted that it is often difficult to definitively disprove alleged vaccine-associated risks. Early on in the evolution

of a safety signal, a conclusion may often be drawn that a lack of robust evidence exists in support of a causal association, but this changes over time as the MHRA continues to monitor the issue for additional information.

775. In the context of pharmacovigilance processes, the MHRA generally uses the term safety 'signals', in line with EU law, rather than 'alleged risks'. Signals may be generated from spontaneous reports, clinical trials or observational studies. Alleged risks may originate from these sources, or from other sources, such as data on the frequency of events (e.g. mortality or cardiovascular statistics). While all Yellow Card reports for the Covid-19 vaccines are reviewed by an MHRA assessor, not all will be considered as safety signals or alleged risks. This may be due to it being considered a greater likelihood of the event being due to other factors such as Covid-19 disease or other illnesses, concomitant medications, lack of biological plausibility, or because there is currently insufficient information provided to support a possible association.

776. The MHRA follows its 'Assessment guidance for Pharmacovigilance' [**JR/429 - INQ000494263**] in making a judgement on causality in relation to a drug/ADR association. The guidance stresses the importance of taking a rounded view of all the available evidence: mechanistic, non-clinical, ADR, epidemiological and clinical trial data, and taking into account the Bradford Hill 'guidelines for causation'; strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.

777. During the weekly Yellow Card meetings, the assessors monitor the number of reports being received and the nature of the reported risks, escalating concerns where appropriate through the signal detection and assessment process. The following factors, which are not exhaustive, will trigger the MHRA to investigate an alleged risk: event is an adverse event of special interest (AESI); event is captured in the Risk Management Plan as a safety concern; event is associated with significant morbidity or a life-threatening/fatal outcome; event involves hospitalisation, child or in utero exposure of a foetus; increasing numbers of Yellow Card reports; intelligence received from external sources e.g. international regulators or scientific literature, possibility of an emerging risk.

778. The Regulatory Pharmacovigilance Prioritisation System (RPPS) [**JR/430 - INQ000494382**] which prioritises pharmacovigilance issues according to strength of evidence,

public health implications, agency regulatory obligations and public perceptions, is also typically used to determine if an investigation should be prioritised. However, during the initial rollout of the Covid-19 vaccines there was near real-time surveillance and rapid assessment of signals on the safety of the Covid-19 vaccines, so formal RPPS scoring was not used routinely, although strength of evidence was still considered at that time as part of the review process. The RPPS has been used more recently by MHRA in relation to prioritising signals for Covid-19 vaccines published on the PRAC agenda.

779. An example of an alleged risk which was investigated by MHRA together with UKHSA and where the available evidence did not support a causal association with the Covid-19 vaccines was excess deaths resulting from the vaccines, which is discussed below.

780. Vaccination and surveillance of large populations means that, by chance (not caused by the vaccine), some people will experience and report a new illness or events in the days and weeks after Covid-19 vaccination. The first priority groups in the Covid-19 vaccination programme were the elderly and those with pre-existing medical conditions [**JR/431 - INQ000408135**]. Older age and chronic underlying illnesses make it more likely that coincidental adverse events including those with a fatal outcome will occur, especially given the millions of people vaccinated.

781. As the number of vaccine doses administered has increased, so has the number of reports of adverse reactions associated with fatal outcomes associated with Covid-19 vaccines. However, this does not mean that there is a link between the Covid-19 vaccines and the fatal outcomes reported. The UKHSA has previously analysed the direct and indirect impact of the vaccination programme on infections and mortality [**JR/432 - INQ000468862**]. It has been estimated that up to 26 September 2021, the UK vaccination programme prevented between 23.9 and 24.3 million infections and between 123,600 and 131,300 deaths.

Excess deaths

782. The MHRA has received reports of adverse events associated with Covid-19 vaccines involving a fatal outcome in patients. These reports are taken very seriously, and each one is carefully reviewed to determine what further information should be requested to help the assessment of the report. Cumulatively during the pandemic, the Yellow Card data were thoroughly analysed for patterns or evidence which might suggest a causal association

between the vaccines and the reported death, alongside data (including international data) presented by UKHSA. Reports of suspected adverse reactions with a fatal outcome were further considered by the CHM and its Expert Working Groups as appropriate, as has been described in relation to some of the fatal outcomes resulting from specific conditions in the chronologies above.

783. It is important to note that a report to the Yellow Card scheme of a suspected adverse reaction with a fatal outcome does not necessarily mean that the suspected reaction and subsequent death were caused by the vaccine, only that the reporter has a suspicion it may have been. Underlying or previously undiagnosed illnesses, unrelated to the Covid-19 vaccines, can also be factors in such reports. The relative number and nature of UK reports of suspected adverse reactions with a fatal outcome are subject to many factors that influence ADR reporting. Therefore, the numbers of reports of suspected adverse reactions with a fatal outcome should not be used to directly compare the safety of the different vaccines. The data and numbers on reports of suspected adverse reactions with and without a fatal outcome as of 8 March 2023 can be found in the Summary of Yellow Card reporting [**JR/432 - INQ000468862**].

784. At the population level, the MHRA also analysed natural death rates over time, to determine if any specific trends or patterns occurred that might indicate a vaccine safety concern. Data on age-stratified all-cause mortality in England and Wales taken from the Office for National Statistics (ONS) death registrations indicates that several thousand deaths are expected to have occurred naturally, mostly in the elderly, within seven days of the many millions of doses of vaccines administered to date.

785. By way of context, weekly death registrations are provided by the relevant statistical authorities in England, Wales, Scotland, and Northern Ireland. In February 2023, the following were registered [**JR/432 – INQ000468862**]:

a. England and Wales – in the week ending 10 February 2023, 12,672 deaths were registered. Of these deaths, 446 involved, but were not necessarily due to Covid-19, accounting for 3.5% of all deaths.

b. Scotland – in the week ending 19 February 2023, 1,263 deaths were registered. Of these deaths, 48 involved, but were not necessarily due to Covid-19, accounting for 3.8% of all deaths.

c. Northern Ireland - in the week ending 17 February 2023, 402 deaths were registered. Of these deaths, 12 involved, but were not necessarily due to Covid-19, accounting for 3.0% of all deaths.

786. The ONS monthly mortality analysis provided the number of deaths in which an adverse reaction to a COVID-19 vaccine has been mentioned on a death certificate which is available here JR/433(a) – INQ000507364. This does not mean that the adverse reaction has necessarily been a cause of the registered death.

787. A number of other organisations and bodies are also responsible for collecting and analysing safety data and data on deaths, including marketing authorisation holders, the UKHSA and coroners.

788. The advice of the VBREWG was sought on reviews of the Covid-19 Yellow Card reports of suspected adverse reactions with a fatal outcome on 15 February 2021 and 29 April 2022, and the advice of the CHM was later sought on 9 and 10 June 2022. When compared to the expected rate of death in a comparable population size, the data did not indicate an increased risk of death associated with vaccination [JR/434(a) **INQ000494278**]. The VBREWG agreed during the meeting held on 15 February 2021 with the conclusion that there was not a signal for an increased risk of death associated with vaccination [**JR/90** - INQ000409514

789. Data presented to the VBREWG on 15 February 2021 noted that a large proportion of reports of suspected adverse reactions with a fatal outcome had very little detail which made assessment of individual cases difficult. The MHRA does not have jurisdiction over healthcare professionals and does not have legal powers to compel healthcare professionals to provide additional information after an initial report of suspected adverse reactions. Timely production of relevant clinical data is important for effective pharmacovigilance. The MHRA has been working with the NHS to explore approaches to facilitate digital linkage of Yellow Card information to clinical records and to potentially enable faster access to information, where considered necessary for an assessment. This work remains ongoing and is discussed further in the "Lessons Learnt" section of this Statement.

790. A study published by the ONS and the Office of Health Improvement and Disparities (OHID) analysed data on Covid-19 vaccination and mortality in young people during the

coronavirus pandemic [JR/435(a) - **INQ000468829**]. The study found no indication of an increased risk of death from cardiac-related or other causes in those aged 12-29 years-old in the six weeks following Covid-19 vaccination, compared with the average for the five years preceding the coronavirus pandemic. Instead, the ONS study observed a decrease in the risk of death for all causes in the first week after vaccination.

791. The study also suggested that the apparent excess in death registrations in young people in 2021 was due to delays in the registration process and early indications of increased numbers of deaths due to non-vaccine-related external causes. On 18 March 2022, the advice of the VBREWG was sought on the study data, and the VBREWG agreed with the conclusion of the ONS report that the Covid-19 vaccines were not associated with an increased risk of death in young people [**JR/420** - **INQ000409539**]. The ONS continued to publish updates on the risk of deaths by Covid-19 vaccination, and in the latest report on 27 March 2023, concluded that there was no increased risk of cardiac or all-cause death for young people in general in the weeks after vaccination [**JR/180** - **INQ000468868**]

792. On 29 April 2022, the MHRA sought the advice of the VBREWG on an updated trends analysis of Yellow Card reports of suspected adverse reactions with a fatal outcome in association with the Covid-19 vaccines, UK vaccine usage data, and data published by other regulators regarding reports with fatal outcomes associated with the Covid-19 vaccines [JR/421(a) - **INQ000494327**]. The MHRA's review had been prompted by the continued receipt of queries on reports with a fatal outcome in the coronavirus vaccine 'Summary of Yellow Card reporting' that was in the public domain. The VBREWG noted that reports of suspected adverse reactions with a fatal outcome received to date remained concentrated in older age groups, which is expected given that this population often has multiple comorbidities and increased frailty, and so the VBREWG did not identify a pattern of concern.

793. The VBREWG also noted that the observed versus expected analyses for all-cause mortality did not suggest any excess reporting of fatal events within 7 days of receiving any of the three Covid-19 vaccines either overall or associated with the first dose **JR/422(b)** **INQ000409541**. The VBREWG agreed that no regulatory action was required, and that the benefit risk remained positive for the majority of individuals for all the Covid-19 vaccines. The VBREWG recommended that the fatal outcome subsection in the MHRA coronavirus vaccine 'Summary of Yellow Card reporting' publication could be updated to provide figures outlining

the context in which reports of suspected adverse reactions with a fatal outcome are being received, and the impact of the Covid-19 vaccination programme in saving lives and preventing hospitalisation. Furthermore, the VBREWG noted that where deaths have been linked to specific ADRs, the summary should reference the measures taken to mitigate these risks.

794. On 9 June 2022, the MHRA also sought the advice of the CHM regarding the fatal reports subsection of the coronavirus vaccine 'Summary of Yellow Card reporting' [**JR/433(b) INQ000494360**]. The CHM noted the advice of the VBREWG with respect to updating the summary of reports of suspected adverse reactions with a fatal outcome included in the coronavirus vaccine 'Summary of Yellow Card reporting' and agreed that this update to the report was warranted, commenting that this should be balanced, and remain transparent and easy to understand. Following the CHM's recommendation, from 4 August 2022 the MHRA added figures outlining the context in which reports with a fatal outcome were being received to the 'Reports with a fatal outcome' subsection in the MHRA coronavirus vaccine 'Summary of Yellow Card reporting' publication [**JR/434(b) INQ000468856**]. These reports were published weekly and gave a stratified analysis of reports by age and gender. This demonstrates the MHRA's commitment to ensure that, as with all reports of suspected adverse reactions, those with a fatal outcome were carefully and rigorously considered.

795. The MHRA continues to monitor and review all reports of suspected adverse reactions submitted to us, particularly those that indicate a possible fatal outcome associated with the Covid-19 vaccines. When a safety issue is confirmed, the MHRA seeks to act promptly to inform patients and healthcare professionals and take appropriate steps to mitigate any identified or suspected risk.

Lessons Learnt and reflections following the Covid-19 pandemic

Introduction

796. The Covid-19 pandemic was a profoundly challenging time for everyone, including for those public servants who were at the forefront of the national response effort. The MHRA leadership and all those who worked for the MHRA were among those at the forefront of the UK's response to the pandemic in relation to access to safe and effective medical products of appropriate quality.

797. The MHRA has carefully considered all the lessons learnt and reflected on opportunities to improve its ways of working in readiness for future emergencies as well as for the availability of healthcare products for the current major public health problems which are themselves 'pandemics'. There are also related recommendations for each of the 12 key lessons learnt.

Scientific preparedness

798. I have described the role of the MHRA laboratories (formerly "NIBSC") within the "Key Individuals, Independence and Impartiality" section of this statement. The MHRA laboratories have many decades of extensive experience in developing biological standards, including for SARS, MERS and other high-hazard pathogens. This critical mass of expert scientific staff, who were able to pivot to undertake work on new biological products, allowed us to rapidly commence work on physical reference materials and publish standards in the literature for SARS-CoV-2. They were also able to swiftly undertake technology transfer in preparedness for batch testing of vaccines, ultimately examining every batch of Covid-19 vaccines manufactured for use in the UK for purity and potency.

799. Additionally, the rapid establishment of Covid-19 specific international groups for real-time scientific discussions and information sharing, including groups led by the WHO, allowed for the rapid development of international standards and agreements. Such international standards or guidelines serve as a benchmark for the global acceptability of products, and as a basis for defining national regulatory requirements for licensing and for post-licensure evaluation.

800. The timeframe to produce an international standard is usually 2-3 years, but as a result of co-operation between MHRA and other international laboratories and the WHO Expert Committee on Biological Standardization (ECBS), this was accelerated to a matter of months. For example, following the announcement of the pandemic in March 2020, the MHRA laboratories were able to rapidly research reagents that would go on to become the international standards. These international standards were made available by December 2020. As the leading WHO Collaborative Centre on biological standardisation, the MHRA laboratories are well positioned to prepare and respond in a similar manner for future pandemics.

801. Scientific preparedness was key to making rapid progress on essential deliverables such as target product profiles for diagnostics. In addition to national and international standards, the scientific expertise of the MHRA laboratories was critical in ensuring our ability to scale up batch testing activities rapidly, ensuring the sufficient supply and quality of vaccines. While some surge resource was made available, this was largely achieved through preparing and training staff to effectively perform their roles in verifying materials, methods and equipment, and documentation within a Quality Assurance System. The MHRA's scientific expertise allowed for a proactive approach to batch testing, which in turn enabled the prompt deployment of millions of potent, quality-compliant vaccines. This work was of both national and international importance, and it is therefore critical that the MHRA maintains sufficient expertise and ongoing training to enable staff to pivot their focus towards batch testing in times of need.

802. The overall lesson learnt on preparedness in the area of MHRA's scientific expertise is that it is vitally important that there is continued investment in MHRA's capability for pandemic preparedness if the government's '100 Days Mission' aim of accessing diagnostics, vaccines and therapeutics within 100 days of a pandemic being declared is to be achieved. The 100 Days Mission can be found here **JR/435(b) - INQ000101061**

Frameworks for collaboration between regulator, industry, and Government

803. The MHRA would not have been able to adeptly navigate the challenges of developing and approving new medicines had it not been for effective national collaborations with Industry, Government, and Academia. This collaboration was exemplified by the Vaccine Task Force, as described in our Module 4 Brief Summary. Vitally important to the success of these collaborations was the flexibility with which the MHRA could operate and our ability to share and receive information across Government, together with effective management of any potential or actual conflicts of interest. Our frameworks for collaboration with Academia will be discussed at the 'Ensuring timely and robust evidence generation' section of this statement.

804. To facilitate product development by the pharmaceutical and medical device industries during the pandemic, the MHRA adapted and enhanced its established scientific and regulatory advice service available to applicants. Usually, the MHRA was able to offer in-person scientific advice meetings, on average, three months after a request. During the pandemic, this process was scaled up and expedited, with advice meetings being held on

request as early as the same day. Prompt interactions and rapid advice enabled the development of scientific dossier content and the scheduling of its rolling review submissions, ensuring the availability of assessors aligned with key milestones for evidence generation. Such interactions never impeded rigorous, objective scientific review, bolstered by independent advice from the CHM on the evidence generated.

805. In addition to collaborations with the pharmaceutical and medical device industries, the MHRA had a role in providing advice to Government organisations, ensuring that supply chains for medicines, medical devices and blood components were safe, secure, and optimised. From the beginning of the pandemic, the MHRA participated in several cross-government configurations with NHSE, DHSC, UKHSA and NICE on medicines supply. These meetings did not directly handle the procurement of medicinal products. Rather lists of critical products were identified and supply positions were discussed. In these meetings, the MHRA's role was to provide regulatory advice on available routes for accessing these medicines in the most efficient way.

806. The MHRA supported the NHSE and DHSC procurement teams by collaborating closely in explaining regulatory principles and requirements to commercial teams that did not have such knowledge. This enabled teams to focus their limited resources on potential sources of medicines that were more likely to be successful in securing supply for UK patients and minimised the risk of procurement teams losing time in potential bids that were likely to be unsuccessful from a regulatory perspective. To avoid any potential conflicts of interests, the MHRA did not provide individualised product advice, but instead explained general principles on supply chains, and the safety, quality and effectiveness of medicines. The MHRA established close working relationships with these operational teams and cross-government departments that remain in place today and enable a quicker and more effective response to system 'shocks'.

807. The overall lesson on regulatory collaboration is the need for integrated national frameworks for collaboration between the MHRA, Industry, and Government in providing safe and timely access to essential medicinal products, both in and outside of a pandemic scenario. The MHRA should continue to invest resources in establishing and maintaining these frameworks in the future, with appropriate management of conflicts of interest to maintain

public trust and confidence. A useful comparator in terms of how such collaborations can be trusted is the EU Innovative Medicines Initiative (now the Innovative Heath Initiative).

Global collaboration

808. The MHRA worked closely with key partners both within the UK and internationally throughout the pandemic. International, bi-lateral, and multi-lateral relationships were essential in understanding the real-world evidence and safety signals associated with the Covid-19 vaccines and therapeutics arising in other territories. This included working with the Covid-19 Working Group of the International Coalition of Medicines Regulatory Authorities ("ICMRA", which the MHRA joined in 2021), the ICMRA Covid-19 Vaccine Pharmacovigilance Network (which the MHRA co-chairs), and the Access Consortium Covid-19 vaccines and therapeutics working group, as well as other international health authorities and groups.

809. As a member of the Executive Committee of the ICMRA, the MHRA contributes to a voluntary leadership entity comprising around 60 national medicines regulatory authorities. Throughout the pandemic, the Executive Committee met regularly to ensure robust liaison and information sharing on clinical trials, vaccines and medicines approvals, and safety issues. Specific committees, including the ICMRA Public Health Emergency Clinical Trials Working Group co-chaired by the MHRA, were established to address urgent issues. The MHRA also co-chaired the ICMRA Covid-19 Vaccine Pharmacovigilance Network with the Therapeutic Goods Administration (TGA), facilitating methodological approaches to vaccine safety monitoring and assessment of emerging safety signals.

810. In addition to the development of guidance and protocols, cooperation between global regulators during the Covid-19 pandemic for the sharing of pharmacovigilance data was essential in ensuring effective patient safety monitoring. The MHRA shared and received assessments and safety data from international regulators through various means and at different levels, depending on the forum and data sharing arrangements in place. High level information on systems, processes, and assessments was shared through the ICMRA Covid-19 Vaccine Pharmacovigilance Network by participating countries, including the UK. Given that wide-scale use of Covid-19 vaccines began first in UK, prompt regulatory action could be

taken by other countries on the basis of the UK pharmacovigilance system outputs, and it was stated by TGA that UK pharmacovigilance data helped save lives in Australia.

811. The overall conclusion is that global collaboration is essential to effectively respond to a pandemic, allowing for the development of standards and protocols and sharing of critical information, particularly safety data. The MHRA continues to invest in and prioritise its relationships and information sharing with other global regulators, both bilaterally and through bodies such as the ICMRA.

Capacity, capability and resilience

812. As described in "Scientific Preparedness" above, the MHRA's contribution in responding to the Covid-19 pandemic was only possible due to the dedication of its highly skilled staff, such as medical, pharmaceutical, statistical, clinical pharmacology, toxicology and risk management assessors, who were able to be redeployed to review complex information at pace and reach appropriate benefit risk decisions in a timely manner. From the start of the Covid-19 outbreak in 2020, the MHRA possessed the scientific and regulatory expertise necessary to provide pragmatic, risk-based advice to companies developing Covid-19 therapeutics and vaccines and to assess applications.

813. Resilience within the workforce and among teams is also a pivotal consideration in any pandemic scenario. The MHRA, with its diverse workforce of highly specialised technical experts and scientists, can experience challenges in resilience, particularly concerning the recruitment of personnel with the required skill sets. Surge resources were permitted for the laboratory functions. For assessment and inspection activities, resources were diverted from non-pandemic work, which has led to post-pandemic backlogs in a number of regulatory functions. It should also be noted that the resilience of a workforce can be significantly impacted by illness and absence. During the pandemic, I monitored logs maintained by our Human Resources Department on staff absence due to illness to understand any risk to staff resilience across the agency.

814. It is therefore essential that the MHRA continues to regularly review its workforce plans and maintains succession plans for subject matter experts to fulfil business critical and specialist roles. This includes local strategies for recruitment, retention, and identifying skills gaps. It is also recommended that MHRA utilises strategies for surge resourcing in all main

regulatory activities as per during the Covid-19 pandemic. There is currently no formal plan for surge resource during a pandemic. It is challenging to hypothetically plan for surge resourcing, as such. In future pandemics, the MHRA would use similar redeployment strategies to those utilised during the Covid-19 pandemic to provide surge resource where required.

Legislation adapted to the specific needs of the pandemic

815. Having appropriate legislation under which it was possible to approve vaccines for emergency use in the shortest possible time in a nationwide vaccination programme helped the UK to be at the forefront of the global Covid-19 vaccination effort. The MHRA operates a number of routes to market for vaccines, therapeutics and devices, on which I go into detail in the 'Pre-approvals' section of this statement. During the pandemic, regulation 174 of the Human Medicines Regulations 2012 (described in detail in paragraphs 150-156, in the 'Pre-approvals' section of this statement) was deemed one of the appropriate authorisation routes for Covid-19 vaccines given the public health emergency. As explained previously this emergency provision is based on EU law.

816. Amendments were made to regulation 174, which included the addition of regulation 174A. The MHRA consulted on this amendment to attach explicit conditions to the temporary authorisation of supply of an unlicensed medicine. This meant it could ensure that manufacturers and suppliers continued to be held to the same robust regulatory principles, including, for example, requirements for pharmacovigilance. Following a public consultation by DHSC held from 28 August to 18 September 2020, these changes to regulation 174 were implemented on 16 October 2020.

817. The overall conclusion is that regulatory routes should have appropriate safety mechanisms and allow for regulatory flexibilities which enable responsiveness during any future pandemics. The regulatory routes in place were proven to be effective in the pandemic. The Windsor Framework will come into effect from 1 January 2025 [**JR/436 –** INQ000507351]. From this point, novel medicines such as vaccines, will be, and can only be, licensed on a UK-wide basis. This then means that they will be available at the same time and on the same basis, across the UK. It is the MHRA's view that we have sufficient regulatory routes to approval to be effective in a future pandemic. However, consideration should be given to enabling legislative changes, especially in the context of future, yet unknown, public health

crises, such as for human challenge studies, better capture of data on adverse reactions, and real-time transparency.

Flexible operation of regulatory frameworks

818. The MHRA adopted a number of regulatory flexibilities and flexible procedures that were crucial in facilitating the approval of vaccines and therapeutics during the pandemic. None of these flexibilities compromised the rigour of our scientific scrutiny. I have, in my statement under 'The MHRA's Innovations for product approval during the pandemic' in the 'Pre-approvals' section, described flexibilities to standard procedures which included expediting the 'rolling review' processes (accelerated rolling review), to ensure that medicinal products were made available in the shortest possible time once benefit risk was found to be positive from the perspective of safety, quality, and effectiveness. The use of the accelerated rolling review procedure meant that the MHRA authorised not only vaccines, but also some Covid-19 therapeutics significantly sooner. For example, during the pandemic, Paxlovid (nirmatrelvir with ritonavir) was authorised in 37 days, Lagevrio (molnupiravir) was authorised in 127 days, and Xevudy (sotrovimab) was authorised in 134 days.

819. As well as rolling reviews, the MHRA supported a number of other flexibilities to address urgent and emerging needs across the healthcare system. For example, during the early stages of the pandemic, it was anticipated that hospital pharmacy services could be called upon to supply significant amounts of aseptically prepared medicines to help service the needs of Intensive Care Units providing Covid-19 patient care. Hospital Pharmacies do so routinely, however, not in the large quantities anticipated to be required. Therefore, the MHRA allowed for larger volumes of medicines to be prepared. This flexibility required the medicines to be on "The ICU COVID-19 Priority Medicines List", a list created by NHS England and NHS Improvement. Only direct supply to NHS ICUs providing Covid-19 care via the hospital pharmacy service was permitted. As a result, on 9 April 2020 the MHRA addressed a letter to all NHS Hospital Chief Pharmacists in the UK setting out in detail the conditions under which this flexibility could be applicable, in a risk proportionate manner, given the exceptional nature of the pandemic [**JR/437 – INQ000336600**]

820. Overall, having legislation that allows operational flexibility in relation to established processes to address urgent and emerging needs of the population in a pandemic scenario is essential and illustrates the need to continue to further develop this: allowing the exceptional

to become the everyday. The rolling review procedure should be repeated in future pandemics and in general for products of public health importance. Critical products subject to shortages should also be considered in relation to operational flexibility such as the MHRA guidance on use of dispensed morphine for terminal care in the Covid-19 pandemic.

Clinical trials yielding actionable data

821. Clinical trials are critically important to efficiently bring forward new evidence-based treatments. This is why the Chief Medical Officers of the UK wrote to every doctor in the UK on 3 April 2020 asking that "any treatment given for coronavirus other than general supportive care, treatment for underlying conditions, and antibiotics for secondary bacterial complications, should currently be as part of a trial, where that is possible". However, of the clinical trials undertaken internationally during the Covid pandemic, only a small percentage (4-5%) delivered actionable results **[JR/438 – INQ000507335**

822. Representative trials that yield actionable data therefore hold great clinical value and are essential to the timely development and deployment of effective treatments, and equally important, to understand treatments which are not effective. During the Covid-19 pandemic the MHRA supported those undertaking clinical trials to optimise the scope, scientific rigour, and decision-relevance of their research protocols. The MHRA supported the development of clinical trials through enhanced engagement with trial sponsors to advise on trial designs and the regulatory flexibilities already available to minimise disruptions to the conduct of trials and to ensure the integrity of data generated. This included advice on remote monitoring of patients, home delivery of Investigational Medicinal Products (IMPs), and building flexibilities into protocols. The MHRA also published guidance on managing clinical trials during the Covid-19 pandemic, to assist those involved [**JR/41 INQ000283562 JR/42 – INQ000283563** These interventions significantly expedited and improved the development and approval of clinical trials.

823. The MHRA supported the development of the protocol for the RECOVERY trial, which was an 'Adaptive Platform Trial' embedded in clinical care that allowed multiple therapies to be evaluated simultaneously, under a master protocol. This led to actionable data and early recommendations for Covid-19 therapeutic treatments, such as on 16 June 2020, when the MHRA issued a Covid-19 Therapeutic Alert, also known as a Central Alerting System ("CAS")

alert, from the Chief Medical Officer, advising use of dexamethasone in the treatment of patients hospitalised with Covid-19 who required oxygen or ventilation.

824. An important area of learning related to the prevention and treatment of Covid-19 in pregnancy. Pregnant women are usually excluded from clinical trials, and the RECOVERY trial successfully enabled the participation of pregnant women in the search for an effective treatment for Covid-19, which required careful safety assessment.

825. Ensuring greater diversity in clinical trials requires a system-wide approach to changing research culture and practice. As such the MHRA consulted on strengthening the clinical trials legislation in this respect in 2021.

826. Including pregnant women in clinical trials requires a culture change as well as addressing liability issues and the MHRA has worked with international regulators to achieve this, as detailed in a 2021 paper published by the MHRA with FDA and EMA [**JR/439 - INQ000507355**]. Furthermore, the ICH is currently developing E21, a framework and best practice guide that the MHRA will use to enable inclusion and/or retention of pregnant and breast-feeding individuals in clinical trials. These guidelines, due for publication in 2025, will establish a common understanding between regulatory authorities, industry, and other stakeholders to harmonise strategies and methodologies for enrolment and retention of pregnant and/or breast-feeding individuals into clinical trials and overall drug development plans.

827. Other forms of diversity important to clinical trials representativeness include children, the elderly, those with co-morbidities and those of diverse ethnicity. Recognising this diversity is important because there are physiological, genetic, and immunological reasons why drugs may respond differently within these groups. Practical steps which may be taken to ensure greater diversity in clinical trials include addressing awareness, accessibility, language barriers, and culture. Initiatives such as 'Be Part of Research', for example, are taking the trial to the patient, 'decentralising' clinical trials. Funding bodies encouraging consideration of diversity and representativeness as part of their funding requirement, regulators monitoring the representativeness of participants for the intended patient population of a product, ethics committees reviewing plans for recruitment, alongside involvement and engagement of patients in study design.

828. It also requires further targeted communication and engagement with patients and the public to raise awareness of research opportunities, and appreciation for the importance of research, and further consideration of the accessibility of trials to support greater participations across different groups. We are working with our partners across the health ecosystem on improving EDI in trials, ensuring patients have access to the health products they need and that they can be confident those products have been tested in people like them.

829. The overall recommendation is that continued regulatory support for clinical trials, through effective guidance and proactive scientific advice, is vitally important because it fosters the timely availability of clinically valuable, actionable data which in turn leads to the rapid development and deployment of innovative diagnostics, vaccines and therapeutics.

Rapid availability of independent expert advice

830. The MHRA approves medicines and vaccines on the basis of rigorous evaluation of the available evidence of safety, quality and effectiveness. This robust system is further reinforced by independent advice from scientific experts of national and international repute on the evidence of the safety, quality and effectiveness of the medicine or vaccine, via statutory committees and their subcommittees. The swift availability of independent expert advice, and the flexibility, responsiveness, and dedication of the CHM and its EWGs (whose roles are described in detail in paragraphs 43-45 of this statement), were of fundamental importance to effectiveness and speed of the MHRA's pandemic response.

831. The pandemic triggered rapid establishment by the MHRA of three new EWGs: in March 2020, the Covid-19 Therapeutics EWG; in May 2020, the Covid-19 Vaccine Safety Surveillance EWG; and in August 2020 the VBREWG. To provide Ministers with timely independent expert advice on the three main Covid-19 vaccines, the CHM and VBREWG met regularly, both prior to approval and during UK deployment, to advise on the evidence of safety, quality, and effectiveness. The VBREWG also met on a weekly basis, sometimes more frequently, to advise on specific safety issues as soon as these were identified. This was a key factor in the MHRA's ability to make timely assessments of safety data and propose regulatory actions to minimise risk including communication to the public.

832. There is a robust policy governing the declaration and management of relevant interests of independent experts. In the interest of transparency and accountability, the Code of Practice

(found within this document [**JR/52 – INQ000274038**], ensures that declarations are made by chairmen and members of the various committees, and that actions taken to manage any potential financial, familial, or personal conflicts of interests are made public.

833. The overall recommendation from the MHRA is that timely independent expert advice by the CHM and its EWGs is fundamentally important to the government's robust decisions about the safety, quality and effectiveness of medicines and vaccines. It is essential that the availability of independent expertise is recognised for its value and importance, sustained and further strengthened for the future.

Comprehensive proactive surveillance

834. While regulatory decisions to approve a new vaccine or medicine are made on the basis of satisfactory evidence of safety and effectiveness, it is accepted that much more will be learnt about benefit and risk when a wider population receives the medicine or vaccine than the population in the clinical trials. Many individuals would receive these vaccines over a short timescale, starting with individuals most at risk of harm from Covid-19, including elderly individuals and those suffering from multiple co-morbidities. It was therefore vital that an effective surveillance strategy was in place from the time that mass immunisation or rollout of a new vaccine commenced. For Covid vaccines this requirement for proactive surveillance was identified early in the pandemic, about 6 months before a vaccine was approved, and this was addressed through the Covid-19 vaccine safety surveillance strategy [**JR/440 – INQ000494265**]. This is described in detail within 'The need for post-authorisation surveillance', in the 'Post-approvals' section of this statement.

835. Additionally, it was recognised early in the pandemic that enhancements to the MHRA's safety data systems would be needed to enable timely management of the large number of reports of suspected adverse reactions that would be expected during deployment of the Covid-19 vaccines and therapeutics. During the pandemic, in 18 months the MHRA received over 450,000 Yellow Card reports of suspected side effects associated with vaccines compared with 82,500 that would be expected in the same time period. In December 2020, before the vaccine rollout, the MHRA deployed an artificial intelligence (AI) tool, to support timely signal detection within 48 hours of receipt of reports. This capability is now being deployed for adverse event reports for all healthcare products through the MHRA's SafetyConnect programme.

836. I am asked about whether it should be mandatory for healthcare professionals to report suspected adverse reactions. Such reporting was not mandatory during the pandemic and is not currently mandatory. A report conducted by the ICMRA indicated an inconclusive picture regarding the impact of mandating healthcare professionals to report suspected ADRs **JR/441** **INQ000507331** Its survey found 67% of the National Competent Authorities indicated that mandatory reporting had no additional effect on national reporting rates at a healthcare professional level. Other factors taken into account by the MHRA include the challenge of enforcement of non-compliance, as well as striking the right balance between access to information potentially of relevance, the administrative burden on the health service, and the risk of inadvertent criminalisation of healthcare professionals.

837. Instead of proposing mandating individuals or organisations to provide safety information, the MHRA has been working with the NHS to explore approaches to facilitate digital linkage of Yellow Card information to clinical records and potentially to enable speedy access to information, where considered necessary for an assessment. There are professional guidelines in place for health care professionals to report safety issues in relation to medicines and vaccines and the MHRA is working to encourage reporting of adverse effects through improvements such as those within the new SafetyConnect system and outreach work with professional bodies.

838. The MHRA works closely with six regional Yellow Card centres (in Scotland, Wales, Northern Ireland, the North-West, Northern and Yorkshire, and West Midlands) that are commissioned by the MHRA to increase awareness as well as educate and promote the reporting of any suspected adverse incidents with medicines or medical devices to the Yellow Card scheme with healthcare professionals, patients and their representative organisations.

839. We are working to further improve the data sources available to support signal detection and assessment, for example through greater linkage and use of other data sources, such as medicines and device registries. Traditionally in vigilance systems, real-world datasets are used to investigate and confirm or refute safety signals from spontaneous reporting. It will be important to further consider how signal detection can be done in large clinical datasets, using all the tools such as AI now available.

840. Timely access to vaccination records data is critical to support vaccine vigilance. A single UK vaccination registry, capturing data on all vaccines administered across healthcare

settings, including in private care, with sufficient patient demographic data and with linkage to primary care and hospital admissions data, would support more rapid identification of adverse events. The requirements for secondary use of data to support safety and effectiveness surveillance and evaluation should be considered as part of the overall design of data capture.

841. Vigilance for vaccines, medicines, and devices would also be substantially further supported by increased capture and collation of data on diagnostic tests and imaging results as well as prescribing in secondary care with linkage of these data on an individual patient level basis to data already collated across primary and secondary care. This needs to be UK-wide in order to support rapid surveillance of rare adverse events and in patient subgroups. More timely availability of hospital admissions data to support the identification of cases while patients remain in hospital, which is currently collated upon patient discharge or death, would also support more rapid safety evaluation.

842. Relevant stakeholders, including the MHRA as well as other public health and academic researchers and collaborators, also need to be able to access these improved data assets in a timely way. This could be achieved through the advancing work being undertaken by NHS E on a national secure data environment. Consideration needs to be given to how such offerings across the four nations can be efficiently accessed.

843. Surveillance strategies are regularly updated to reflect the latest public health data and emerging trends, seeking advice from the appropriate experts where necessary. Currently, there is no single surveillance strategy in place for the next pandemic. However, strategies are product and scenario specific, and numerous factors determine the most appropriate/effective approach. Looking to future pandemics, the four-stranded Covid-19 vaccine surveillance strategy would form the basis of any future model. However, the MHRA would take account of various factors relevant to both the product and disease when refining the strategy for the specific circumstances. There may also be unique factors to the product/ disease of interest that would facilitate additional surveillance opportunities. Any strategy would need to take account of factors such as the delivery model, population size, type of product, call/ recall mechanism, data transfer/flow/storage, as these are all factors which determine the most effective approach.

844. Whenever new products are launched the MHRA will consider whether there is a need for specific additional pharmacovigilance activities. As with the strategy developed for the Covid-

19 pandemic, the strategy for any future pandemic would be informed by past experience and learnings and adapted accordingly to suit the current situation. Recommendations for achieving a surveillance strategy for future pandemics would be dependent on the particular risk, however, based on the learnings from the Covid-19 pandemic the Agency is currently exploring linkage of Yellow Card data to electronic healthcare records as a mechanism to both increase the data available to support surveillance and also to reduce the burden of requests for additional details on healthcare professionals. There may also be further opportunities for cross healthcare family partnerships and data sharing to support both surveillance and care delivery.

845. The overall learnings are that a robust, proactive surveillance strategy should be planned well in advance for any future vaccine for mass immunisation. Surveillance strategies should be continuously updated to ensure safety signals are identified as quickly as possible. There is significant further potential in the use of new AI technologies, for instance in enhancing how Yellow Card data can be integrated with electronic healthcare records to provide greater insights. Opportunities for analysis of real-world data for signal detection will be further explored as the technology advances and data sources allow.

Robust benefit risk evidence generation

846. The MHRA's proactive surveillance strategy for Covid-19 vaccines depended on timely access to epidemiological evidence and research from a diverse range of sources. Through leveraging academic collaborations and active engagement with researchers throughout the pandemic, the MHRA was able to access data required to support evaluation of benefit risk in clinical use at the scale and speed required during the pandemic.

847. The new approach of Rapid Cycle Analysis (as detailed in the 'Post-approvals' section of this statement) utilised real-world data and compared occurrence rates of events in patients following vaccination with occurrence rates pre-pandemic, utilising pseudonymised patient level data on vaccination provided by the Clinical Practice Research Datalink rather than patient-submitted Yellow Card reports. This methodology mitigated against evidence gaps from underreporting, ensuring more complete evidence on safety.

848. Additionally, the MHRA shared and received assessments and data from international regulators depending on the forum and data-sharing arrangements in place. For example,

high level information on systems, processes and assessments was shared through the ICMRA Covid-19 Vaccine Pharmacovigilance Network by participating countries, including the UK. For specific safety topics, bilateral Memoranda of Understanding (MoUs) and data-sharing agreements were used to exchange detailed information on ADR reports and observational data relevant to assessment in each country. Whilst additional MoUs and data-sharing agreements were developed at pace, there were still occasions where these were limited in their scope and as a result, information sharing was slow or restricted.

849. The overall conclusion is that there is great potential to use real-world data more effectively, in support of robust and timely regulatory decisions. A more established network of those conducting epidemiological research using real-world data, including public health authorities, would be beneficial in providing access to a range of sources of epidemiological data. To further improve such collaboration, researchers and academics should be more informed about data needs and standards for regulatory decision-making. Establishing UK Centres of Excellence in Regulatory Science and Innovation (CERSIs) will be likely to include a focus on data science with the ambition to build a network of both data and analytical expertise that can rapidly research and analyse sources of real-world data to provide evidence meeting regulatory standards.

Special approaches for vulnerable populations

850. Special population groups, including pregnant people and children, need careful consideration in relation to the safety, quality and effectiveness of healthcare products. I have described in the "Meaningful clinical trials yielding actionable data" section of this statement how well-designed clinical trials are essential for evaluating safety and efficacy. That said, clinical trials in special populations are generally more challenging to undertake and slower to recruit.

851. For example, clinical trial data on the safety of exposures in pregnancy can be slow to accumulate given the time taken to reach pregnancy outcomes, difficulty in recruiting and delays in data availability for secondary research purposes. Early in the pandemic, the UK considered data on safety of the mRNA vaccines in pregnancy from across a number of areas including the US and from data from the UK Teratology Information Service (UKTIS), which captures information on exposure to drugs in pregnancy. Drawing upon this data, the MHRA was able to use its own expert advice to inform the benefit risk assessment of the vaccines

early on in the initial vaccine rollout, deeming them safe for use in pregnant women when compared with the risk of Covid-related injury or death.

852. Following the authorisation of the vaccines, frequent and continual review of case reports from pregnant individuals was conducted throughout the initial vaccine rollout. This involved MHRA experts reviewing each individual case report that detailed an event that occurred following vaccination of a pregnant woman. Specialist MHRA assessors also reviewed these reports, resulting in a detailed, cross-agency review process which provided valuable safety information to inform guidance on Covid-19 vaccine use in pregnancy. By January 2021, based on safety monitoring data, the Pfizer/BioNTech (Comirnaty), AstraZeneca (Vaxzevria) and Moderna (Spikevax) Covid-19 vaccines had all been deemed safe for use in pregnancy.

853. When considering vaccination in children, the Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax) Covid-19 vaccines were authorised for use in children and deemed safe, with clinical trials finding that the majority of side effects are mild and comparable to that seen in adults. Crucially these findings were supported by real-world evidence where vaccines had been deployed in children in the UK and internationally. However, the vaccines were not authorised for children until May 2021 and August 2021 respectively, over a year into the pandemic.

854. Ultimately, there are significant challenges to overcome when considering special population groups in a pandemic scenario, particularly when it comes to clinical trials and post-authorisation safety monitoring. The importance of a robust surveillance strategy in special groups such as pregnant women, where availability of pre-authorisation study data may be limited, is clear. Access to international and real-world data is equally valuable for vulnerable groups in the development of robust recommendations. The MHRA must continue to work closely with trial sponsors and across the healthcare matrix, including with Royal Colleges and learned societies for available real-world evidence to support the benefit risk of medical products across all populations.

Effective, timely and transparent communications

855. It is imperative that the MHRA maintains public trust to promote better health through uptake of vaccines and access to safe and effective medicines. The MHRA builds trust through

transparency about our role, our actions, and our decision-making. During the pandemic, when vaccine uptake rate was a concern, the MHRA changed its established communication practices to share more information on how regulatory decisions were made. Communicating effectively can be challenging during a pandemic due to the rapidly changing landscape and emerging evidence. The MHRA navigated these challenges with not only greater transparency but also, adaptive formats for publication of data, and proactive and reactive communications.

856. To address the challenge of vaccine hesitancy among some groups, cross-governmental plans were implemented. These included the MHRA's engagement with multicultural groups and Black, Asian, and minority ethnic groups to produce specific media to support vaccine education and public confidence [**JR/442 – INQ000494269; JR/443 – INQ000494274**]. From the start of the vaccination campaign in December 2020 and throughout the pandemic, representatives of the MHRA also spoke at events aimed at communities that were less likely to be vaccinated [**JR/444 – INQ000494270; JR/445 – INQ000494276**]. The MHRA received positive feedback from the Muslim Council of Britain about our level of engagement with their organisation and with Muslim communities during the pandemic [**JR/446 – INQ000494335**]. This strategy to adapt and tailor data to different groups to support communication is vital to supporting public health, and the MHRA seeks to continue this in future.

857. Prior to the Covid-19 pandemic the MHRA did not publish ADR data for vaccines. Covid-19 highlighted the importance of disseminating information to the public in easily accessible formats, and in a timely manner. As of January 2021, the MHRA started publishing ADR data for vaccines, and further developments were made to the format in December 2022, with the MHRA now publishing this in the form of interactive Drug Analysis Profiles (iDAPs), a new enhanced format of data visualisations which can be accessed via the Yellow Card website. Each iDAP contains a complete listing of all suspected ADRs reported to the MHRA via the Yellow Card scheme by healthcare professionals, members of the public, and pharmaceutical companies. The iDAPs provide improvements in accessibility and data protection, whilst allowing access to more data than has been published previously, thus also increasing transparency.

858. Concerning a specific safety issue, the MHRA worked with the Winton Centre for Risk and Evidence Communication on the communication of data on the age-related risk of the AstraZeneca (Vaxzevria) vaccine in the form of informational graphics, which is discussed

within the "ADR Chronologies" section for thrombosis with thrombocytopenia syndrome. The subsequent presentation of data by the Winton Centre was used by the then DCMO as part of the press conference on 7 April 2021 [**JR/230 - INQ000421323**]. Following publication of the age-gradient risk data, the vaccine uptake continued to increase in all age categories as can be seen in monthly publications of Covid-19 vaccinations, all of which can be found on the NHS England's web page [**JR/447 - INQ000421854**]. This type of accessible presentation of data, which was also then published by the Winton Centre, is a valuable approach to presenting the benefits and risks of treatment for future pandemics.

859. The overall conclusion is that robust systems for timely communication were essential to ensuring that patients, the public, and stakeholders remained informed on the latest safety information concerning vaccines and therapeutics, and so should be continued. These approaches should continue to be developed with the MHRA continuing to invest in resources for communication with patients and the public and in improved presentation of data.

Conclusion

860. On behalf of the MHRA, I would like to express my sincere condolences and sympathy to all those adversely affected by the Covid-19 vaccines, and our determination to continue to strengthen our safety systems.

861. Responding to the scale and urgency of the pandemic required all the MHRA's strengths: a willingness to innovate and utilise regulatory flexibilities to reach robust decisions in the shortest possible time, a commitment to independent science-based decision-making, and staff who fully demonstrated their determination to work in partnership with other healthcare organisations in their commitment to protect public health. The MHRA is committed to continuously learning and improving and it is clear from this reflective piece that there are areas where we can go further to ensure our readiness for future emergencies.

Statement of Truth

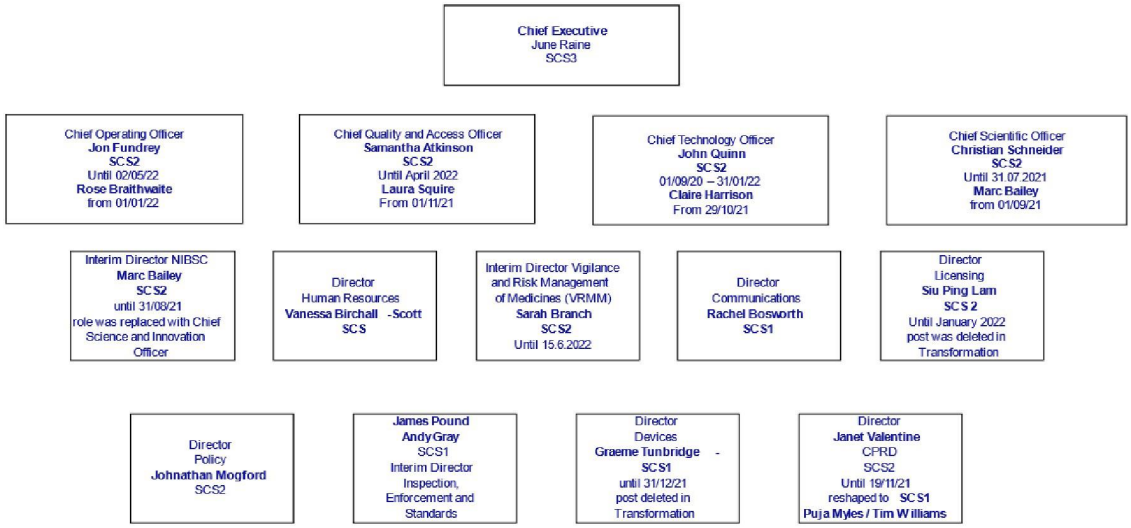
I believe that the facts stated in this witness statement are true. I understand that proceedings may be brought against anyone who makes, or causes to be made, a false statement in a document verified by a statement of truth without an honest belief of its truth.

Signed: Personal Data

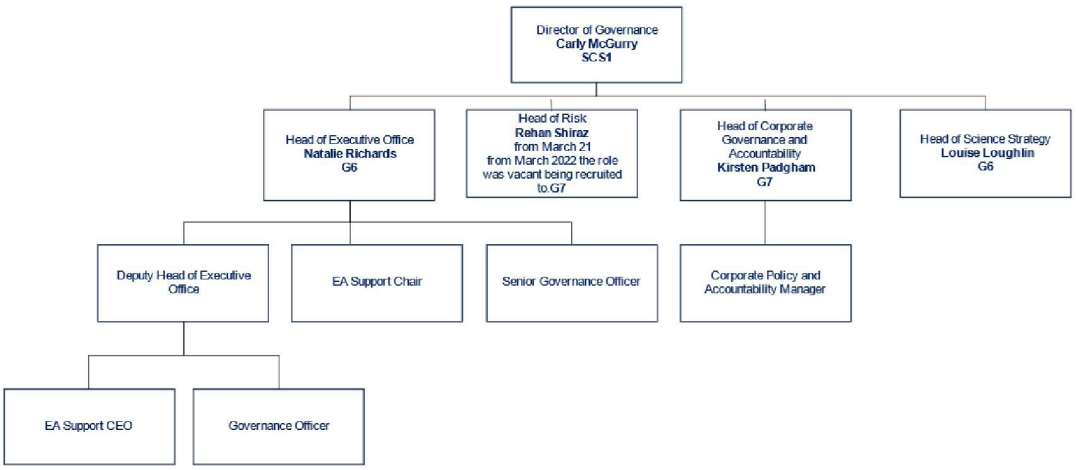
Dated: 11 September 2024

Annex A: MHRA membership - Structural Organograms (Pre-transformation)

Senior leadership structure

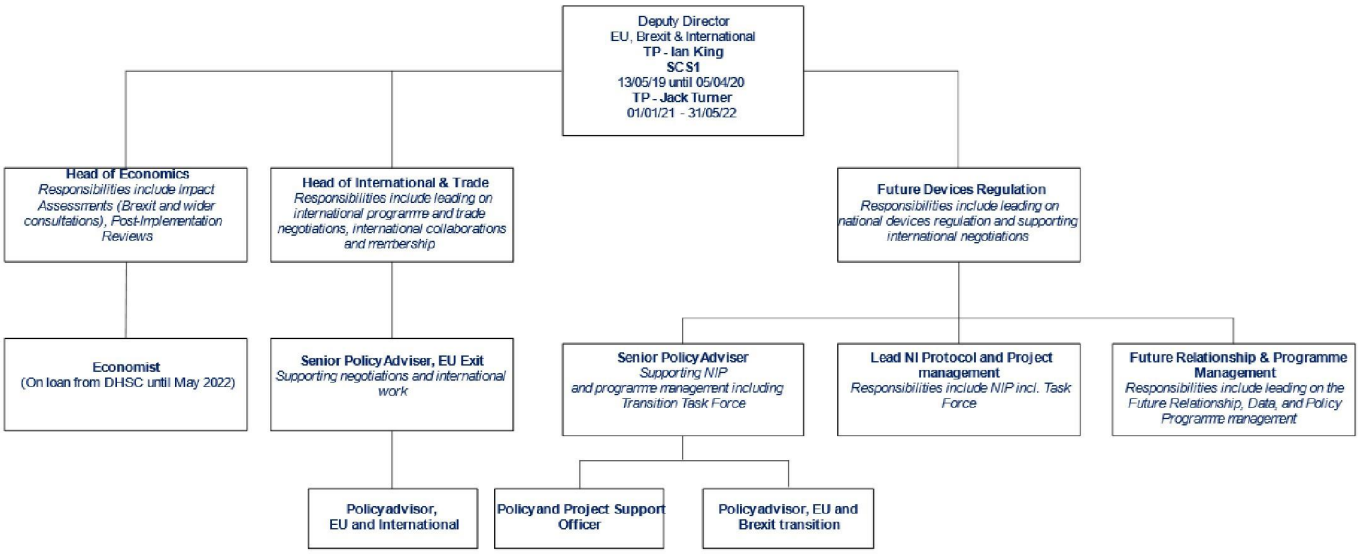


Governance Office

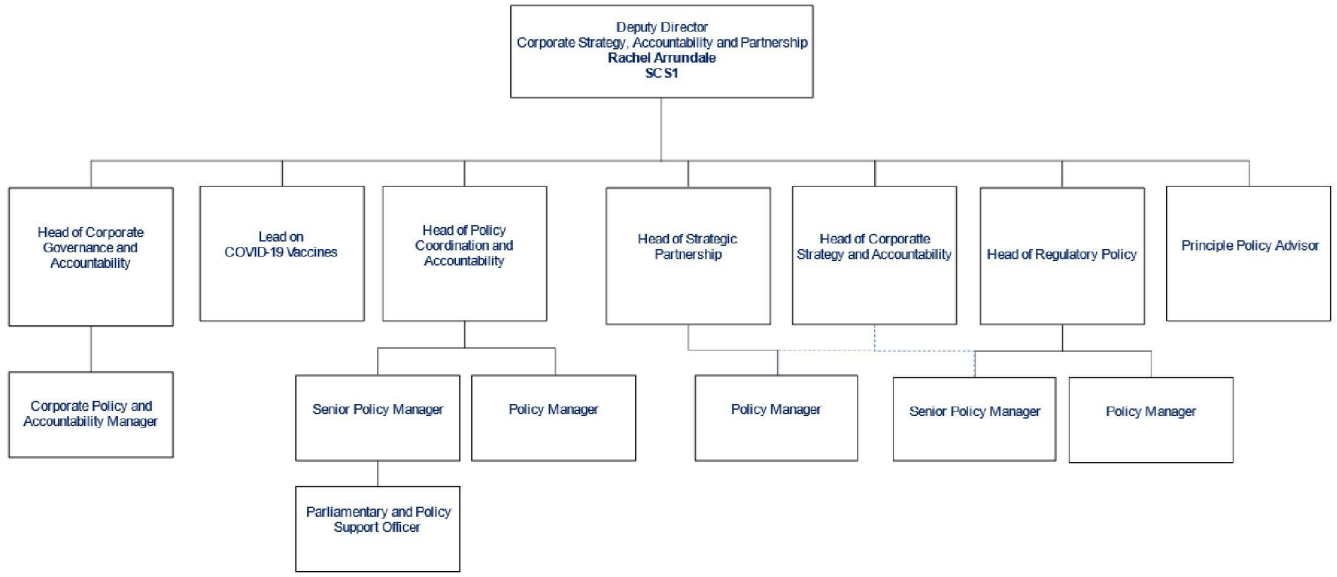


Policy Division

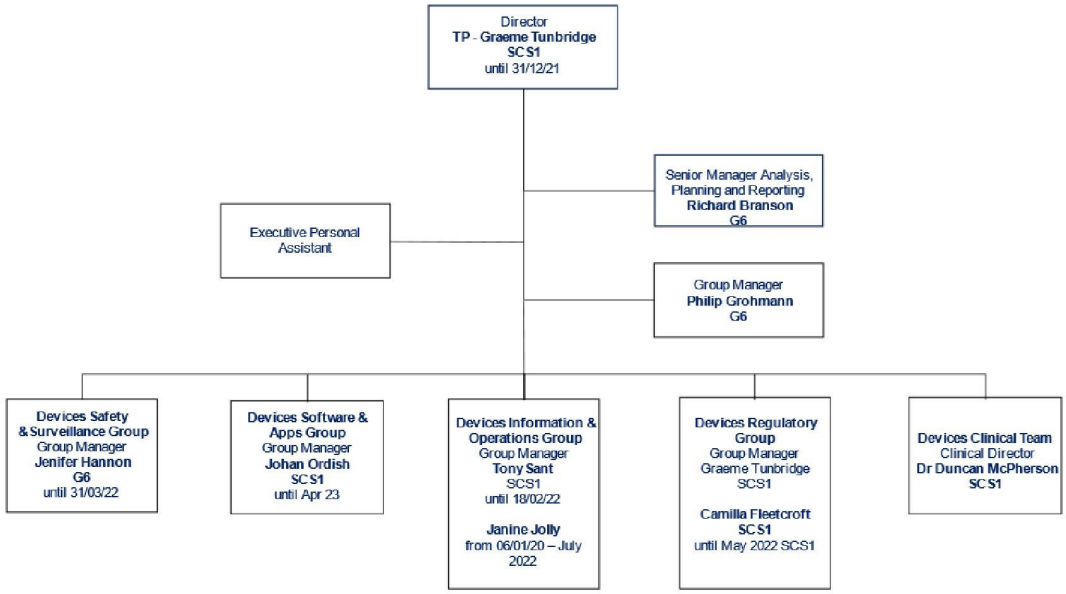
EU, Brexit & International



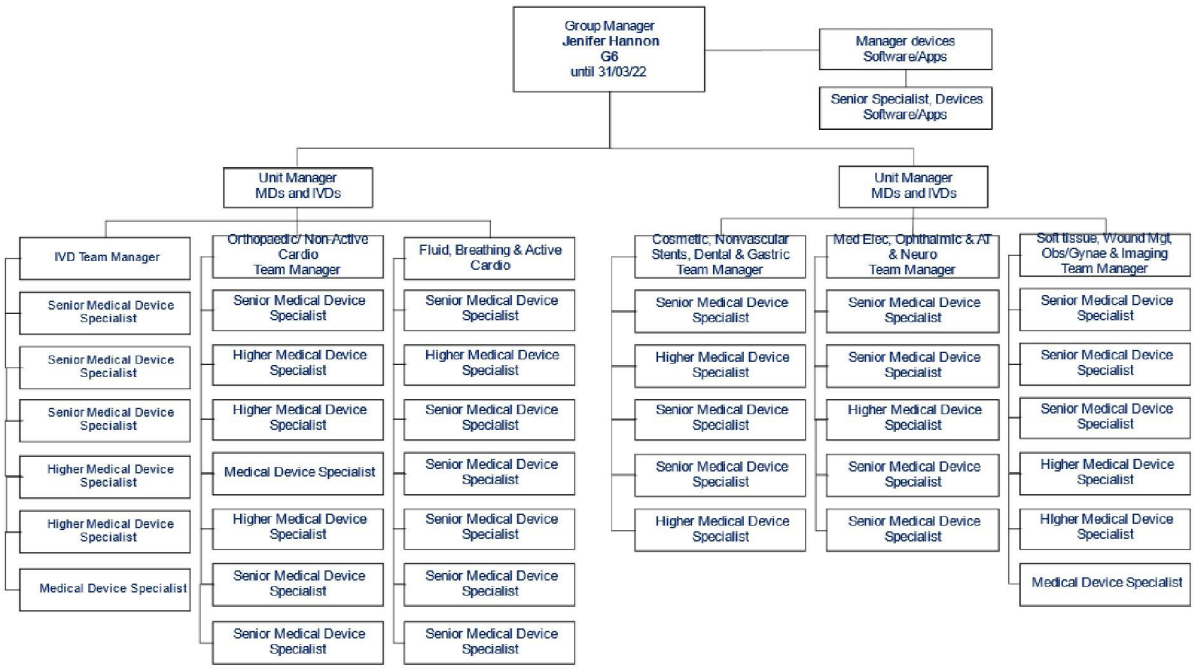
Corporate Strategy, Accountability and Partnership



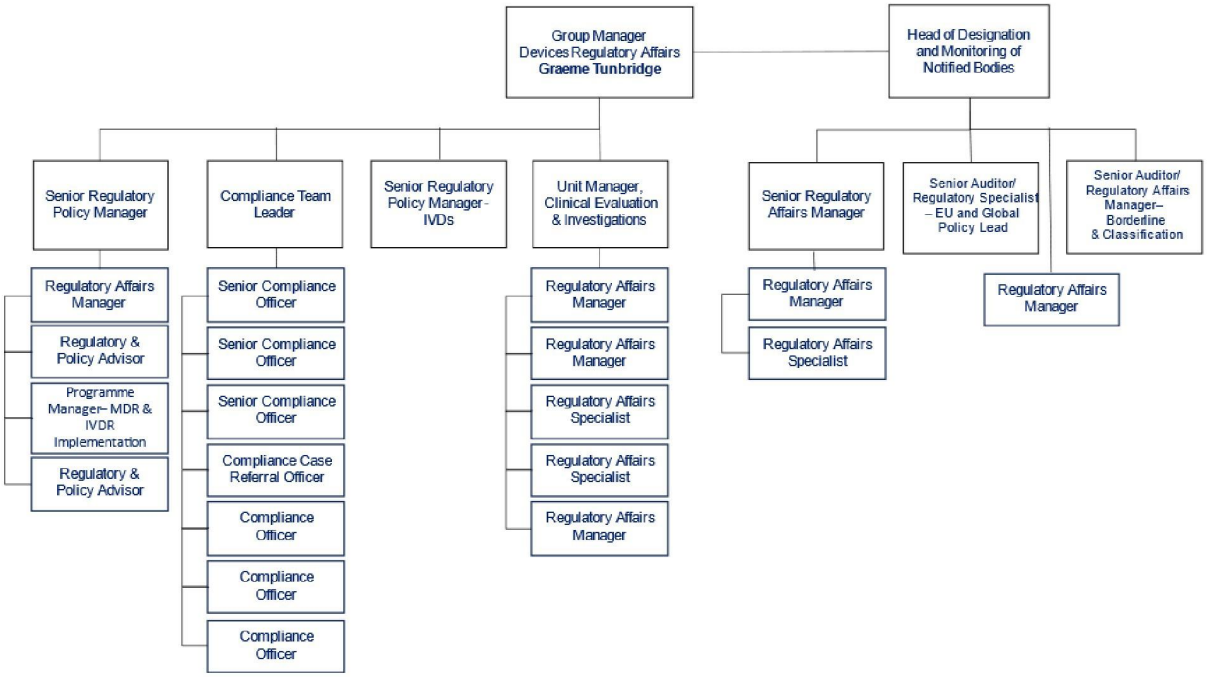
Devices Division



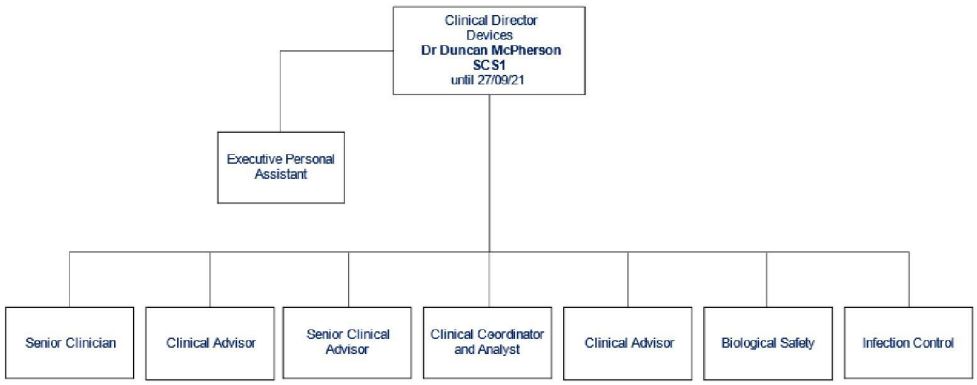
Devices Safety and Surveillance Group



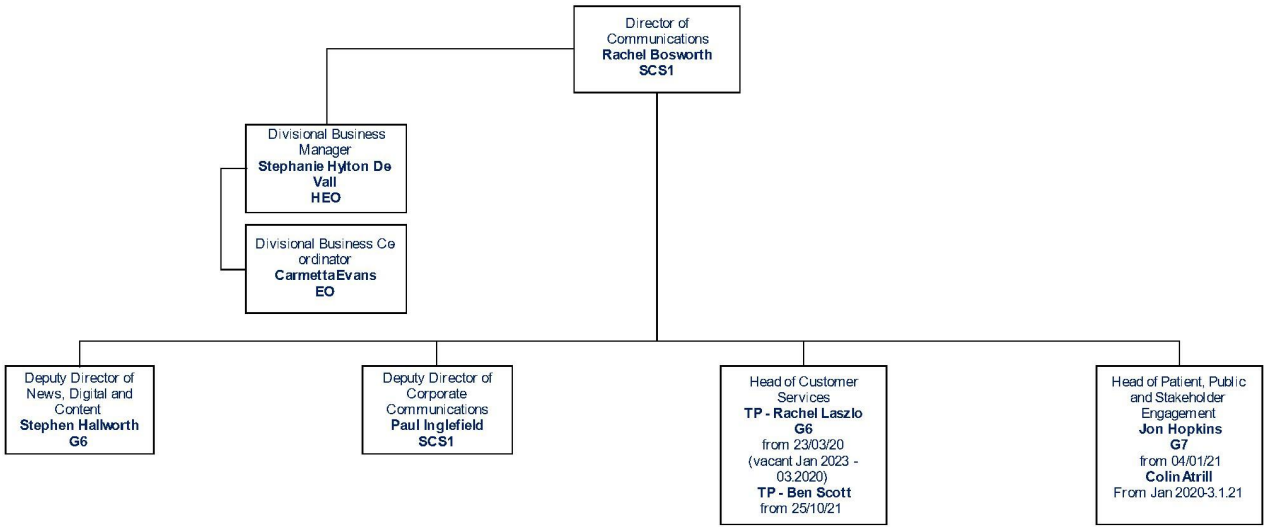
Devices Regulatory Group



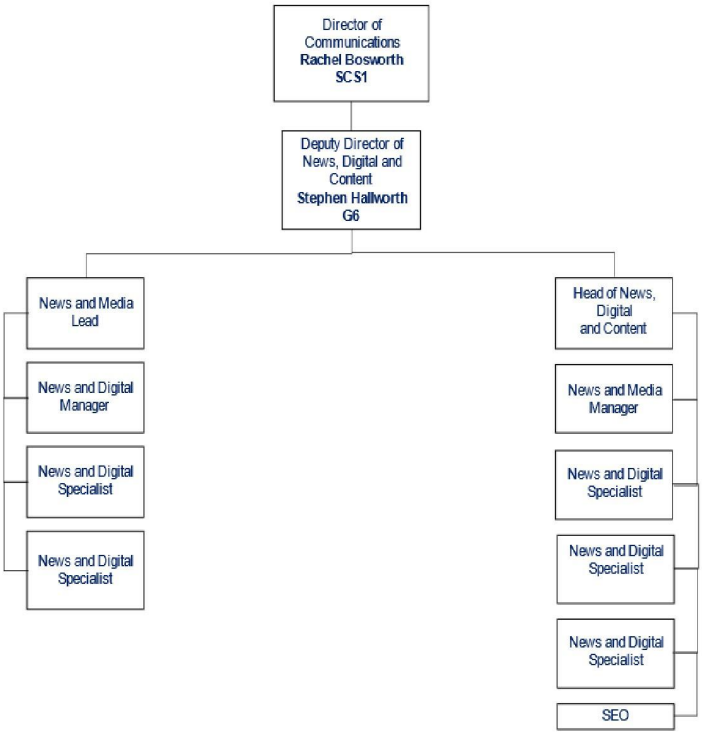
Devices Clinical Team



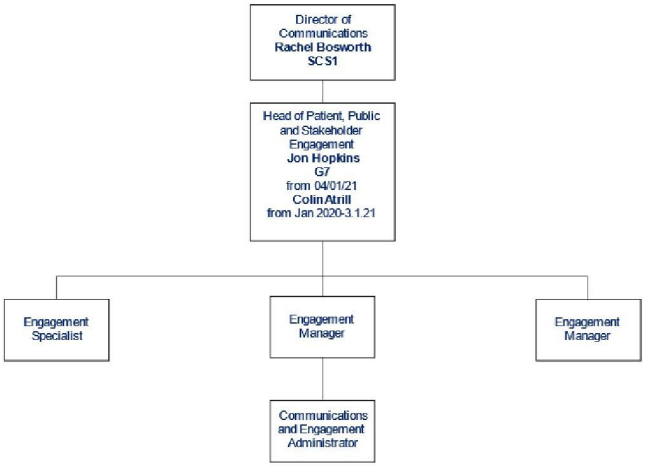
Communications Team



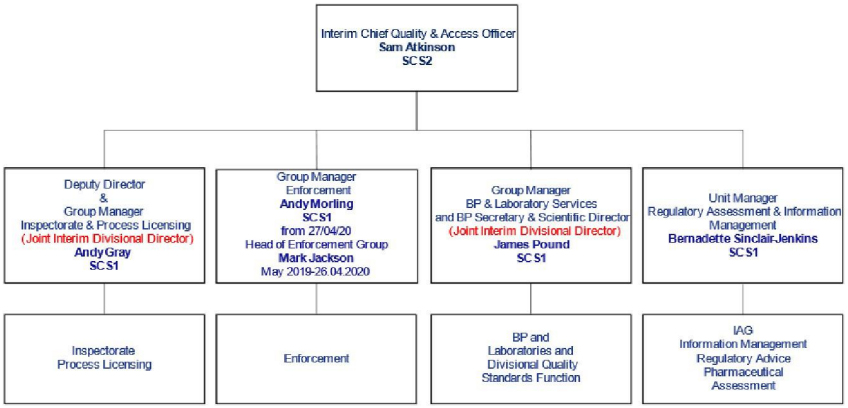
Communications Team



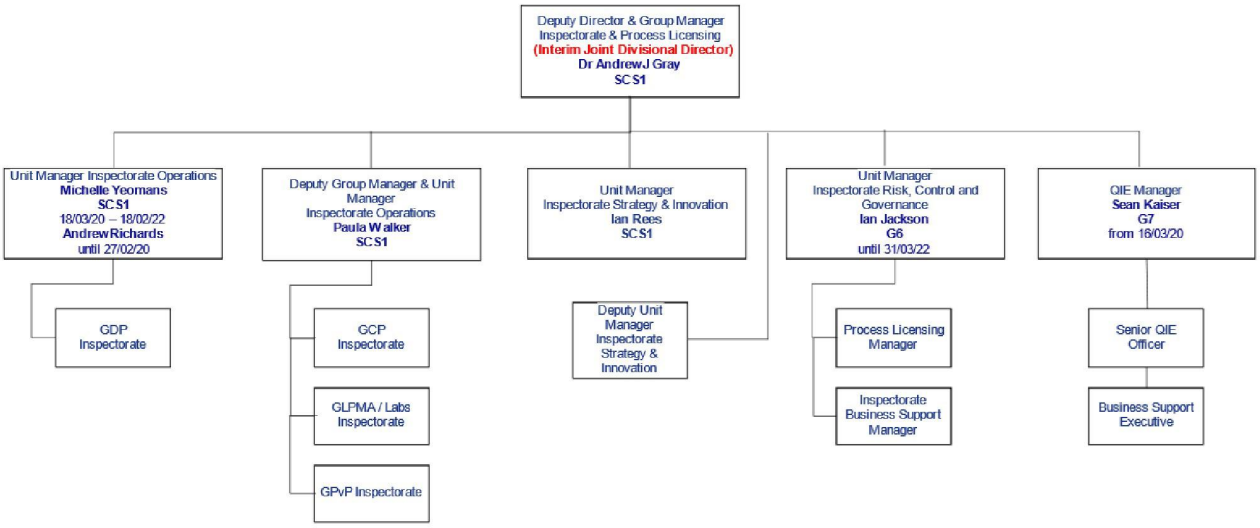
Communications Team



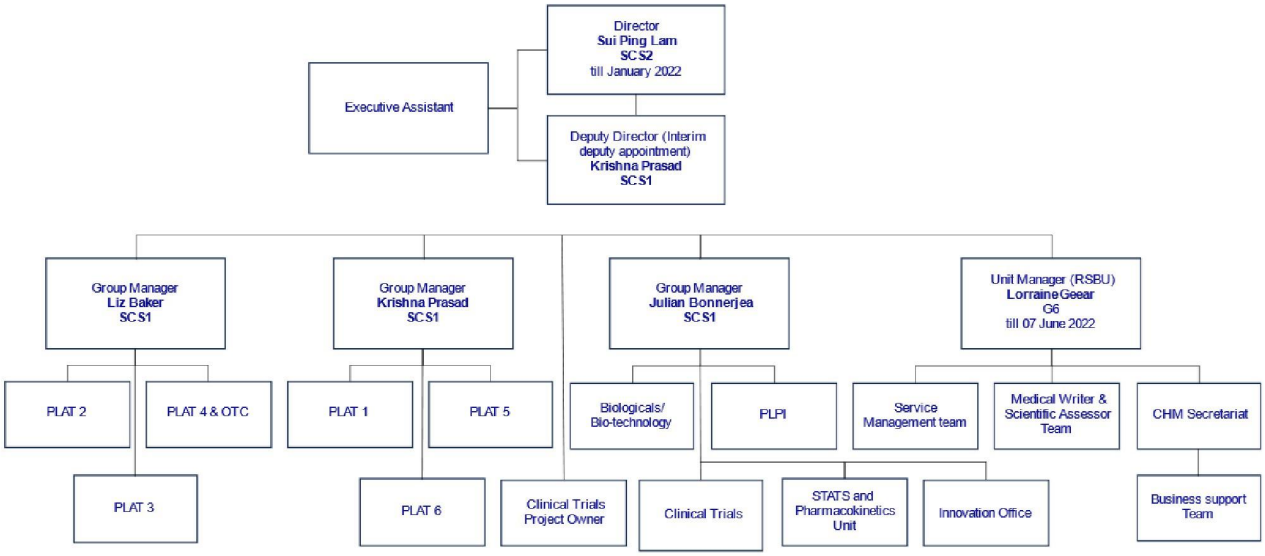
Inspection, Enforcement & Standards Division



Inspection, Enforcement & Standards Division

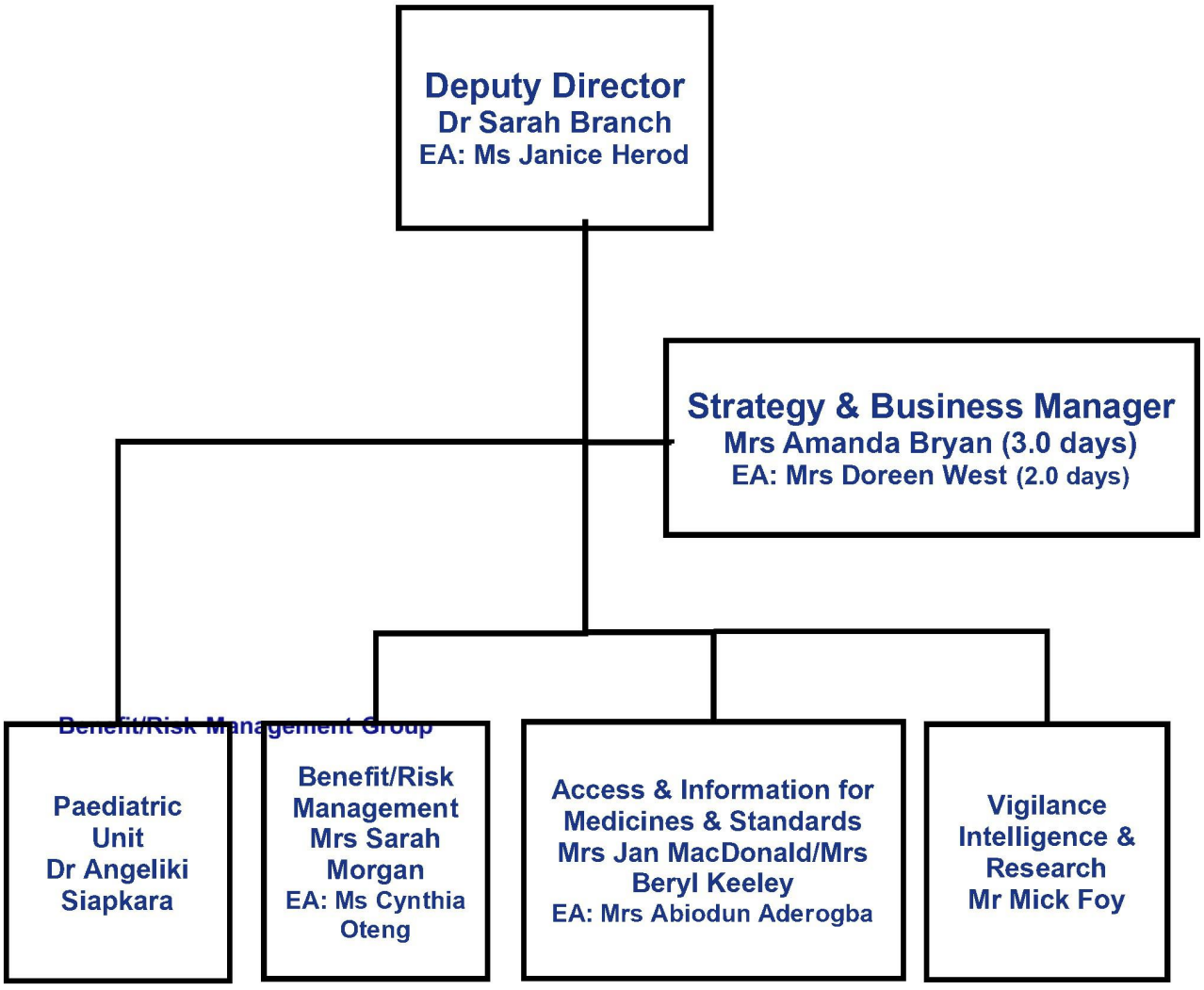


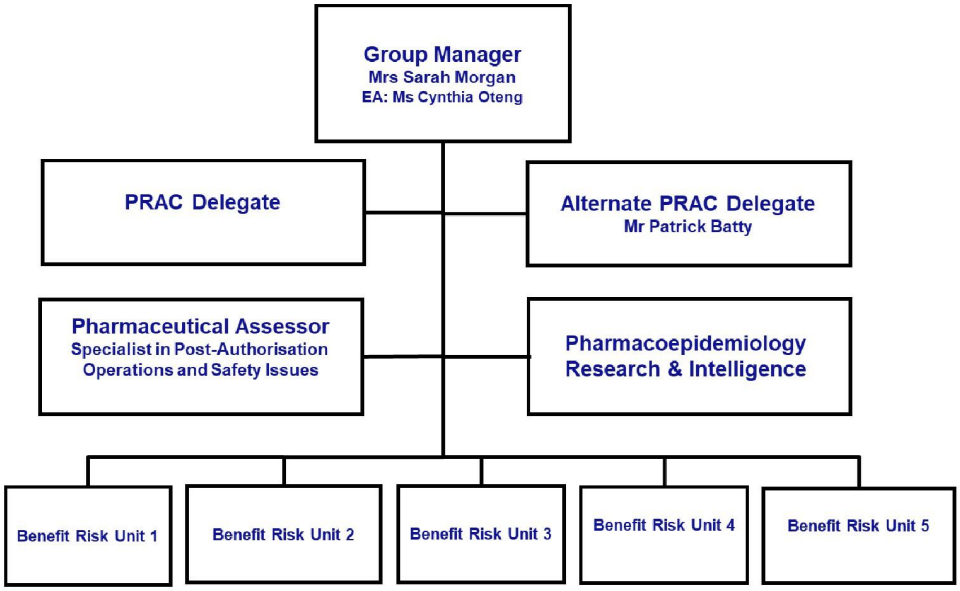
Licensing Division



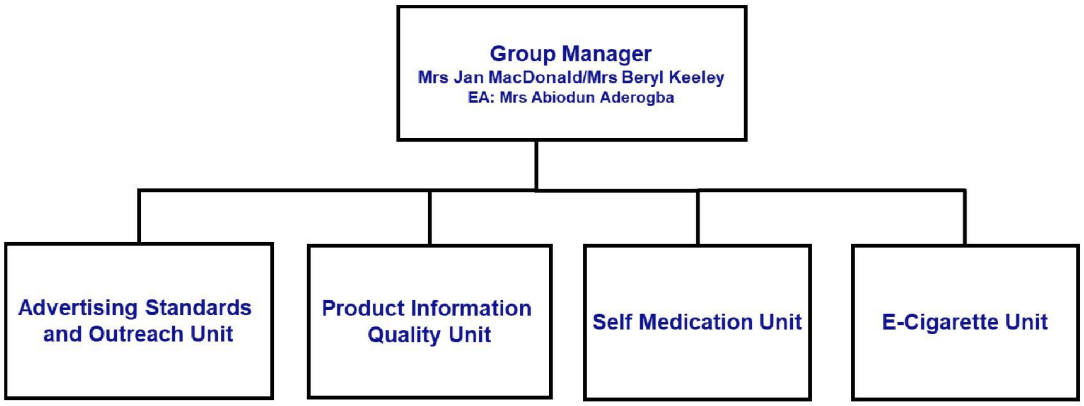
PLAT = Product Lifecycle Assessment Teams
PLPI = Product Licence (Parallel Import)

Vigilance and Risk Management of Medicines (VRMM) Division

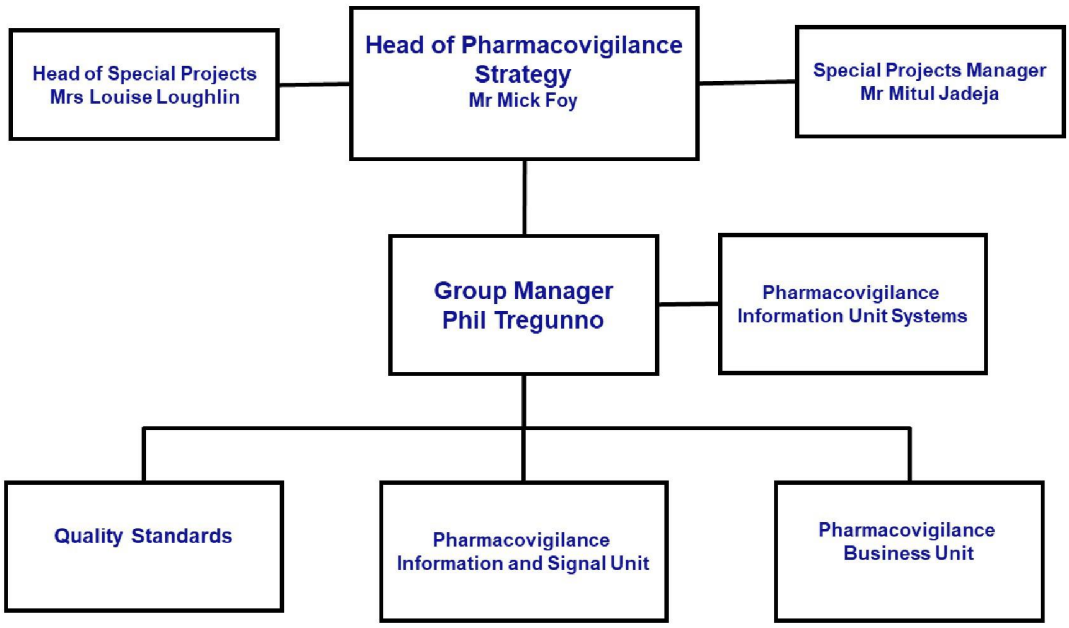


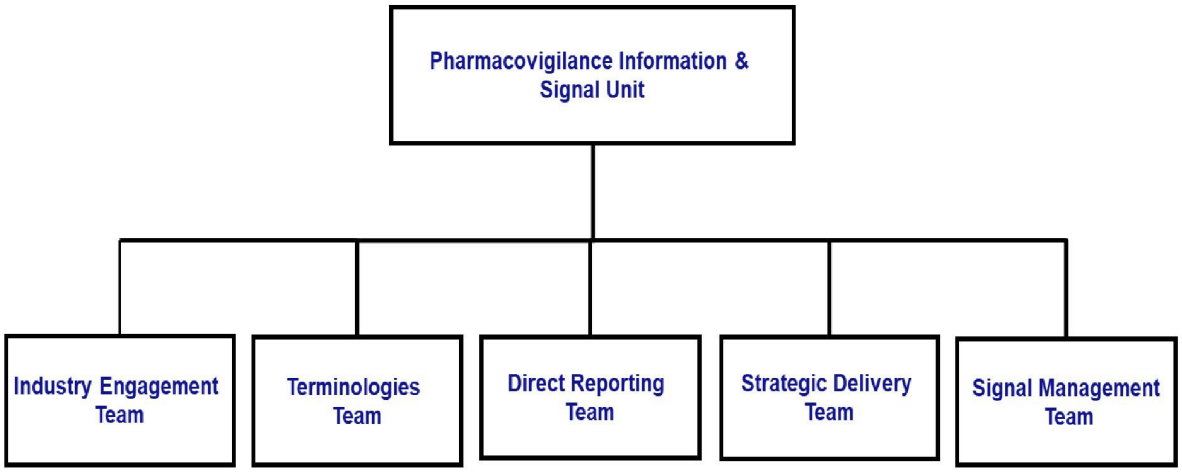


Access & Information for Medicines & Standards Group



Vigilance Intelligence & Research Group


Head of Special Projects
Mrs Louise Loughlin
Head of Pharmacovigilance Strategy
Mr Mick Foy
Special Projects Manager
Mr Mitul Jadeja
Group Manager
Phil Tregunno
Pharmacovigilance Information Unit Systems
Quality Standards
Pharmacovigilance Information and Signal Unit
Pharmacovigilance Business Unit


Pharmacovigilance Information & Signal Unit
Industry Engagement Team
Terminologies Team
Direct Reporting Team
Strategic Delivery Team
Signal Management Team

Annex B: Pre-approval medicines tables

Vaccines

i. COVID-19 Vaccine Janssen – adenoviral vector vaccine

Based on an adenovirus that has been modified to contain the gene for making a protein found on SARS-CoV-2. On 23 October 2020 the MHRA approved pre-authorisation UK clinical trials at Phase III.

Date	Event	Associated documents
11 March 2021	EMA granted a CMA for the use of the vaccine. This applied in Northern Ireland.	N/A
13 April 2021	Janssen submitted its application to the MHRA for a GB CMA via the ECDRP.	[**JR/448 - INQ000400214**]
6 and 7 May 2021	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/449** **INQ000409503**
26 May 2021	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA.	[**JR/450 - INQ000400216**]
28 May 2021	MHRA granted a CMA for patients aged 18 years and older, conditional upon the fulfilment of conditions included in said CMA.	[**JR/451 - INQ000400303**]
20 February 2023	The GB CMA was converted to a full GB MA by MHRA.	[**JR/452 - INQ000400275**]

ii. COVID-19 Vaccine Novavax (Nuvaxovid) – protein subunit vaccine

An adjuvanted monovalent vaccine, produced using recombinant DNA technology. On 23 September 2020 the MHRA approved pre-authorisation UK clinical trials at Phase III.

Date	Event	Associated documents
20 December 2021	EMA granted a CMA for the use of the vaccine. This applied in Northern Ireland.	N/A
26 January 2021	Novavax submitted its marketing authorisation application to the MHRA.	[**JR/453 - INQ000400200**]
27 and 28 January 2022	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/454 - INQ000409557**
2 February 2022	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA.	[**JR/455 - INQ000400255**] Despite bearing 'draft' markings, this is the document submitted to the Minister.
3 February 2022	MHRA granted a CMA for patients aged 18 years and older, conditional upon the fulfilment of conditions included in said CMA.	[**JR/456 - INQ000400315**]
26 August 2022	MHRA granted a CMA extension via the ECDRP to authorise the use of the vaccine in Great Britain for patients aged 12 to 17 years old.	[**JR/457 - INQ000400323**]

iii. COVID-19 Vaccine Valneva – inactivated whole virus vaccine

An inactivated adjuvanted Covid-19 vaccine. With this type of vaccine, the virus is grown in a laboratory and then made completely inactive so that it cannot infect cells or replicate in the body but can still trigger an immune response to the Covid-19 virus. This process is widely used already in the production of flu and polio vaccines. On 14 December 2020 the MHRA approved pre-authorisation UK clinical trials at Phases I and II.

Date	Event	Associated documents
20 August 2021	Valneva submitted its marketing authorisation application to the MHRA.	[**JR/458 - INQ000400244**]
7 April 2022	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/459 - INQ000409558**
12 April 2022	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA.	[**JR/460 - INQ000400313**]
13 April 2022	MHRA granted a CMA for patients aged 18 to 50, conditional upon the fulfilment of conditions included in said CMA.	[**JR/461 - INQ000400304**]

iv. COVID-19 Vaccine Sanofi-Pasteur (VidPrevtyn Beta) – protein subunit vaccine

A protein-based adjuvanted Covid-19 booster vaccine. VidPrevtyn Beta combines the spike protein from a COVID virus variant, Beta, with an 'adjuvant' – an additional ingredient designed to trigger a stronger immune response. The Agency was not involved in authorising clinical trials for the Sanofi-Pasteur (VidPrevtyn Beta) vaccine as they were conducted outside of the UK.

Date	Event	Associated documents

10 November 2022	EMA granted a MA for the use of the vaccine. This applied in Northern Ireland.	N/A
11 November 2022	Sanofi-Pasteur submitted its application to the MHRA for a GB MA via the ECDRP.	[**JR/462 - INQ000400270**]
15 December 2022	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/463 - INQ000400327**]
15 December 2022	MHRA sent a ministerial submission to the Licensing Minister recommending a MA.	[**JR/464 - INQ000400274**
20 December 2022	MHRA granted a MA for patients aged 18 years and older for the use of the vaccine in Great Britain as a heterologous "booster".	[**JR/465 - INQ000400305**]

v. COVID-19 Vaccine SK Chemicals (SKYCovion) – protein subunit vaccine

This vaccine combines SARS-CoV-2 virus spike protein with an adjuvant. The MHRA was not involved in authorising clinical trials for the SKYCovion vaccine as they were conducted outside of the UK.

Date	Event	Associated documents
15 March 2022	SK Chemicals submitted its marketing authorisation application to the MHRA.	[**JR/466 - INQ000400256**]
23 March 2023	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a	[**JR/467 - INQ000400328**]

	product licence should be granted.	
16 May 2023	MHRA sent a ministerial submission to the Licensing Minister recommending a MA.	[**JR/468 - INQ000400287**] Despite bearing "draft" markings, this document is the document which was sent to the Licensing Minister.
26 May 2023	MHRA granted a MA for patients aged 18 years and older.	[**JR/469 - INQ000400306**]

vi. Bimervax (previously COVID-19 Vaccine HIPRA) – protein subunit vaccine

This vaccine contains a protein produced in the laboratory that consists of part of the SARS-CoV-2 spike protein from the Alpha and Beta virus variants. Bimervax combines this part of the SARS-CoV-2 virus spike protein with an 'adjuvant' – an additional ingredient designed to trigger a stronger immune response. The MHRA was not involved in approving pre-authorisation clinical trials for this vaccine as they were conducted outside of the UK.

Date	Event	Associated documents
30 March 2023	EMA granted a MA for the use of the vaccine. This applied in Northern Ireland.	N/A
4 April 2023	The HIPRA Human Health submitted its application to the MHRA for a GB MA via the ECDRP.	[**JR/470 - INQ000400284**]
19 July 2023	MHRA sent a ministerial submission to the Licensing Minister recommending a MA.	[**JR/471 - INQ000400289**]
31 July 2023	MHRA granted a MA for the use of the vaccine in Great Britain as a	[**JR/472 - INQ000400290**]

	"booster" in adults aged 16 years and older.	

Four strain adapted vaccines that are authorised by MHRA:

vii. Moderna (Spikevax) bivalent Original/Omicron BA.1 vaccine

A booster vaccine. In each dose of the booster vaccine, half of the vaccine (25 micrograms) targets the original virus strain from 2020 and the other half (25 micrograms) targets Omicron. On 11 August 2020 the MHRA approved pre-authorisation UK clinical trials at Phase III.

Date	Event	Associated documents
21 June 2022	Moderna submitted its marketing authorisation application to the MHRA.	[**JR/473 - INQ000400258**]
4 August 2022	DHSC wrote to request the Agency's view on whether the vaccine would be suitable for temporary authorisation for supply under regulation 174.	[**JR/474 - INQ000400259**]
12 August 2022	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/475 - INQ000409561**
12 August 2022	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA for the use of the vaccine as a "booster" in Great Britain, and regulation 174 temporary authorisation for Northern Ireland,	[**JR/476 - INQ000400260**] Despite bearing "draft" markings, this document is the document which was sent to the Licensing Minister.

	conditional upon the fulfilment of conditions included in said CMA and regulation 174 authorisation.	
12 August 2022	MHRA granted a CMA for patients aged 6 years and older who have previously received at least a primary vaccination course against Covid-19, conditional upon the fulfilment of conditions included in said CMA.	[**JR/477 - INQ000400307**]
12 August 2022	MHRA granted an emergency use R174 authorisation for Northern Ireland to ensure access to the vaccine across the whole of the United Kingdom, conditional upon the fulfilment of conditions included in said R174.	[**JR/478 - INQ000400261**]

viii. Pfizer/BioNTech Comirnaty Original/Omicron BA.1 vaccine

A booster vaccine. It contains tozinameran and riltozinameran, an mRNA molecule with instructions for producing a protein from the Omicron BA.1 subvariant of SARS-CoV-2. The MHRA authorised a number of Phase II pre-approval clinical trials for the Pfizer/BioNTech Comirnaty Original/Omicron bivalent vaccines.

Date	Event	Associated documents
24 August 2022	Pfizer/BioNTech submitted its marketing authorisation application to the MHRA via the ECDRP.	[**JR/479 - INQ000400262**]
1 September 2022	EMA granted a CMA for the use of the vaccine. This applied in Northern Ireland.	N/A

1 and 2 September 2022	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/480 - INQ000400329**]
2 September 2022	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA.	[**JR/481 - INQ000400337**] Despite bearing "draft" markings, this document is the document which was sent to the Licensing Minister.
2 September 2022	MHRA granted a CMA for patients aged 18 years and older, conditional upon the fulfilment of conditions included in said CMA.	[**JR/482 - INQ000400309**]

ix. Pfizer/BioNTech Comirnaty Original/Omicron BA.4-5 vaccine

A bivalent vaccine. In each dose of the vaccine, half of the vaccine (15 micrograms) targets the original virus strain and the other half (15 micrograms) targets Omicron (BA.4-5). The MHRA authorised a number of Phase II pre-approval clinical trials for the Pfizer/BioNTech booster vaccines.

Date	Event	Associated documents
12 September 2022	EMA granted a CMA for the use of the vaccine. This applied in Northern Ireland.	N/A
27 October 2022	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/483 - INQ000409564**
7 November 2022	The Licensing Minister agreed to receive monthly submissions	[**JR/484 - INQ000400269**]

	"for information" about regulatory decisions made by the Agency, and received information regarding MHRA's decision to grant a GB CMA for the vaccine.	
9 November 2022	MHRA granted a GB MA for patients aged 6 months and older.	[**JR/485 - INQ000400310**]

x. Moderna (Spikevax) bivalent Original/Omicron BA.4-5 vaccine

This vaccine contains elasomeran and an additional mRNA molecule, davesomeran, with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2. On 4 February 2022 the MHRA approved pre-authorisation UK clinical trials at Phases II and III.

Date	Event	Associated documents
19 October 2022	EMA granted a CMA for the use of the vaccine. This applied in Northern Ireland.	N/A
22 November 2022	Moderna submitted its marketing authorisation application to the MHRA via the ECDRP.	[**JR/486 - INQ000400271**]
26 January 2023	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/487 - INQ000400283**]
21 February 2023	MHRA granted a MA for patients aged 12 years and older.	[**JR/488 - INQ000400308**]

New medicines for Covid-19 in the UK

a. Casirivimab and imdevimab (Ronapreve)

A monoclonal antibody combination (MAB) product containing equal amounts of casirivimab and imdevimab. Ronapreve was authorised for prophylaxis (to prevent Covid-19 infection) as well as for the treatment of Covid-19. The only other prophylactic medicine the Agency approved for Covid-19 was Evusheld, which is described from paragraph 273. On 18 September 2020 the MHRA approved pre-authorisation UK clinical trials at Phase II.

Date	Event	Associated documents
30 April 2021	Roche submitted its marketing authorisation application to the MHRA.	[**JR/489 - INQ000400335**] The MHRA continues to use EMA template application form since leaving the European Union.
27 July 2021	MHRA sought advice from the Covid-19 Therapeutics EWG.	[**JR/490 - INQ000400317**]
5 August 2021	The EWG made recommendations to the CHM.	[**JR/491 - INQ000409505**
10 August 2021	DHSC wrote to request the Agency's view on whether the medicine would be suitable for temporary authorisation for supply under regulation 174.	[**JR/492 - INQ000507346**
16 August 2021	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/493 - INQ000400266**]
18 August 2021	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA and R174 for the use of	[**JR/494 – INQ000400241**]

	Ronapreve in GB and Northern Ireland.	
19 August 2021	MHRA granted regulation 174 authorisation for supply in Northern Ireland and the GB CMA, conditional upon the fulfilment of conditions included in said R174 and GB CMA.	[**JR/495 - INQ000400243;** **JR/189(a) - INQ000400242**]

b. Molnupiravir (Lagevrio)

The oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has shown antiviral activity against SARS-CoV-2. On 2 October 2020 the MHRA approved pre-authorisation UK clinical trials at Phases II and III.

Date	Event	Associated documents
30 June 2021	Merck Sharpe & Dohme submitted its marketing authorisation application to the MHRA.	[**JR/496 - INQ000400218**]
17 August 2021, 20 September 2021 and 15 October 2021	MHRA consulted the Covid-19 Therapeutics EWG.	[**JR/497** **INQ000409552** **JR/498 - INQ000409553** **JR/499 - INQ000409554**
12 October 2021	DHSC wrote to request the Agency's view on whether the medicine would be suitable for temporary authorisation for supply under regulation 174.	[**JR/500 -** **INQ000067797**
28 and 29 October 2021	MHRA sought advice from the CHM who advised that the benefit	[**JR/143 - INQ000400267**]

	risk was favourable and that a product licence should be granted.	
2 November 2021	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA and R174 for the use of Molnupiravir in GB and Northern Ireland.	[**JR/501 - INQ000400247**]
4 November 2021	MHRA granted regulation 174 authorisation for supply in Northern Ireland and the GB CMA, conditional upon the fulfilment of conditions included in said R174 and GB CMA.	[**JR/502 - INQ000371345; JR/503 - INQ000400292**]

c. Sotrovimab (Xevudy)

A monoclonal antibody, a type of protein designed to recognise a specific target on the SARS-CoV-2 virus. On 27 October 2020 the MHRA approved pre-authorisation UK clinical trials at Phases I, II and III.

Date	Event	Associated documents
19 July 2021	GlaxoSmithKline submitted its marketing authorisation application to the MHRA.	[**JR/504 - INQ000400220**]
5 October 2021	DHSC wrote to request the Agency's view on whether the medicine would be suitable for temporary authorisation for supply under regulation 174.	[**JR/505 - INQ000067190**

15 October 2021 and 16 November 2021	MHRA consulted the Covid-19 Therapeutics EWG.	[**JR/499 - INQ000409554 JR/506 - INQ000400280**
29 November 2021	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/507 - INQ000400268**]
1 December 2021	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA and R174 for the use of Sotrovimab in GB and Northern Ireland.	[**JR/508 - INQ000400251**]
1 December 2021	MHRA granted regulation 174 authorisation for supply in Northern Ireland and the GB CMA, conditional upon the fulfilment of conditions included in said R174 and GB CMA.	[**JR/509 - INQ000400252**; **JR/510 - INQ000400311**]

d. Nirmatrelvir with ritonavir (Paxlovid)

An oral protease inhibitor active against coronaviruses that are known to infect humans.2 which is co-administered with ritonavir to increase nirmatrelvir concentrations to the target therapeutic range. On 5 May 2022 the MHRA approved pre-authorisation UK clinical trials at Phases II and III.

Date	Event	Associated documents
22 November 2021	The DHSC wrote to request the Agency's view on whether the	[**JR/511 - INQ000067444**

	medicine would be suitable for temporary authorisation for supply under regulation 174.	
24 November 2021	Pfizer submitted its marketing authorisation application to the MHRA.	[**JR/512 - INQ000400249**]
20 December 2021	MHRA consulted the Covid-19 Therapeutics EWG.	[**JR/513 – INQ000400334**
30 December 2021	MHRA sought advice from the CHM who advised that the benefit risk was favourable and that a product licence should be granted.	[**JR/514 INQ000409510**
30 December 2021	MHRA sent a ministerial submission to the Licensing Minister recommending a CMA and R174 for the use of Paxlovid in GB and Northern Ireland.	[**JR/515 - INQ000400302**]
31 December 2021	MHRA granted regulation 174 authorisation for supply in Northern Ireland and the GB CMA, conditional upon the fulfilment of conditions included in said R174 and GB CMA.	[**JR/516 - INQ000287719** **JR/517 - INQ000400291**]