Scanned 12/3

From: Name Redacted

Date: 11 March 2015

PRIME MINISTER

cc: Jeremy Heywood
Chris Martin
Name Redacted
Jean-Christophe Gray
Jo Johnson
Helen Bower
Michael Gove
Name Redacted

1) See scribbles.
2) DRD letter is incoherent: it says "we need a no strategy" & then says "our current approach is working". Pls get me the right answer: which is it?
3) No stopping doctors. No direct flights. No compulsory.

DC 12.3.15

EBOLA UPDATE

A roundup of live operational and policy issues on ebola.

Incoming case(s)

1. Name Redacted a 25-year old UK Army medic (NB these details are not public yet), is being flown back overnight on a C-17. Dr Name Redacted from the Royal Free will be on the flight, and will take the patient directly to the Royal Free. As with previous cases, we will prepare a draft letter for you to send to her asap – and given this is now the third case that Name and his team have handled (as well as numerous false alarms), we thought it might be a good idea for you thank him for his work so far as well, so unless you object will send you a draft letter to this effect. ✓

2. We do not yet have the full facts around Name case – we know that she was working in the Irrelevant & Sensitive and presented with symptoms late on Monday. Following the contact tracing exercise, there are four individuals identified as at-risk – One Irrelevant & Sensitive developed flu-like symptoms and tested negative for ebola earlier today. This will need re-testing several times before we can be sure she is really in the clear. There are also three doctors at the centre who conducted ✓

the initial assessment of the patient and were not wearing full PPE while taking swabs, with two assessed at higher risk than the other. None of the doctors are symptomatic at this stage but we are planning to bring them back to the UK in accordance with our protocol for high-risk cases.

3. As discussed this morning, this will stretch the capacity of the specialist NHS teams covering ebola cases here. The plan is to fly Name and the two higher-risk doctors back to the Royal Free immediately, but to take the Irrelevant & Sensitive and the lower risk doctor to Newcastle's infectious disease ward. Because we are at maximum capacity of the MoD medical transport teams (while holding one team back in case there are any more positive cases in the 36 hours required for the other teams to recover), the quickest means to deliver the evacuation to Newcastle will be a commercial medevac over the weekend. We have tested this thoroughly today and it really does look like the fastest these extractions can be done safely, and are separately comfortable that the NHS in Newcastle have sufficient facilities and fully trained staff to handle both cases there if they ended up developing symptoms (which would be preferable to moving patients around the country if they developed symptoms, or extending the Royal Free facility in a way which undermined the hospital's A+E capacity).

4. Finally, you should be aware that we have been alerted to the possibility of a further, case of a Irrelevant & Sensitive official who may have been exposed to a confirmed ebola case in Sierra Leone. We'll know more through tomorrow, and will also keep you posted on any changes to the condition of the returning patients.

Outstanding letters

5. You have received a number of letters on our ebola effort in recent days:-

6. Justine Greening has written following her recent visit with a useful summary of what the effort in Sierra Leone now looks like and where we're heading. She is also giving an oral statement to Parliament tomorrow.

7. Jeremy Hunt has written to suggest targeting screening efforts on airports with the highest volume of incoming passengers from West Africa, with other arrivals asked to register for telephone screening. In response to Jeremy's letter, Patrick McLoughlin has also written to request permission to tell airlines that they can restart direct flights. The Home Secretary has also responded tonight (annexed below) to support Jeremy Hunt's request and ask

for £1.5m to cover the cost of the Border Force role in screening through 2015/16.

8. Taking the Home Secretary's ask first, I've discussed with Brendan and we think that given the role of Border Force officers in the screening process is relatively minor compared to (for example) PHE, and that it is unlikely we will need screening through the whole of the 2015/16 financial year, we are not in favour of pushing for this request with HMT. I'd suggest that we should not agree to this ask now but should keep it under review for the remote likelihood that the number of imported cases dramatically increases. **Do you agree?** Yes - it is a small figure it's in contain.

9. While the Health Secretary's proposals have some merit and I can see why the Transport Secretary is keen to restart direct flights as soon as possible Oliver Letwin and Ed Llewellyn are not convinced that we have the room to risk a 'complacency on ebola' story at this stage of the response. We face a bumpy road to zero cases in West Africa and will need to fight against waning attention and interest from the international community. We agree with Oliver and Ed – while a middle ground of scaling back screening at St Pancras, Manchester and Birmingham would be less risky, **are you happy for us err on the side of caution and block these proposals altogether?** Yes Correct

10. Finally, Name Redacted has written to follow up on the discussion you had with him during the Business Advisory Group meeting, with his proposal for a Biodefence Preparedness Organisation. No need to peruse in depth if you are busy, and we're getting a response from DH for you to send to Andrew. ✓

11. You should know that Oliver is working hard with the CMO (and teams in DH, FCO and DfID) to pull together a credible long-term international response across the areas which we discussed with the panel of medical experts before Christmas, which will continue during purdah and will draw on Name Redacted's sensible thinking (though will almost certainly end up looking a bit different). We're making some good progress, particularly on establishing the rapid response force as a bolt-on to the WHO, but it's a crowded pitch and we have some way to go yet. I think this is one to return to at the G7 when there will ample opportunity to continue our global leadership on stopping ebola happening again, building on your intervention at the G20. We'll keep you posted.

Name Redacted

Letter from the Home Secretary

I am grateful for the opportunity to comment on Public Health England (PHE) proposals for refocusing Ebola screening at ports and their recommendations for deciding how and when the screening process should come to an end. The proposals as outlined seem sensible and are supported by Home Office officials.

As you are aware Border Force has supported the screening process by identifying and referring passengers of interest to PHE. My officials have been working closely with DH officials to minimise the impact on operations at the Border. I welcome PHE's commitment to keep the screening process under review: if the number of passengers identified for screening increases there is a corresponding impact on queues. This can be better managed if PHE officials are also in attendance.

To date Border Force has supported the screening process by diverting resources from elsewhere. But Border Force estimates the total cost of continuing the screening regime at current levels is £1.5 million per annum. This includes the cost of 31 Border Force officers who have been moved from other frontline duties. Following recent reductions in the Home Office budget Border Force will only be able to support the screening process in the next financial year if these costs are reimbursed, which would allow for the retention of these posts.

I note your plans to explore opportunities to further strengthen the legal framework to deal effectively with public health emergencies such as Ebola. Home Office officials and Border Force have been working closely with Department of Health

colleagues to support their work on the development of contingency powers and this should continue.

I am copying this letter to the Prime Minister, the Foreign Secretary, the Secretary of State for International Development, the Transport Secretary, the Minister for Government Policy, the Cabinet Secretary and the National Security Advisor.

Department
for International
Development

10th March 2015

PRIME MINISTER

Update on Ebola

I have recently returned from my third visit to Sierra Leone, and wanted to update you on progress and challenges in delivering our response.

Our strategy is working. The number of cases per week has reduced from over 500 in November to less than 80. Our objective was to get transmission in Sierra Leone down to one by the turn of the year. We achieved this objective in December, and since then have been focused on getting transmission down to zero.

We now face a new and different challenge in 'getting to zero'. This involves redoubling our efforts on social mobilisation to persuade everyone who may have Ebola to present early; focusing on active surveillance to ensure cases are quickly spotted; and ensuring full contact tracing, working through transmission chains to work out who may be at risk. The resources and expertise to do this are in place.

Getting to zero requires a new strategy. My visit brought home to me the challenges of this new phase. Last week, one Ebola positive individual travelled from Freetown to Bombali district, was treated by traditional healers and subsequently given a traditional burial. As a result 43 people have now been infected. Our team have the situation under control, but we will need to hold our nerve as progress on the 'bumpy road to zero' is knocked by such events.

The biggest risk to progress is complacency. As the number of cases decrease, there is a growing tendency to return to business as usual. The President is critical to stopping this happening. When I met him, I was clear that he must maintain the leadership he has shown thus far. He said the right things and publicly reiterated these messages at the Brussels Conference. I believe that he is genuine, but we need to see these positive intentions translate into action. The team are monitoring progress.

The UK footprint on the ground will decrease as we transition into the next phase. RFA Argus will leave at the end of March and we anticipate that we will see the last deployment of NHS staff this month. But the resources and expertise to beat Ebola are in place and will be there as long as they are needed.

We need others in the international community to step up and play their part. The Brussels Conference was an important moment to focus international efforts on getting to zero as soon as possible. Together with the UN, US and French we are working to manage the risk of cross-border infection from Liberia and Guinea, and are investing in prevention and preparedness across West Africa to manage the risk of a fourth country outbreak.

We need to start providing support to the provision of basic services, particularly health. The 'transition' to the next stage of the response is critically important and we need to ensure that opening up basic healthcare services doesn't risk further transmission. We are working closely with WHO, Government of Sierra Leone and other donors to create an approach that will see clinics opening and operating safely with good Infection Prevention Control.

We will see further progress in the coming weeks. I am confident that our current approach to getting to zero is the right one and our plans for transition will set the foundations for longer term, transformational change.

The Ebola Crisis Response has shown the very best of what the UK can do overseas. I am incredibly proud of the way DFID and the rest of government has stepped up to this huge challenge, and delivered. We must ensure that the energy and unity of effort we have brought to the UK Ebola response is sustained until we reach zero cases, and beyond as we look to change the game in the coming years.

I am copying this letter to Cabinet colleagues.

Best Wishes,

Personal Data

SECRETARY OF STATE
FOR INTERNATIONAL DEVELOPMENT

FROM THE RT HON JEREMY HUNT MP
Secretary of State for Health

Department of Health

IMC: 922535

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Rt Hon David Cameron MP
Prime Minister
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24 February 2015

Dear Prime Minister,

Ebola: Domestic Public Health Measures and NHS Preparedness

I am writing to you to set out proposals for refocusing Ebola screening at major ports, and my recommendations as to the triggers for standing down screening in due course. Public Health England's (PHE's) system for proactively monitoring high risk returning workers will remain in place until the last such worker has returned. Below, I also provide an update on NHS preparedness and current progress on ensuring that our public health legislation is fit for purpose to address serious public health emergencies in the future.

I last wrote to you concerning our domestic arrangements to tackle Ebola on 4th December. Since then, much progress has been made. PHE have screened more than 4,000 people; the NHS has demonstrated its preparedness; and contingency regulations have been drafted that would enable us to mandate screening and quarantine individuals where necessary to reduce public health risks.

As you will know, there have been encouraging developments in the course of the epidemic in West Africa. Full control (i.e. elimination of Ebola disease in humans) in Sierra Leone is likely to be gained over a period of three to twelve months from now, although this is dependent on the maintenance of vigilant local interventions. At the same time PHE, working closely with UK Border Force, have developed a very good understanding of passenger flows from the affected region, and have successfully piloted a telephone screening approach for individuals arriving at ports where there is no PHE presence. We are of course not complacent; in particular PHE have assured me that they will continue to

Department of Health

monitor proactively all high risk returning healthcare workers until the end of the epidemic. It is timely however to review our current preparedness arrangements, and agree the triggers for changing our public health measures.

Screening and Monitoring High Risk Workers

The cornerstone of our domestic public health measures with regard to Ebola is the returning workers scheme, which ensures that all high risk workers (predominantly healthcare workers) working in any of the three currently affected countries are pre-registered with PHE, screened on return and monitored proactively to the end of the 21 days incubation period. As noted above, this will continue until the epidemic is definitively over. It is a key part of our reassurance to the public that we are proactively managing the risks from Ebola to the UK population.

What can we do now?

There is scope however for refocusing PHE's on-site presence at major ports. Having run screening for over four months, PHE now have very good intelligence on when flights of interest arrive. For example, most passengers of interest arrive at Heathrow (82%) or Gatwick (9%); the small numbers of relevant passengers travelling to Birmingham and Manchester arrive on two days of the week. If PHE limited its physical presence to those days, they could make much better use of their resources to ensure capacity was available to monitor returning high risk workers in the community, and to deal with other health protection outbreaks such as for example E.coli. The one to two passengers a day arriving outside of those days could then be asked to self-refer for screening by telephone.

The position with regard to screening at St Pancras is slightly different: again the number of relevant passengers is very small (less than one per day on average), but there is no pattern to arrivals. Given that the numbers are so small, that high risk returning workers will already be flagged up under the returning workers scheme, and that direct flights from the affected region are already screened on entry at airports in both Paris and Brussels, there is a very strong argument for removing PHE's physical presence at the terminus entirely and relying on telephone screening.

I have agreed with PHE that these are sensible operational steps to take and I would recommend that we ask PHE to proceed accordingly. Given our screening policy would remain essentially the same, I do not suggest proactively communicating such operational changes, but we will of course ensure that we have appropriate communications in place to respond to any enquiries.

Triggers for Removing Screening

Assuming that the outbreak continues to decline, we need to consider collectively what our triggers for reducing and removing screening should be. I have taken advice from PHE and the CMO. Their advice to me is very clear, namely that we should be driven by WHO announcements on when community transmission had ceased in each of the affected countries. At that point PHE's recommendation is that they cease to screen low-risk passengers from that country. High-risk returnees (principally healthcare workers) would

Department of Health

continue to be targeted for screening and monitoring until the end of the outbreak, again ensuring we manage risk and provide reassurance to the public. We would of course step up screening services again, should that prove to be necessary.

The paper at Annex A sets out these proposals in more detail. I believe they represent a proportionate stepping-down of our public health measures, clearly linked to the epidemiological risks. I would welcome views from you and other colleagues.

NHS preparedness

I am confident that we are as prepared as we can be to tackle any possible or confirmed cases of Ebola that may arrive in the UK, but we are taking steps to avoid complacency. Further to the assurances I mentioned in my letter of 4th December, we have tested operational resilience with national and regional multi-agency exercises and I remain assured that the NHS is prepared and on alert for any potential cases of Ebola.

We have two specialist isolation Trexler beds available immediately in the Royal Free, where the cases we have seen so far in the UK have been successfully treated. We now have another Trexler bed on-line in the Royal Victoria Infirmary in Newcastle. Capacity can be scaled up to six beds, with the addition of 3 PPE beds in Newcastle, Liverpool and Sheffield. CMO believes this capacity is more than sufficient to meet UK needs given the continuing low risk to the UK, and I am assured that NHS England's arrangements for further capacity surge are satisfactory.

Volunteers

Since October 2014 we have sent over 130 NHS volunteers to help with the crisis in Sierra Leone. In addition, over 130 volunteers have been deployed to work in PHE-run laboratories in Sierra Leone, and a further rotation of 47 are due to go out later this month.

Legal powers

As I set out in my last letter, we have developed contingency legislation which would allow us to mandate screening at the border, and detain, quarantine or isolate travellers where necessary for public health reasons. It is now looking less and less likely that this will need to be laid in response to the current outbreak. However, as set out in my letter of 23th October, we are exploring what changes might be made to our public health legislation to ensure we can better address public health emergencies such as Ebola, should cases emerge in the community. We are now working with other government departments to embed this as part of the legacy of the current outbreak.

Conclusion

The risk to the UK of Ebola remains low and we are well-prepared for any cases that do emerge. Given PHE's experience of screening we are in a position to focus our resources at ports more efficiently without increasing the risk to the population. Longer-term, we believe that the trigger for ceasing screening should be driven by WHO's assessments of community transmission. PHE will continue with the returning workers scheme until the outbreak is definitively over.

FROM THE RT HON JEREMY HUNT MP
Secretary of State for Health

Department of Health

I am copying this letter to the Foreign Secretary, the Secretary of State for International Development, the Home Secretary, the Transport Secretary, the Minister for Government Policy, the Cabinet Secretary and the National Security Adviser for their comments by 5th March 2015.

Personal Data

JEREMY HUNT

Department for Transport

From the Secretary of State
The Rt. Hon. Patrick McLoughlin

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Prime Minister
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SW1A 2AA

Dear Prime Minister

- 3 MAR 2015

Ebola: Domestic preparedness

I have seen the Secretary of State for Health's letter on Ebola preparedness. It is pleasing to see that the screening programme is working well and I support the proposals in the letter which seem to set out a proportionate and effective approach moving forwards. I understand the desire not to communicate proactively about any operational changes but I would however ask that relevant transport operators are kept well informed about the timing of and rationale for them.

Direct air services between the UK and Sierra Leone.

As you are aware, as part of the UK's domestic response to Ebola there are currently no direct air services between the UK and the Ebola affected countries. During 2014, BA decided to cease operations to Liberia and Sierra Leone; in October, Gambia Bird expressed an interest in operating from Sierra Leone but at that time case numbers were still increasing rapidly and we did not yet have a screening regime in place. It was rightly decided that direct air services between the UK and Sierra Leone should not be allowed.

The Ebola outbreak is, of course, still ongoing, but the recent significant slowdown in case incidence is very encouraging. Most importantly though, as the Secretary of State for Health's letter emphasises, we now have a well-established screening regime and processes in place for identifying people travelling from the affected countries, which mitigate the risk of Ebola entering the UK. This is a very different situation from that which existed last October and I think that now might be a good time to review our position on direct flights. The recent Public Accounts Committee report into Ebola also raised this question.

Subject to your agreement, I propose that my officials indicate to BA, or any other airline designated by the UK or Sierra Leone, that we are prepared to consider direct air services between the UK and Sierra Leone. Whether or not to begin operations, and on what basis, would then however be a matter for airlines themselves.

I am copying this letter to the Secretary of State for Health, the Foreign Secretary, the Secretary of State for International Development, the Home Secretary, the Minister for Government Policy, the Cabinet Secretary and the National Security Adviser.

Yours ever

Personal Data

RT. HON. PATRICK MCLOUGHLIN

A key contribution to global health security – concept proposal for a Biodefense Preparedness Organization (BPO)

This paper outlines a proposal to create a Biodefense Preparedness Organization (BPO) that will develop and manufacture vaccines to anticipate and prepare for global biodefense threats. The body of the paper describes the need for such an organization, what activities it would undertake, the capabilities and infrastructure that would be required, and outlines some budget considerations. It also identifies a number of policy issues relevant to the BPO that will need to be addressed. A series of Appendices cover various technical issues.

Key points from the paper

Need:

- Biodefense threats occur regularly.
- There have been significant failings in global preparedness for previous such threats, as well as the current Ebola threat. A more strategic and proactive approach to preparedness is needed.

Solution:

- A key part of this new approach should be a dedicated, permanent biodefense preparedness response organization (BPO) that is able to continuously design and develop vaccines against previously identified and newly occurring pathogens that potentially present a threat to global health. The pathogens to be targeted would be selected through an agreed process.
- The BPO would be permanent and proactive, ensuring a state of readiness to respond; it would offer a fully integrated, end-to-end approach, from vaccine design to vaccine dose supply; and it would be fully embedded in a permanent and highly experienced vaccine R&D organization.
- This would deliver a very fast, predictable, financially planned and high quality way to enable rapid provision of needed vaccines.
- The BPO would select, develop and optimize at least two, and up to four, flexible vaccine platform technologies and keep them up-to-date with cutting edge immunology/vaccinology science.

What [redacted] can deliver:

- [redacted] has a potential site ready and available. This could deliver, in 12 months, the full transfer of [redacted] and I&S proprietary and non-proprietary technology processes, and in 18 months a fully refurbished and GMP-qualified Pilot Plant with attached laboratories at BL2 bio containment level. Considering critical path development activities, this would allow for first vaccines in clinical development at the end of year 3 for the most generic platforms.

Practicalities:

- Start-up costs would be about [redacted] for each of the first 3 years, with a steady state budget thereafter of around [redacted]
- The BPO would act as a contractor on a retained basis or a program fee basis, and deliver vaccine doses generated during development as part of its contract.
- [redacted] wishes to work with a range of international stakeholders to secure support for the establishment and operation of this project.
- A range of policy considerations would need to be addressed to take forward the BPO concept.

[redacted] believes this proposal represents a forward-looking, practical, and financially manageable contribution to increasingly intense efforts to improve the world's readiness for global health and

biodefense threats. We seek discussions with interested stakeholders to assess the alignment of the BPO with global policy objectives and, if appropriate, to identify how the concept can best be advanced.

The need for a Biodefense Preparedness Organization (BPO)

A number of biodefense scares, both human-inflicted and naturally occurring, have occurred in the recent past, including events such as the Flu H1N1 pandemic, the spread of highly pathogenic H5N1, SARS, the current Ebola outbreak, and bioterrorist threats including anthrax and smallpox. Unfortunately, there is no reason to expect that this trend for regular, yet still unpredictable, threats will subside.

Each of the above-mentioned threats provoked emergency actions and an accelerated response from many stakeholders, often in an uncoordinated way. Major commitments were made by stakeholders under emergency situations to try and control or prevent major public health impact. It is important to note that fortunately none of the above events progressed beyond widespread concern/fear and localised impact. In all cases, the response required massive, highly disruptive efforts from manufacturers racing against the clock, with no guarantee that the required preparation would be completed in time if the event developed further. A full testing of the current fragmented, ad-hoc approach for its capacity to respond to these threats did not occur, but clearly a more proactive "ready to run" approach is needed for a more effective response.

The response to pandemic H1N1 was effective, but the nature of this outbreak was unusual - pre-existing technology was appropriate and well-matched to the scale of the global threat, meaning that it could be scaled up and made available in a timely manner. The responses to anthrax and smallpox also largely focused on scaling up and stockpiling of existing interventions.

Unfortunately, for many other biothreat agents, existing solutions either do not exist or are not well-matched to the potential scope of the threat. The current response to the West African Ebola outbreak is a good example of the latter – where the WHO, funders, research organizations and industry have all struggled to respond in a timely and effective manner. **The list of dangerous pathogens for which adequate readiness should be in place, yet isn't, remains long – see Appendix 1.**

In times of emergency, Governments are under pressure to act quickly and also understandably are keen to minimise potentially uncapped cost liabilities. This creates circumstances in which speed and low unit cost becomes paramount. This brings major challenges when technical responses such as vaccines essentially represent prototype technology, which by definition comes at unusually high unit cost and requires time to develop.

This situation is sub-optimal. Given that these biodefense challenges are likely to recur, [redacted] believes an alternative approach based on proactive preparedness is needed to allow timely readiness when a threat materialises and facilitate management of the financial uncertainty associated with an 'emergency response'. This approach would be practical, viable and sustainable.

This proposal is aimed at helping improve global biodefence preparedness by creating a dedicated, permanent biodefense preparedness response organization (BPO) that is able to continuously design and develop vaccines against previously identified and newly occurring pathogens that potentially present a threat to global health. This would be done in a very fast, predictable, financially planned and high quality way to enable rapid provision.

Such an organization would operate alongside already established approaches and organizations focused on biodefense. However, it would differentiate itself through 3 features - (i) its permanent and

proactive nature, ensuring a state of readiness to respond; (ii) its fully integrated end-to-end approach, from vaccine design to vaccine dose supply; and (iii) it being fully embedded in a permanent and highly experienced vaccine R&D organization. This will ensure the BPO stays at the cutting-edge of production know-how and platform technology,

and employs methodologies that will have a high likelihood of successful scale-up and acceptance by regulators.

The BPO would act as a contractor on a retained basis or a program fee basis, and deliver vaccine doses generated during development as part of its contract. Once a selected vaccine is developed to the point of proof-of principle, decisions could be made, depending on the urgency of the threat, to either "mothball" the technology or to progress to full approval by regulators and manufacturing from a permanent manufacturing site. Vaccine supply would be driven by currently established, or novel, "per vaccine dose" procurement mechanisms.

What would a BPO look like and what would it do?

The BPO would select, develop and optimize at least two and up to four flexible vaccine platform technologies and keep them up-to-date with cutting-edge immunology/vaccinology science. These technologies (described in **Appendix 2**) would be selected for their capacity to predictably and rapidly produce vaccine antigens in a form that elicits known protective immune responses (neutralizing or bactericidal antibodies, memory T cells, CD4 and CD8 T cell responses, innate immune response etc). They will have the flexibility to permit targeting of viral, bacterial or parasitic pathogens and hence will be appropriately selected depending on the bio-threat under consideration.

The BPO would cover the following activities in a fully integrated co-localized setting:

1- *Design and develop vaccines against a continuously updated list of pathogens* (using one or more rationally-selected platform technologies). The pathogens to target would be selected and prioritized though a yet to be defined process. Specific features of the vaccine design activities would include their "plug and play" characteristics that permit going from threat identification to preclinical candidate vaccine in as little as three months. This timeframe is medically credible in terms of responsiveness, but it would require a highly optimized set of design tools that would allow rapid "cassetting" of target antigens into expression/vector systems, as well as a team of highly skilled scientists and technicians who have mastered the learning curves for these approaches and could likely deliver more than 90% of candidates "right first time".

2- *Fully characterize, test and document the efficacy and safety of the vaccines in relevant preclinical animal models to a point allowing for Phase1 clinical trials evaluation.* This would include an appropriate set of toxicology studies that, through continuous discussions with regulators, could be designed to be rapid and efficient, recognizing that common features of the platform technologies could permit extrapolation of safety profiles and focus risk assessment on the pathogen component included in the vaccine. Identification and use of biomarkers relevant to vaccine safety that are linked to the platform technology would further streamline and strengthen preclinical assessment of candidate vaccines.

3- *Design and conduct Phase1/Phase2 clinical programs in healthy volunteers to select optimal dose and formulations and to document the safety and the induction of the relevant protective immune responses the vaccine was designed to induce.* Where possible, clinical studies would include a clinical or immunological proof of concept. The clinical development component would

establish links with experienced clinical trials centers and employ wherever possible standardized protocol designs and processes that incorporate both flexibility and timely review and approvals. The clinical development team would be small and skilled at managing fully outsourced clinical trials conducted through contract research organizations (CRO). Preferred provider contracts with one or two CROs would be established to control costs and to enhance efficiency. An in-house immuno-readout team would have the capacity to conduct rapid and high quality serology/Cell Mediated Immunity (CMI) and bridge preclinical and clinical data - these capabilities could be expanded through use of predefined contractor organizations as required by the specific development program.

4- *Scale up and prepare the manufacturability of each of the components of the above mentioned platform technologies independently from the type of vaccine expressed.* Everything except the specific antigen would be optimized ahead of time in such a way as to have a "plug and play" system. Once a pathogen is identified as a target to pursue, the relevant platform technology would be selected, the antigen would be "inserted", tested and then relatively quickly (given that a few tweaks are likely to be needed to optimize the process for that very specific construct) the vaccine manufacturing process would be scaled-up for manufacturing on an appropriate scale.

5- *Run and maintain two pilot plant manufacturing trains* allowing for scaling up of either mammalian/insect or bacterial/yeast fermentation going up from 25L to 1600L fermenters. These will be used for the scaling-up of the processes for each of the platform technologies' generic parts as described in 4 above, as well as for the scale-up of each of the specific vaccines produced, and, when needed, for the mass manufacturing of any of the vaccines in stock. The facility and the resources to run it will be dedicated to this use (i.e. no disruption or opportunity costs associated with its urgent usage).

6- *Serve as a resource to scale up and produce up to 1600L, third party technology/vaccines* if these turn out to be the preferred choice to control the biothreat.

What kind of capabilities/resources/ facilities are required?

Vaccine technologies should be continuously optimized and their mode of action characterized as our scientific understanding of the immune system in general, and of the protective immune responses against various types of pathogens in particular, progresses. The same platform technologies that could be used for a bio-defense vaccine can of course also be used, as such or slightly modified, for more "planned vaccines". This makes for obvious synergies in capabilities knowledge, expertise and experience between the biodefense organization and a fully-fledged vaccine R&D organization.

The BPO will require a state of the art facility including wet laboratories designed for molecular biology, immunology, characterization and QA/QC, animal husbandry and two GMP pilot plants with vessels ranging from 25L to 1600L as well as downstream facilities for purification, formulation and fill-finish of vaccine. It will also require a talented workforce of PhDs, MDs and technicians who will comprise a core staff that will ensure that all critical activities are covered, while relying on a significant contractor component to permit expansion as required to meet the needs of specific projects. Finally, access to the intellectual property as well as to the critical know-how for the platform technologies will be maintained via continuous interactions with the teams that discovered these platforms and continue to optimize them within [redacted] mainstream vaccine R&D organization.

Where could the BPO be embedded?

The goal is to create a dedicated, permanent biodefense preparedness response organization. We believe this can delivered more quickly and effectively if it is fully embedded in a permanent and highly experienced vaccine R&D organization. This will ensure it stays at the cutting-edge of production know-how and platform technology, and employs methodologies that will have a high likelihood of successful scale-up and acceptance by regulators.

[redacted] owns a state of the art facility located in Irrelevant & Sensitive in close proximity to the Irrelevant & Sensitive Irrelevant & Sensitive and many other important scientific and political/funding stakeholders. This facility is fully equipped to host both a significant vaccine R&D organization and a significant bio-defense preparedness organization. Beyond classical research and development bench laboratories and animal facility, the facility is equipped with 2 pilot plants each capable of hosting two trains scaling up from 25 to 1600L, and state of the art downstream GMP manufacturing facilities. Up to 50% of this facility can be dedicated to the biothreat preparedness program.

Irrelevant & Sensitive other vaccine R&D centres in Irrelevant & Sensitive and our major pharma centre at Irrelevant & Sensitive in the UK, would enable close connectivity with many of the key stakeholders in biopreparedness policy.

[redacted] and the I&S vaccine organization, already own and are familiar with all platform technologies described in Appendix 2. Not all are ready for a "plug and play" approach, but all can be progressed to that level reasonably quickly. Three of the platforms have already been into humans, and the two newest ones should proceed to first time in human trials within the next two years (in vivo conjugation and mRNA platforms).

It is our intent, if the BPO concept is supported, to transfer all [redacted], and potentially I&S vaccines R&D activities in the [redacted] (currently based in the Irrelevant & Sensitive, to the same Rockville facility. This co-localization will allow for synergies and read-across opportunities between the "planned vaccines" R&D and the Biodefense vaccines organizations.

How will the BPO be created? How long will this take? Preliminary BPO platform readiness & vaccine candidates' timelines

To get the BPO up and running as fast as possible, the proposal is to launch and implement the BPO unit in two parallel phases, by a core organization of about 150 FTEs at steady state.

Phase A will focus on the tech transfer of the selected technology platforms and on the establishment and ramp up of the GMP facility (see **Appendix 3**). This will deliver in 12 months the full transfer of I&S and I&S proprietary and non-proprietary technology processes, and in 18 months a fully refurbished and GMP-qualified Pilot Plant with attached laboratories at BL2 bio containment level.

Phase B – at completion of Phase A, all facilities and technologies will be ready for "plug and play" development of two vaccines in parallel on a steady state basis. Phase B will run in parallel to Phase A and will focus of the build up of the capabilities, technical staff and methodologies required to discover and develop 2 vaccines in parallel on a steady state basis (see **Appendix 4**).

Considering critical path development activities, this would allow for first vaccines in clinical development at the end of year 3 for the most generic platforms. A top level roadmap can be found in **Appendix 5**.

Budget Requirements - BPO financial structure

Set-Up period

The table below summarizes the human (quality and quantity) and financial resources required in years 1, 2 and 3, after which time the BPO will be running at steady state.

Table 1 – Financial and Human Resources in Years 1-3

Activities	FTE Year 1	FTE Year 2	FTE Year 3	US$ M Year1	US$ M Year2	US$ M Year3
Process development	Irrelevant & Sensitive					
Pilot Plant						
QC						
Molecular Biology						
Preclinical development						
Laboratory Animal Sciences						
Clinical Immunology						
Clinical development						
QA						
Support Functions						
Total						

Steady State period

Reflecting all the above proposals and based on the assumption that the BPO organization will deliver two vaccine programs on an ongoing basis, the global budget required is approximately Irrelevant & Sensitive a year (see Table 2 below).

The Steady State structure will be fully running from Year 4 onwards and would include the different activities described in the previous chapters. Each type of activity is defined as being "core" or "outsourcing". A "core" activity means the BPO would have and wants to keep the know-how in-house, whereas an "outsourcing" activity will be performed by an externalized CMO.

The Clinical development activity is estimated to cost Irrelevant & Sensitive a year and is split between a core team of 4.5 FTEs, representing 1m US$ budget, and all the outsourcing activity (clinical operations, investigators fees, sample management, etc) that costs Irrelevant & Sensitive a year.

The Preclinical development activity annual cost would be Irrelevant & Sensitive a year where Irrelevant & Sensitive would be outsourced (for all the tox, preclinical studies and the highly specialized assays). The core budget of Irrelevant & Sensitive consists of Irrelevant & Sensitive across Preclinical, Lab Animal Services and Clinical Immunology.

The Process Development activities will rely on a team of Irrelevant & Sensitive working in the Technology Platforms and Irrelevant & Sensitive in the Molecular Biology team. Their annual cost amounts to Irrelevant & Sensitive a year.

The GMP activity requires an annual budget of Irrelevant & Sensitive made up by the Irrelevant & Sensitive required to run one Pilot Plant production train. An initial investment of Irrelevant & Sensitive for the equipment, building refurbishing

and classification has been taken into account. Depreciation has been considered on 10 years for equipment and 25 years for the building.

The QA and QC activity to support this GMP production will cost Irrelevant & Sensitive a year.

Finally, the budget for facility, shared services and support functions amounts to approximately Irrelevant & Sensitive Irrelevant & Sensitive a year. This includes:

- the rent of the facility and equipment
- all the operating expenses (repairs, maintenances, utilities, security, insurance, etc)
- the cost for the shared facilities with the US "planned' Vaccine R&D
- And a fully dedicated team of Irrelevant & Sensitive in Support functions (Legal, Regulatory, Project Management)).

Table 2 – Steady state 10 years budget

	STEADY STATE BPO BUDGET (in kUS $)									
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Clinical	Irrelevant & Sensitive									
Core										
Outsourcing										
Preclinical										
Core										
Outsourcing										
Process										
GMP										
Core										
Outsourcing										
QA/QC										
Support Functions										
Facility & Shared Services										
Grand Total										

Flexible budget

On a vaccine project need basis or in case of emergency situation, a potential flexible budget can also be considered.

Each additional Phase I study will require an extra budget of Irrelevant & Sensitive assuming 50 subjects with an average number of 15 visits, based on US based investigator fees benchmark.

A Phase II/POC study with 30 subjects and about 20 visits, would amount to a budget of Irrelevant & Sensitive based on US benchmark fees.

Finally, if a stockpiling/mass manufacturing activity is required, assuming a production of 1 million doses per month during 1 year (or 12 million doses per year), an additional cost of approximately 45m US$ should be considered. This includes the second Pilot Plant GMP production line and related FTEs to run it, additional QA and QC release support, filling, packaging and shipping costs at CMOs. However, depending on the type of vaccine, this budget can vary by + or – 50%.

Table 3 – Flexible Budget

	FLEXIBLE BUDGET (in kUS $)									
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Additional Phase I	-	-	-							
Additional Phase II	-	-	-							
Mass Manufacturing	-	-	-							
Grand Total	-	-	-							

Irrelevant & Sensitive

Conclusion and Next Steps

[redacted] is committed to this initiative and ready to scale building from the second half of 2015 if there is sufficient interest. A trivalent Ebola vaccine could be the first priority.

We recognize that our stakeholders will wish to address a number of questions relating to this concept, including:

- Whether and to what extent other companies can use the facility;
- What steps can be taken to ensure product is developed for, and available to, developing countries;
- Who will set the agenda to ensure the right health needs/priorities are addressed;
- To what extent it will be possible to engage with other private sector actors (including developing country manufacturers) in vaccine development;
- How many, and which countries and other 'contributors' would be involved;
- How will the organization be governed? Who would it be accountable to?
- What would be the funding cycle? (5 years? More?)
- How would Intellectual Property generated be owned/ managed?

We stand ready to discuss these and other questions with interested parties.

4.3.2015

APPENDICES

APPENDIX 1 -THREATENING PATHOGENS

- Bacillus Anthracis
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia mallei
- Burkholderia pseudomallei
- Chapare virus
- Chickungunya virus
- Chlamydia psittaci
- Clostridium botulinum toxins A, B E, F
- Clostridium perfringens epsilon toxin
- Coccidiodes immitis
- Coxiella burnetii
- E coli 0157:H7
- Eastern equine Encephalitis Virus (EEEV)
  Ebola Sudan virus
  Ebola Zaire virus
- Francisella tularensis
- Guanarito virus
- Hanta virus
- Kyasanur Forest virus
- Lassa fever
- Listeria monocytogenes
- Lujo virus
- Machupo virus
- Marburg virus
- Mayaro virus
- MERS-coronovirus
- Murray Valley virus
- Nipah virus
- Omsk virus
- Onyong-nyong virus
- Powassan virus
  Smallpox
- Rickettsia prowazekii
- Rickettsia rickettsia
- Rickettsia typhi
- Rift valley fever virus
- Rocio virus
- Ross River virus
  Venezuelan Equine Encephalitis Virus (VEEV)
- Sabia virus
- Salmonella serotypes Enteritidis, Typhimurium, Newport
- SARS coronavirus
- Semliki Forest virus
- Shigella dysenteriae
- Shigella flexneri
- Shigella sonnei
- Sinbis virus
- St. Louis virus
- Staphylococcal enterotoxin B
- Vibrio cholera
- West Nile virus
- Western Equine Encephalitis Virus (WEEV)
- Yersina pestis

APPENDIX 2: DESCRIPTION OF PLATFORM TECHNOLOGIES

a- **Adjuvant and recombinant proteins platform technology:** The use of bacterial, yeast, insect and mammalian cell expression systems for the production of full length or fragments of recombinantly expressed protein antigens at small and very large industrial scales is now a well-established set of platforms at both [redacted] and I&S Vaccines. Critically, the use of recombinant protein antigens as vaccines can be significantly enhanced by formulation together with adjuvants. Both [redacted] and Irrelevant & Sensitive are leaders in the field of adjuvant technologies compatible with human use, with adjuvants included in approved vaccines or files under regulatory review. These include but are not limited to:

i) AS03 oil in water emulsion used in the Pandemic flu vaccines. This adjuvant has been shown, using numerous vaccines, to significantly increase the quantity and quality of antibodies produced against the vaccine antigen. This adjuvant additionally accelerates the kinetics of the immune responses in humans. These are two characteristics that may be particularly relevant in emergency immunization scenarios where, given the imminent threat, speed and strength of protection are paramount.

ii) AS01 adjuvant formulation combining two immunostimulant molecules: MPL and QS21 in a liposomal formulation. This formulation, and a number of related ones using the same immunostimulants or a third one (CpG) have been shown to induce potent antigen specific T cell responses particularly of the CD4 phenotype, as well as long lasting memory T and B cell responses. The AS01 adjuvant formulation is used in I&S Malaria vaccine for infants and toddlers which is currently under review for approval by the EMA (European Medicines Agency). It is also used in I&S herpes zoster virus vaccine for the elderly population that recently met its Phase III efficacy endpoint.

iii) Both I&S as well as the vaccines field in general, remain very active in discovering new adjuvants tailored to induce very specific innate and adaptive immune responses designed to optimize protective responses against a diverse array of pathogens (intracellular, extracellular, bacteria, viruses, parasites, fungi etc.)

These platform technologies could be used in the design of vaccines against most pathogens. They are very well understood and industrial scaling up is fully established. The adjuvant systems are patent protected and their formulations involve very significant knowhow embedded in both Irrelevant & Sensitive Speed of development and costs of vaccine doses could be characterized as "average" when contrasted with some of the other technologies described below.

b- **Live attenuated viral vector technology**: An alternative platform to the adjuvanted recombinant antigen approach described above, involves the use of recombinant live attenuated viruses expressing pathogen derived genes as vaccine antigens. This approach aims to mimic natural viral infections known to elicit broad immune responses, particularly those immune responses most effective against viral infections, such as CD8 T cells. Several viral vectors have been produced and characterized in the field, I&S through its recent acquisition of Okairos, has developed a series of Chimpanzee Adeno (ChimpAd) virus vectors for use as live attenuated non-replicating genetic vaccines. The vectors have been selected for their ability to elicit significant immune responses after a single immunization as well as for the excellent safety profile both for the vaccine recipients and for the environment given the non-replicating phenotype. Several vaccine candidates using ChimpAd as a vector are in human clinical trials (vaccines against Hepatitis C, HIV and Malaria

amongst others) and this vector is currently used in the most advanced vaccine against Ebola virus, soon to be introduced in field efficacy trials in Ebola outbreak countries. The live attenuated vector approach can be further enhanced if needed by a "prime-boost" approach, whereby one live vector is used to provide the first immunizing dose (prime) and a heterologous live vector expressing the same vaccine antigen(s) is used for the booster dose. This second dose usually elicits much stronger and long lasting immune responses and protection. [redacted] as well as others, owns a second vector called MVA (Modified Vaccinia Ankara virus) that has been shown in various clinical trials to be a very effective "booster" of immune responses induced with a ChimpAd vector prime.
The Live attenuated vector technology is highly versatile in that the same vector using the same cell substrate, and substantially the same "generic" manufacturing processes which, once developed, can be used for various different vaccines (only the antigen insert(s) varies in each case), making it particularly well suited for Bio-defense applications where a rapid development is needed. This streamlined development, depending on the vaccine dose, results in the potential for substantially lower cost of goods compared to more classical recombinant protein based approaches.
Several such live attenuated vectors should be developed and optimized for manufacturability to ensure that populations can be immunized against different threats over time. Indeed, once a vector has been used once, it cannot be reused in the same population due to the induction of immunity to the vector itself, in addition to the response to the vaccine antigen. Thus the proximity to a mainstream R&D organization who will continually discover new vectors and optimize existing technologies represents a substantial advantage to the BPO.

c- **Self Amplifying mRNA (SAM) immunization technology:** as described above, one of the limitations of the live attenuated viral vector approach is its "single use" potential. An alternative to multiplying the number of vectors for use is the SAM platform technology. As its name implies, this is a technology relying on using messenger RNA (mRNA) encoding an antigen of choice as the genetic material injected for immunization. Its advantages are that mRNA once delivered in the cytoplasm of cells upon immunization, amplify themselves without spreading to neighboring cells (an important safety consideration), drive the cell to express the vaccine antigen and no other proteins thereby avoiding the generation of an immune response against the SAM vector. This allows for its reuse to boost the immune response with the same antigen and its repetitive use with different antigens, making it potentially an even more versatile technology than the live attenuated viral vector platform. Its limitations currently are the complexity of the formulations required to deliver the mRNA inside the cells (currently complex cationic nanoemulsions, or liposomes) and optimizations needed to industrialize the manufacturing process (*in vitro* transcription from plasmid DNA and post-transcriptional modification to stabilize the transcript).

Positive preclinical data exist with this rapidly evolving platform, but as yet no clinical data have been generated. Conceptually, this could be the most versatile of the vaccine platforms. Importantly, Irrelevant & Sensitive and hence potentially [redacted] upon approval of the transaction, owns the intellectual property and know how to this technology and is preparing to take it in Phase 1 clinical trials with an RSV vaccine antigen in the next several months.

d- **New platform technologies to come**: New platforms are continuously discovered and developed, such as the Glycovaxyn platform to which [redacted] has a license in certain fields. This technology eliminates many steps from the classical chemical conjugation approach and potentially enables targeting more complex pathogens. The technology allows the covalent association of a protein antigen with a bacterial polysaccharide via live bacteria in vivo, potentially making the generation of such vaccines much faster, and their cost per dose much lower. Secondly, the Liquidia nanofilm

based particle technology to which [redacted] has a license, enables a vaccine to mimic viral particle shapes as a means to stimulate a potent immune response against delivered antigens. As the mainstream R&D organization continually assesses many more such technologies to come, the BPO will be in a position to leverage these breakthroughs and to introduce them into its menu of technologies for use in Bio-defense preparedness.

Platform	Average Timing (from Ag definition to GMP material available)	Characteristics	Generic Process?
ChAd +/- MVA	2 yr	-Expression of viral antigens in native conformation -Expression of bacterial antigens -Potent induction of CD8 T cells -CD4 and Abs may also be induced	Yes
SAM	2yr (assumption)	-Expression of viral antigens in native conformation -Expression of bacterial antigens -Potent induction of CD8 T cells -CD4 and Abs may also be induced	Yes
Mammalian protein +/AS	3yr	-Optimal expression of mammalian antigens in native form /glycosylation for induction of high titer neutralizing antibodies. -Addition of AS to broaden/increase Ab responses and for potent CD4 T cells	-Generic master cell bank -All other process aspects to be adapted to specific antigen. -Standard AS platform -Specific formulation work with each Ag to be done
E coli protein +/- AS	2.5yr	-Expression of bacterial antigens to optimize induction of high titer functional antibodies -Expression of mammalian T cell antigens where conformation is not critical. -Addition of AS to broaden/increase Ab responses and for potent CD4 T cells	-Generic master cell bank -Generic fermentation -All other process aspects to be adapted to specific antigen. -Standard AS platform -Specific formulation work with each Ag to be done

Yeast protein +/- AS	2.5yr	-Expression of viral or bacterial antigens for induction of Antibodies and T cells - Addition of AS to broaden/increase magnitude of responses	-Generic master cell bank-All other process aspects to be adapted to specific antigen. -Standard AS platform -Specific formulation work with each Ag to be done
Polysaccharide Bioconjugation (– Glycovaxyn technology platform)	2-2.5 yrs	-Induction of T cell dependent functional antibody responses to surface exposed bacterial polysaccharide antigens. Versatility of the technology allows to target a diversity of complex pathogens	-Some families of enzymatic pathways may be generic across different pathogens, but strain engineering required anew for each pathogen -Fermentation is generic -Purification to be adjusted for each antigen

APPENDIX 3 – PHASE A: TECHNOLOGY PLATFORMS TRANSFER AND GMP FACILITY SET UP....

PHASE A: TECHNOLOGY PLATFORMS TRANSFER & GMP FACILITY SET UP

1- All selected platforms (see appendix 2) will be tech transferred, established and validated to be ready to "plug and play" within the first twelve months by a "Technology Platforms core team".
2- The GMP facility will be refurbished and set up to be ready to run for GMP manufacturing within the first eighteen months by a Pilot Plant core team.

Technology Platforms Core team

- Will be responsible for the tech transfer of the selected technology platforms from Irrelevant & Sensitive Irrelevant & Sensitive R&D organizations and the set-up of the generic technology platforms in the BPO within the first twelve months.
- Will include experts in the different steps of the process: Upstream (cell culture, E. Coli/yeast processes), downstream (purification and formulation processes) and analytical support (physico-chemistry/ immuno-tools).

Two identically constituted units running in parallel will allow for a rapid tech transfer of all platforms. These same teams will then transition to become the process development core teams, where their mission will become to use the technology platforms expressing selected antigens to develop 2 vaccines in parallel on a steady state basis.

Each unit will include Irrelevant & Sensitive distributed as follows:

- 1 PhD supervising the team,
- 1 scientist and 5 technicians specialized in upstream process development,
- 1 scientist and 5 technicians specialized in downstream process development,
- And an analytical team with 2 scientists and 4 technicians as a minimal critical mass to cover the span of different analytical tools.

In addition, 10 logistic technicians for material (cleaning, sterility, connections ...) and media preparation (buffer, cell growth media) will provide support to 2 full platforms transfer in parallel.

Overall: 4 Irrelevant & Sensitive

Pilot Plant (PP) GMP core team

During the GMP facility set up, the PP GMP core team will ensure the set-up and validation of the Pilot Plant, as well as a proactive preparation of cell banks and seeds for production readiness, in collaboration with the Technology Platforms core teams.

Assuming;

- That a BL2 bio containment level for the facility is adequate for the vaccine targets to be developed;
- 3 months' due diligence for facility evaluation & initial user requirement has already taken place prior to year 1 (with a team of 3 contingent engineers and 3 Pilot Plant users).

Refurbishing of the facility to upgrade it to a BL2 bio containment level should start immediately at the inception of the BPO.

A first group of Irrelevant & Sensitive will supervise all refurbishing work and be responsible for defining detailed user requirements in collaboration with a contingent engineering & procurement team.

The engineering team Irrelevant & Sensitive will design and coordinate the refurbishing work and manage all subcontractors. We estimate an outsourced budget of Irrelevant & Sensitive to be required over years 1 and 2, depending on the refurbishing needs.

Starting in the last quarter of year 1 until mid-year 2, the engineering team will also coordinate activities related to GMP qualification (IQ, Installation qualification/OQ, operations qualification) and the fully sized PP GMP core team will be responsible to further define detailed user requirements, to launch the Pilot Plant structure (such as installed equipment verification) and to develop the required documentation for GMP activities readiness (SOPs, incoming materials).

The production and QC release of generic GMP material (cell banks and seeds related to the Technology Platform transfer in Phase A), will be done through CMOs. The PP GMP core team will also need to prepare for possible future outsourcing of generic process development testing in Phase B (i.e. sterility, endotoxin, DNA...) and for fill and finish GMP activities.

Starting year 2, the PP GMP core team will be fully trained for GMP operations and will transition from GMP readiness (Phase A) to actual GMP production (Phase B). We assume that one train/production line (upstream/downstream) can support the GMP production required for 2 vaccines on a steady state basis.

The PP GMP core team (35FTEs) will comprise the following:

- For upstream/downstream (excluding formulation): 2 PhDs, 12 scientists, 1 technician
- For Formulation: 1 PhD, 2 scientists, 1 technician
- For Logistics (Material & Media preparation): 2 managers, 5 scientists, 4 technicians
- Quality Operations (on line quality preparedness): 1 manager, 3 scientists
- 1 PhD PP Head

Quality Control (QC) team

An independent QC team of 3 managers and 9 scientists will ensure the QC release testing of material produced by the line.

APPENDIX 4 – PHASE B: TECHNOLOGY PLATFORMS USE.

PHASE B: TECHNOLOGY PLATFORMS USE

Resourcing of the teams detailed below has been estimated based on the assumption of a steady state level of two vaccine programs ongoing at any one time within the BPO. We have used our extensive experience with both large and smaller R&D organizations to resource each team with the right skill sets, aiming to create a lean organization, while ensuring the necessary critical mass to achieve the objectives of the BPO.

Preclinical Core Team

The preclinical team is responsible for the definition of the scientific rationale behind a given vaccine candidate. This includes:

1) Identification of vaccine antigen(s)

2) Input of pathogen/immunology expertise to the molecular biology/bioinformatics team to contribute to antigen design (gene/protein of interest versus protein segment versus epitope based approaches).

3) Identification of vaccine delivery platform based on assessment of what is the likely profile of a protective immune response

The preclinical team is responsible for designing and conducting *in vivo* studies in an appropriate animal model to evaluate immunogenicity/potency of the vaccine candidates based on immunological read-outs including binding antibodies (ELISA), functional anti-viral or anti-bacterial antibodies and cell mediated immune responses.

The preclinical team is responsible for assessing whether a preclinical challenge/efficacy model is appropriate as an intermediate step in candidate selection prior to Phase I and in most cases will identify an external collaborator to assess the vaccine candidate in the model of choice. The preclinical team will input into the collaborative research plan and oversee the collaboration as R&D lead.

The preclinical team will collaborate with the In-house DVM/Toxicologist to design a toxicology study for outsourcing to a CRO (if a toxicology study is needed) and will conduct any in house GLP serology needed to support the study.

The preclinical team will support regulatory submissions by actively contributing to non-clinical sections of regulatory documents.

One preclinical team per project consists of one PhD scientist and four well qualified laboratory technicians. It is assumed that the PhD scientist will be the accountable for experimental design and interpretation and may also spend a portion of their time hands-on in the lab. Assuming two vaccine projects at any given time, we propose an overall team of 2 PhD scientists and 8 technicians, starting in year one. Starting in year two, a qualified veterinarian/toxicologist will support the validation of tox study designs and interpretation of CRO authored tox reports. This individual will also provide veterinary input to the Lab Animal Services facility. It is assumed this individual will be 50% supported by BPO and 50% by the mainstream R&D organization.

One PhD level biostatistician will be shared between the preclinical and clinical teams.

Outsourcing expenses for vaccine projects will be incurred to conduct toxicology studies at a CRO (estimated at Irrelevant & Sensitive for two projects per year) and external preclinical efficacy studies (estimated at Irrelevant & Sensitive for two projects per year)

Laboratory Animal Services Core

Access to the R&D in house animal facility will be required to accommodate immune competent mice in a specific pathogen free (SPF) environment. On site breeding will not be required.

Starting in year two, 3 technical staff will be required to operate the animal husbandry for BPO. Veterinary oversight will be provided by the above-mentioned DVM.

Clinical Immunology Core Team

In close partnership with the Clinical Organization and with Preclinical, the Clinical immunology group is responsible for adapting and validating clinical immune read-outs for Phase I II and III testing. These include serology samples (ELISAs and anti-bacterial and anti-viral functional assays) and human Cell Mediated Immunity (CMI) testing (FACS or ELISPOT) under GLP conditions. Sample processing, sample management and data management will be outsourced. Quality oversight will be provided by the central QA unit.

The Clinical Immunology team will include Irrelevant & Sensitive and start in year three. This breaks down to Irrelevant & Sensitive to run the CMI unit and Irrelevant & Sensitive technicians to run the serology unit.

Highly specialized assays will be accessed through outsourcing to CROs or collaborations with academic groups as non-core external fees.

Molecular Biology Core Team

This team focuses on the design and production of antigen constructs and on producing small scale material for preclinical testing. They will perform characterization of the vaccine candidates including analytics and buffer screening activities. Finally Molecular Biology will generate RAMATRA seeds (i.e. full traceability documentation) to be provided to the Process organization for amplification, banking and GMP production of clinical material.

To fulfil the above objectives and assuming a steady state of two vaccine projects ongoing at any one time, the team should include Irrelevant & Sensitive to start in year one:

Irrelevant & Sensitive

Process Development Core team

The Process Development core team will be responsible for the new antigens process development, from target to final process using the available Technology Platforms. It will be composed of the same staff as the Technology Platforms core team described above and as of year 2 be able to develop two vaccines in parallel.

From a timing perspective, we assume that vaccines using the Adenovirus or the Bioconjugates platforms will require 12 months from initiation of antigen design to availability of reproducibility lots and an additional year prior to Phase1 trials start. The Recombinant protein platform will require more time (6-12 months) given its higher tailoring requirements to the particular protein antigen expressed.

Pilot Plan (PP) GMP Core team

Once the GMP facility set up is completed, the Pilot Plant (PP) GMP core team will be responsible for the GMP production and release of (clinical) lots at a scale up to 1600L.

Vaccines programs will be transferred from the Process Development core team over a period of 1 to 3 months.

Depending on the vaccine target developed, the PP GMP core team will

- Produce specific cell banks (constitutive expression) and seeds
- Produce clinical lots

Depending on the platform, a GMP production campaign would take between 3 to 6 months.

On specific BPO Vaccine project needs or in emergency situation, an expanded team could be added to manage a second large scale line.

To ensure full focus of the PP GMP core team on producing GMP lots, CMOs will be used for generic cell bank production and release, as well as for the fill and finish (assuming 1 month fill and 3 months release).

The infrastructure maintenance has been included as part of facilities rental costs.

Quality Control team

After some 3 months of specific testing on lots produced by the Pilot plant, the QC team will release the specific cell banks (constitutive expression), seeds and clinical lots.

As is proposed for the in-process development testing, generic testing would be managed by the mainstream R&D organization or could be outsourced.

Clinical development Team

The clinical development team is responsible for designing Phase 1 & 2 clinical trials that will assess vaccine safety, select optimal dose and formulation, and where possible achieve clinical or immunological proof of concept (POC).

The team will develop study timelines and budgets, generate concept protocols and informed consent templates to be developed into final protocols and study documents by the CRO. The team will review and approve CRO-generated CRFs, data management plans, safety review and reporting procedures, and other study/site-related documents required to permit study starts.

The team will review and approve CRO selection of study investigators and sites and will ensure proper maintenance of the electronic Trial Master File.

The team will be responsible for preparing the clinical development sections of the IND and for preparing and maintaining the Investigator's Brochure and ensuring appropriate public registration of the trial.

The clinician will be responsible for reviewing safety data including all SAEs generated during clinical trials. The biostatistician and the clinician will prepare study report and analysis plans and review and approve complete study reports at study end. The clinical team will proactively track and follow study activities to ensure adherence to study timelines and study quality/GCP. The clinical team will participate in Investigator meetings and interact with clinical sites if required to answer study related questions as needed. The clinical team will interface with I&S medical governance and advisory committees as required by [redacted] policies and processes.

The time required from target selection to availability for clinic trials is estimated at 18-24 months. The assumption on lead time to prepare clinical activities prior to Phase 1 start is 6 to 8 months.

The minimal internal clinical core team will consist of [redacted] working with a full study outsourced (FSO) model. The clinical core team will include Irrelevant & Sensitive

Irrelevant & Sensitive

This team will have the capacity to manage two projects during Phase 1 (at least one study per program and any additional study to be accounted as flexible on a vaccine project basis need). On a vaccine project basis need, a Phase II/POC study could be added. In such case, an additional dedicated clinical core team will be added.

Clinical development costs are dependent upon study Phase and study design, but generic costing estimates have been generated for a base scenario (2 Phase I programs with each, one study and one core Clinical team). For illustration purpose, some study costs scenarios are shared in Appendix 4.

Budgets do not include trial insurance but do include pass-through costs from CRO, cost associated with CRO resourcing, plus investigators fees (calculated on a per subject basis, including site costs, laboratory fees, screening failures, advertisement, subject compensation, etc).

CRO costing are estimated on an FSO basis using experience with Ebola as a model.

APPENDIX 5 – TOP LEVEL ROADMAP