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VACCINE INSIGHTS

SPOTLIGHT ON:

Advances in vaccine manufacturing part 1: upstream advances and intensifying production

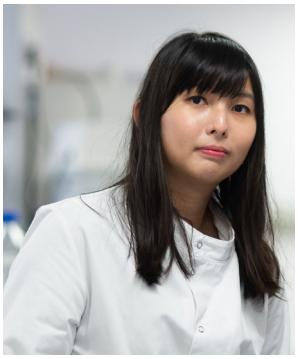
VACCINE INSIGHTS Volume 2, Issue 4

Advances in vaccine manufacturing Part 1: Upstream advances and intensifying production

SPOTLIGHT

INTERVIEW

Optimizing adenovirus vector based vaccine production



Arriving at the University of Oxford in late 2019, postdoctoral researcher Carina Joe hoped to apply her skills in biologics manufacturing to viral vector vaccines, a new area for her. Within months, she was at the center of efforts to produce the Oxford/AstraZeneca COVID-19 vaccine, one of the first and most widely used COVID-19 vaccines. **Charlotte Barker,** Editor, *Vaccine Insights*, caught up with **Carina Joe** (pictured), now a Senior Scientist, to find out more about her role in scaling up the adenovirus-vectored vaccine, and her plans for the future.

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Q What is the focus of your research?

CJ: I'm working at the Jenner Institute at the University of Oxford as a Senior Scientist, developing processes for large-scale GMP manufacturing of viral vector vaccines. Recently, I have focused on the Oxford/AstraZeneca COVID-19 vaccine (ChAdOx1 nCoV-19 (AZD1222, Vaxzevria)), but I am also involved with developing processes for adenovirus-vectored rabies and Ebola vaccines, amongst others.

I would describe myself as a generalist. During my master's and PhD studies, I did a lot of large-scale cGMP manufacturing of viral-like particle vaccines, monoclonal antibodies, and novel proteins for targeted drug therapies. When I finished my studies, I saw an opportunity at the Jenner Institute to develop skills in an area I hadn't worked on before – viral vector technology.

Developing efficient manufacturing processes is very important. People often don't understand that even if you make a 100% effective vaccine or drug, it means nothing if you cannot produce it at a large scale because a vaccine needs to be distributed to a large number of people to get the benefit of herd immunity.

Q The Oxford/AstraZeneca COVID-19 vaccine was developed and scaled up in record time – what was your role in that effort and what were the key factors for success?

CJ: A big part of why we were able to get the vaccine out so quickly was the collaboration between the university and a number of industrial partners. We also worked closely with the government and health regulator to seek advice on how we could move things forward faster.

My involvement was to develop the large-scale process. Before I joined, the group at Jenner Institute had a process to manufacture the ChAdOx vaccine platform (then being used for rabies vaccines), but could not produce a large number of doses, and the process was not scalable. My goal was to develop a process that could be scaled up to 4,000 L and improve productivity [1]. The other important thing is that the process has to be kept simple because we aimed to do technology transfer not only to developed countries but also to many low-or-middle income countries that may not be able to adopt a complex process in such a short time.

Q How did you go about making the process faster and more efficient than previous methods for manufacturing adenovirus-based vaccines?

CJ: Initially, upstream production of ChAdOx was carried out in shaker flasks, with purification via ultracentrifugation. This was expensive and required a lot of batches to get the number of doses required, even for relatively small-scale production. We wanted to ensure a simple and cost-effective manufacturing process that could be implemented in bioprocessing facilities around the world.

Before I joined the team, they had developed a process that can be scaled up to 3 L in a small bioreactor. They had replaced ultracentrifugation with a three-step process involving an initial tangential flow filtration (TFF) step, followed by anion exchange chromatography (AEX), then a final TFF step. However, productivity was still not sufficient, with only 500 doses per L.

My first focus was to improve the upstream process. One of the problems with producing a viral vector vaccine is the cell density effect, bringing the total productivity down at high cell densities. To alleviate that problem, I started by optimizing the conditions for cell growth. I developed a protocol for the composition and timing of nutrients in the media – a relatively simple change that improved productivity tenfold.

Next, I optimized and automated other aspects of the upstream process, for example, how much virus should be used to infect cells and when to harvest.

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"I started by optimizing the conditions for cell growth. I developed a protocol for the composition and timing of nutrients in the media – a relatively simple change that improved productivity tenfold."

We then adapted the purification process from a 3-L to a 50–200-L bioreactor, and then up to 4,000 L. The initial TFF step was not suitable for the 1–4,000-L scale. This is important because most contract manufacturing organizations (CMOs) around the world have the capacity to run 1000+ L reactors, which will help us a lot in speeding up the global COVID vaccine supply. With 1,000 L of lysate, this would have required up to 10,000 L of buffer, which very few CMOs would have been able to accommodate, plus faster pump speeds and larger filter areas.

We modified the process by removing the initial TFF step so that the cell lysate was loaded directly onto anion-exchange (AEX). After AEX the material is quite pure, so although we still have to do TFF after anion exchange, the buffer exchange doesn't require as much filter area and, most importantly, we don't compromise on the quality of the final vaccine product.

Q How did the team at the University of Oxford transfer the technology you developed to facilities around the world?

CJ: Early on, we had limited funding and our lab at the University was only lab-scale and not fit for cGMP production. We sent out a call for help via the UK Bioindustry Organization. Pall, Halix, and Cobra Biologics were quick to join our consortium. Pall offered us the use of their lab in Portsmouth to test the process on a larger scale, while Halix and Cobra transferred the process to their cGMP facilities.

Soon, larger CMOs such as Oxford Biomedica, Serum Institute of India, and Wuxi Biologics came on board and gave us access to 1,000–4,000-L scale facilities. In May 2020, we partnered with AstraZeneca, who were able to bring on board more CMO partners. Within a few months, we had 25 manufacturing facilities spread across 15 countries and five continents, all using precisely the same protocol.

We were still producing data in the lab to fully characterize and optimize the process, but we needed to press ahead with tech transfer, so it was a process of continuous improvement. Information flowed both ways – as we obtained results in the lab, we would update the protocol, and scientists at our CMO partners would report any problems. Between us, we had a range of expertise and experience (many sites had never worked with adenovirus vectors before), so there were lots of different challenges, which we would discuss and solve together. Many of these companies are competitors but came together in these exceptional circumstances.

Q What was it like to find yourself suddenly one of a small group of people the whole world was relying on?

CJ: There was immense pressure but we had no other choice. For months, I spent 16–18 h per day, 7 days a week, in the lab. At that point, no one else knew the process in depth, so I had to take it from the beginning to the end. I focused on prioritizing what the next experiment should be so that we could drive this process as quickly as possible for clinical trials and eventually commercialization.

Q What's next for your work?

CJ: The ChAdOx platform can be applied to produce vaccines against many viral infections. Prior to COVID, we developed a vaccine for the Sudan ebolavirus, which has already been deployed in Uganda, and I am now continuing work on the manufacturing process for that vaccine.

We also want to be ready for the next pandemic. Recently, we published a blueprint for how a billion doses of adenovirus-vectored vaccines can be produced within CEPI's 100-day target [2,3].

Q What would be top of your wish list for technology innovation in vaccine manufacturing?

CJ: Right now, I can produce a lot of vaccine in the upstream process, even amounts that the world has never seen before. Our bottleneck is now downstream. There is no filter in the world that can handle those loads and still produce vaccines at the quality standard we need for human use. So top of my wish list would be innovation in purification methods.

Q In your view, how prepared are we for the next pandemic?

CJ: Prior to and in the early days of the pandemic, we had very little funding, time, or trained staff. The UK government provided funding during the pandemic, but now that COVID-19 appears under control, policymakers seem to be losing interest again.

At this time, there is not enough support for the vaccine field to tackle the next pandemic, and the UK government is cutting funding for science and vaccine development. We have all the knowledge and the technology to develop vaccines even faster than 1 year, but we don't have enough support.

BIOGRAPHY

DR CARINA JOE is a senior research scientist in vaccine development focusing on viral vector vaccines at the University of Oxford. Prior to joining Oxford University, she worked in the manufacturing department of CSIRO, where projects range from manufacturing monoclonal antibodies, protein-based novel antigens, vaccines, viruses and cells in order to translate lab discoveries

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into pre-clinical, clinical and commercial phase drugs. As of 2019, she has been working as the lead scientist in process development for large scale cGMP manufacturing of the Oxford/AstraZeneca COVID-19 vaccine, which the team managed to develop in record time. Since then, their manufacturing technology has been transferred to multiple GMP manufacturing facilities around the world, enabling clinical trials and global vaccine supply at cost to 189 countries. As of January 2022, more than 3 billion doses of vaccine have been administered around the world, saving millions of lives. She and her colleagues continue to work to improve the manufacturing process with the goal of mass producing the vaccine in less than 100 days for the pandemic preparedness plan. Other than the COVID vaccine, she has taken up other projects such as a rabies and ebola vaccine, the latter of which was successfully deployed within 2 weeks to Uganda to control the Ebola outbreak.Affiliation

Carina Joe
Senior Scientist,
University of Oxford

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

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VACCINEINSIGHTS

ADVANCES IN VACCINE MANUFACTURING
PART 1: UPSTREAM ADVANCES &
INTENSIFYING PRODUCTION

SPOTLIGHT

EXPERT INSIGHT

Resolving facility design conflicts between biocontainment & good manufacturing practices for vaccines manufacture

Faye Litherland & Ranna Eardley-Patel

Many vaccines are manufactured using disease-causing agents or genetically modified organisms. However, many of the standard design principles for vaccines manufacturing facility biocontainment (encompassing biosafety and biosecurity) conflict with design for hygienic operation in good manufacturing practice facilities.
This article presents an overview of risk-based approaches to resolve the competing requirements with specific regard to the design of:
- Facility layout, people, material, and waste flows
- Heating, ventilation, and air conditioning
- Construction methodology
- Utility supply

This insight aims to inform those involved in the design of human vaccine production facilities, or contract manufacturing organization selection, where a new organism or platform process is to be introduced. It is a small part of a much wider knowledge area required for ensuring biosafety, and conducting risk assessments when developing, testing, and manufacturing vaccines.

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INTRODUCTION

Approximately 25% of all new drug approvals are biological products [1], for example, vaccines and blood products. This percentage is likely to increase following the success of vaccines used during the recent COVID-19 pandemic, leading to capability and capacity expansions globally for pandemic preparedness. One thing that these biological products have in common is that they almost all require some form of biological containment and biosecurity during the manufacturing process. This could be due to using a characterized wild-type organism, a genetically modified organism (GMO), or both. Vaccine production often involves the use of a genetically modified host cell line, a live virus seed stock, or cell culture processes that could propagate human pathogens if contaminated during production operations.

Relevant local, national, and international health and safety regulations in relation to the use of chemicals, GMOs, and the handling of biological materials need to be applied when designing and operating vaccine manufacturing facilities and supporting testing laboratories. Table 1 gives an overview of the hazard groups (HG) used in the UK, which relate to the biological containment level (CL) associated with either a pathogen and/or GMO. The term Biosafety Level (BSL) is commonly used in other countries and GMO containment is considered separately, and is sometimes used interchangeably with CL.

Many of the guidelines available have been developed for laboratories rather than manufacturing facilities, and there is little international regulatory harmonization for biorisk management for vaccine manufacturing at production scales (typically greater than 10 L liquid volumes). For UK-based facilities, these include, but are not limited to, those listed in the references section [2–18]. Subject matter expertise input into structured risk assessments is therefore essential to ensure compliance and biosecurity.

The UK COSHH Regulations [6] and the revised tables in EU Directive 2000/54/EC [15] do have separate tables for laboratories and industrial processes, but neither covers the requirements for the safe design and operation of the large scale equipment within the facility. This brings us back again to the importance of structured risk assessments involving the right people who have a working knowledge of how to apply the relevant guidances and regulations.

This is especially relevant for pandemic response, where surge vaccine manufacturing

TABLE 1

Overview of biological hazard groups.

Biological hazard group	Description	Example organisms/disease
1	No or low individual and community risk Unlikely to cause human disease	Brewers Yeast, *E. coli* (wild type, non-pathogenic strains)
2	Moderate individual risk, low community risk Can cause human disease and may be a hazard to employees; it is unlikely to spread to the community and there is usually an effective vaccine or treatment available	*Bacillus Pertussis* (whooping cough), *Legionella spp.*
3	High individual risk, low community risk Can cause severe human disease and may be a serious hazard to employees; it may spread to the community, but there is usually an effective vaccine or treatment available	*Bacillus anthracis* (anthrax), *M. tuberculosis*, Rabies virus, Poliovirus
4	High individual and community risk Causes severe human disease and is a serious hazard to employees; it is likely to spread to the community and there is usually no effective prophylaxis or treatment readily available	Ebola viruses (hemorrhagic fevers)

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is required, and facilities may need to be repurposed at short notice. The organisms used to make vaccine materials may not be fully characterized at the outset, so a higher containment level may be required until data is obtained.

Although this article refers to more to human vaccines, the same principles apply to veterinary vaccine production facilities. The zoonotic risks of all organisms must be assessed whether for human or animal vaccines. Some countries have separate regulations relating to animal pathogens and those with cross-species risks, for example in the UK there is the Specified Animal Pathogens Order (SAPO) [5].

SELECTED DESIGN CONSIDERATIONS FOR BIOCONTAINMENT IN A GMP VACCINES PRODUCTION FACILITY

Many of the standard GMP design principles for vaccines manufacturing facilities and biosecurity are in conflict. For example, production cleanroom suites are typically positively pressurized to the outside environment, with a net outward flow of air in order to maintain the appropriate hygienic air classification, but a typical laboratory with a pathogen or GMO containment classification is negatively pressurized to the outside environment and/or has a net inwards flow of air (negative to the surrounding areas) to provide the appropriate level of biocontainment.

The following sections discuss the key aspects and propose some design solutions to address these conflicts.

Facility location & layout

Facility location and layout are the first considerations for a GMP vaccine manufacturing facility with a biological containment requirement.

If the facility is in a geologically active area, or in an area prone to extreme weather events or similar, it must be built to withstand those forces. The degree of protection required will depend on a risk assessment of the organisms being handled and whether the requirement is to minimize or prevent release but could include seismic rafts, additional structural reinforcement, building damping, vibration shielding, and the use of earthquake-resistant materials.

If the containment cleanroom is near a road and/or located on an outside wall at ground level, then measures need to be taken to prevent damage from a road traffic accident or a vehicle being forcibly used to enter the cleanroom. Mitigation measures such as the installation of very large bollards, bulletproof glass or metal barred windows, and solid walls, ceiling, and floors (brick, concrete, etc.) on the containment boundary to prevent unauthorized personnel access from inside and outside the facility, are also likely to be required. These have consequences for the facility's capital cost and operation.

With regards to layout, GMP flows such as the movement of people, waste, and raw materials also need to be examined for biosecurity and GMP compliance. A recent production facility design required the movement of the HG3 inoculum from the working seed bank to the CL3 manufacturing suite. This route used the same corridor as another manufacturing suite and there was no alternative route. The route had to be carefully managed using temporal separation so that there were no other personnel or material movements through the corridor at the same time as the transfer, and decontamination measures were put in place after the transfer before the corridor went back to normal use.

Containment cleanrooms that will involve handling of classified organisms should be located away from other areas, even in their own wing where practical, but this needs to be balanced against the requirements of the process flow. Depending on the risk associated with the organism, it may be appropriate to have a separate entrance and access corridor for those people working in containment cleanrooms, but this requires

a greater footprint and is not always practical. Unidirectional flow is an advantage, but is not always possible, especially where the containment cleanroom is part of a retrofit of an existing facility.

When locating a containment cleanroom suite, it is important to always consider the principles of primary and secondary containment. The primary containment barrier is the equipment containing the contaminated material. For open processing, this is the isolator (glove box), or microbiological safety cabinet. For closed processing, it is the pipework, vessels, etc, and the joints between them.

The secondary containment barrier is formed by the architectural and HVAC elements of the room or suite of rooms. A critical and often missed element affecting the building architecture for facilities handling GMOs is the requirement that "the controlled area should be designed to contain spillage of the entire contents of closed system" [4,6]. Bunding of a large liquid waste inactivation system is relatively simple, but bunding a production suite, where people and materials movement on trolleys is required, takes a bit more creativity. Mobile bunds with sufficient integrity to meet the requirement are often not suitable for GMP operations in terms of materials and cleanability. Built-in elements are preferred, but the materials movement requirements must be carefully assessed, plus this can be more difficult to achieve in a retrofitted facility.

Vaccine facilities typically produce large volumes of contaminated liquid that needs treatment (e.g., inactivation, neutralization, dilution) before it can be safely discharged. The plantroom for the liquid waste inactivation systems should be located as close as possible to the containment cleanrooms. Long gravity drainage pipe runs containing contaminated waste and running outside the containment boundary represent an increased risk of loss of containment. Risk assessments will show what is most appropriate for a specific organism and facility, but wherever possible, best practice is to avoid pipe runs outside the containment area by locating the liquid waste inactivation room directly below the containment cleanrooms it serves. This means that because the secondary containment boundary is continuous, the liquid waste inactivation room can be considered part of the suite.

Heating, ventilation & air conditioning (HVAC)

The flow of air in, out, and around the facility also needs to be considered for biocontainment, so the next most critical aspect of your containment cleanroom is the HVAC system. The pressure cascade between the rooms is one of the primary containment measures and as such it needs to be treated as a critical system.

A standard pharmaceutical facility HVAC design protects products from external contamination (airborne dust and other contaminants) and internal cross-contamination (other airborne products) as well as protecting the operators from the product. However, these pharmaceutical facility HVAC designs are usually insufficient for a biologics facility handling classified organisms (see Table 1), where, in addition, the operators/environment need to be protected from any potentially hazardous biological agents.

When assessing the HVAC system requirements, it is very important to consider which rooms/suites are served by each air handling unit (AHU) and what impact the failure of an AHU would have on the overall facility pressure cascade, which is essential to maintain the secondary containment barrier.

Case study: HVAC design for a CL3 facility

Below is a review of the HVAC design for a derogated CL3 facility (bloodborne organism not transmissible by airborne routes) with the containment cleanroom at a small

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positive pressure to atmosphere, but negative to the rest of the facility (Figures 1A–C). The containment airlocks (Airlock 1) were on the same AHU as the non-contained corridor. This meant that if the corridor AHU (AHU2) had failed, the containment cleanroom would have been positively pressurized to the facility and there would have been a loss of containment. In this case, the problem was easily resolved by moving the containment airlocks (Airlock 1) onto the containment cleanroom AHU (AHU 1) (Figures 1D & E).

Another often overlooked area of HVAC systems is the controlling instrumentation, including proportional damper position feedback. HVAC analogue signals commonly work on the principle of 0–10 V. Therefore, an open circuit failure of 0V would not be detected as an abnormal condition. If signals are specified as 4–20 mA instead, then an open circuit of 0mA can be detected and an alarm raised.

The location of high efficiency particulate air (HEPA) filters is another aspect that is open to debate. For the purposes of biological containment, they are not required until higher containment levels (CL3 or 4) are reached. They can be located inside the room or remotely within the ductwork. It is important to remember that if the HEPA filters are located remotely from the cleanroom, the filters define the containment boundary and therefore the ductwork leading to the filters forms part of the containment boundary. This has implications for the specification of the ductwork. If a containment-classified cleanroom has HEPA filters that are remote from the room boundary, the ductwork up to the filters must be constructed to the same airtightness specification as the containment cleanroom and able to be subjected to the same decontamination measures.

According to current UK regulatory guidance, HEPA filters on the inlet air are not required until CL4. This is based on the principle that the net air flow is inwards and therefore the containment boundary is secure. However, the AHU failure case must be considered. If there is a failure of the containment cleanroom AHU, then there is an airflow path direct to the atmosphere via the inlet air ductwork, resulting in a breach of containment. If an inlet HEPA is not installed, then a gas-tight damper wired to a pressure sensor or some other suitable isolation method should be installed to prevent the loss of containment.

Vaccine manufacturing cleanrooms for aseptic operations will generally have an inlet HEPA filter for GMP purposes. This inlet HEPA can be considered as the containment boundary if it is correctly located; a design strategy that is sufficient for GMP, but not for biocontainment is locating the inlet HEPA for Grade D cleanroom suites close to the AHU, before the ductwork divides to different areas. This means that in the event of an AHU failure, an air path could be present between containment and non-containment areas.

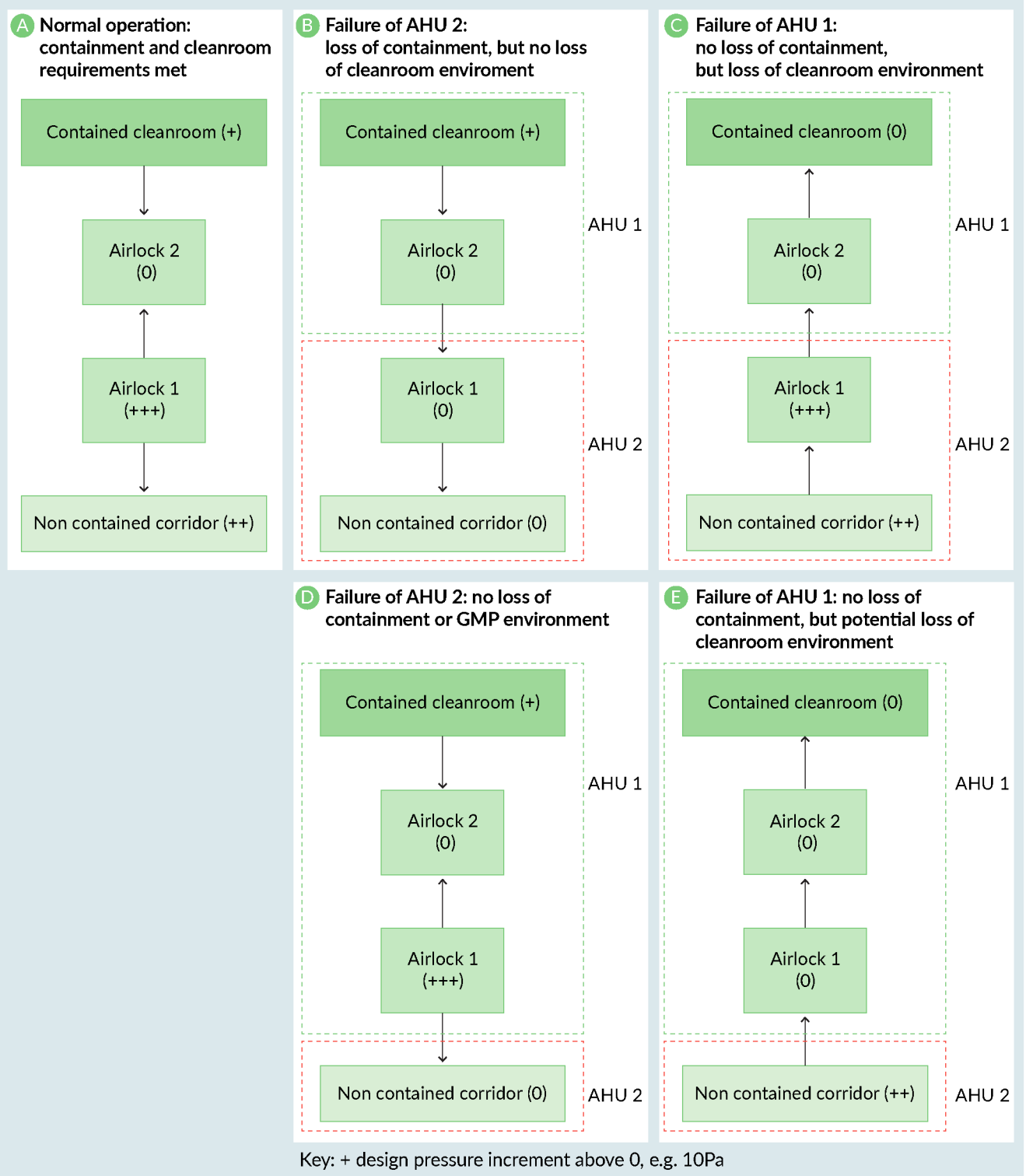
If there are potential bioterrorism risks, multiple small HVAC ducts may be considered to prevent entry by a malicious person crawling through intakes or vents.

Construction methodology

The construction of the containment cleanroom presents a challenge both in terms of specification and constructability. Proprietary cleanroom fabrication systems are usually designed for standard positively pressurized cleanrooms. In a positively pressurized cleanroom, the airtightness of the cleanroom system is important, but not critical, because the air would flow outwards through any small gaps and still maintain the cleanroom environment. Even though the cleanroom panels usually have gaskets in the joints, polymer-based sealant is used to improve cleanability and also improves the airtightness of the cleanroom system. The sealant will degrade over time and outwards air leakage will increase slightly; inspection of all sealed joints should be a routine part of any facility's planned preventive maintenance program. The HVAC system should therefore be

FIGURE 1

The design of a CL3 facility.



designed with this in mind and have sufficient capacity to increase airflow rates to maintain the pressure cascade between the rooms until maintenance is carried out.

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Not all containment cleanrooms will need to meet a specific airtightness standard, but it is important to identify those which do as early as possible so that the details are included in the specifications and checked during construction.

This can be illustrated with an example of a -30Pa, Grade B, CL3 containment cleanroom with a proprietary cleanroom system. As the containment cleanroom is under negative pressure, the engineering team needs to ensure that the cleanroom walling system is physically strong enough to withstand the pressure differential. There have been incidents of panel damage and cleanroom windows getting sucked in during commissioning because the cleanroom system was not specified for vacuum.

The next issue to consider is the airtightness of the cleanroom walling system, not considering any applied sealant. This is important to prevent particulates being sucked into the cleanroom from wall cavities, ceiling voids, etc. The cleanroom system must be specified to achieve a defined airtightness standard and be tested following installation before any sealant is applied to improve cleanability.

Next, we will look at an example of a -30Pa, Grade D, CL3 containment cleanroom constructed using a non-proprietary cleanroom system. Standard building materials, such as plasterboard walls with vinyl, will create the containment barrier. The degree of tolerance of each stage of construction is even more critical. As above, it is important that sealants are not relied upon to achieve the required airtightness. This type of containment cleanroom often causes more issues than those using a cleanroom system. The reason is that standard building tradespeople are used to construct the facility. These contractors are usually not used to building to the tolerances required for this specialist type of work. Unless they are carefully supervised, and the work inspected at every stage, the quality of the construction is unlikely to achieve the required airtightness.

Best practice involves including in the project brief and user requirement specifications that the cleanroom system vendor will build a mock-up for testing prior to committing to the cleanroom system products, then getting the contractor to complete and test one room as a sample before progressing to the other rooms, so that costly mistakes can be avoided.

UTILITY SUPPLY

The supply of GMP utilities into biological containment classified cleanrooms presents some very interesting engineering challenges. The cleanroom construction discussed above is only part of the story. An essential part of most containment cleanrooms is the how utilities are supplied through walls and ceilings. In a standard cleanroom, a hole would be drilled in the cleanroom system, the pipe threaded through, and a trim plate applied and sealed with a polymer-based sealant. For a containment cleanroom, where a high airtightness standard needs to be achieved, this method is not suitable. Proprietary, gasketed, gas-tight, pipework and cable transit systems are available, but their use must be specified early so that the utility pipework and cables can be grouped together to ensure as few penetrations as possible are made in the containment barrier. Penetrations through the containment barrier for other items such as autoclaves, utility panels, pass-through hatches, etc. must also be gasketed and airtight to preserve the integrity of the containment barrier.

Firstly, let us consider a simple dry non-returning service such as clean compressed air, that serves bioreactors, product transfer lines, filter integrity testers, etc. In normal operating conditions, the service will be pressurized. It is therefore safe to assume that containment is maintained by the net inward flow of the gas. The challenge arises when the system depressurizes due to breakdown or maintenance. There is now an open flow path between containment and non-containment areas. In a classical biological containment laboratory this would probably not be an issue because, depending

on the containment level, the laboratory is likely to be under a small vacuum or at atmospheric pressure so the flow of air would be inward or neutral. If the HVAC system has been designed to be able to deal with the increased inwards leakage rate, then containment can be maintained. However, with GMP manufacturing we try to avoid having the cleanrooms under vacuum because of the potential to draw particulates from unclassified ceiling voids, wall voids, technical spaces, etc. This means that at CL2, where the requirements are to minimize release, often the cleanroom is positively pressurized to the atmosphere and the containment is managed through strict construction controls to minimize air leakage through the cleanroom wall and ceiling system, and pressure sinks and pressure bubbles in the personnel and materials airlocks and any transfer hatches. It is CL3 containment cleanrooms that are more likely to be under vacuum.

There are several ways of controlling this open-air flow path, which seem obvious until one investigates further. All need careful consideration and risk assessment. For example, if a barrier device such as a filter is fitted in the line, how do you safely manage the decontamination of the pipework downstream of that device following depressurization? When that device needs maintaining or replacing, how do you manage the flow path that is now open again? Probably the most obvious solution is to decontaminate the cleanroom prior to carrying out any maintenance work. This works for planned preventative maintenance, but not in a breakdown scenario. Recovery from a loss-of-containment event is an important consideration that is often overlooked and must be included in the facility design i.e., non-routine operations.

Careful consideration has to be given to the provision of looped services to containment cleanrooms, with a full understanding of the potential risks and characteristics of the organisms being handled. Unlike the example of a dry compressed gas service above, where isolation of different plant areas with valves and/or filters can be achieved, looped utilities such as purified water or water for injection (WFI) often flow through all areas of a manufacturing facility and return to a central tank without any interruption. For a recent vaccine facility project requiring a Grade C cleanroom with a CL3 containment classification, the WFI user point was located outside the containment area in a separate cleanroom and WFI dispensed into single-use bags which were then transported into the containment area. For particularly high-risk applications, where the demand is higher, utilities distribution dedicated to the containment suite may have to be considered.

TRANSLATION INSIGHT

Biocontainment (biosecurity and biosafety) measures are a key aspect of vaccine manufacturing facility design and operation but are often in conflict with standard GMP design principles for the manufacture of biologics. Maintaining biocontainment is ultimately the responsibility of the vaccine product developer, and loss of containment can have very serious consequences. Like product quality and safety in general, this aspect cannot be compromised on.

In addition, most countries have a list of organisms that they consider represent a risk for bioterrorism. If any of them will be present in the facility, then the relevant government agency will need to be consulted and additional security measures are likely to be needed to prevent theft or unintentional release. Comprehensive guidance for handling of classified organisms at production scales is still to be developed. However, there is a wide range of guidance for handling classified organisms at laboratory scales that can be leveraged.

Non-routine operations need to be considered, as well as operations that may take place in the future. e.g., the introduction of a new manufacturing process into a CMO facility.

Key questions to ask the product and process development teams, facility designers,

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and/or CMO operations team if you are planning to manufacture a vaccine should include:

- Do the manufacturing processes (all steps including testing and known/likely future activities) involve any classified organisms, i.e., that are biologically hazardous, and/or genetically modified, and/or considered a bioterrorism risk?
- Does the facility location present any abnormal risks for loss of containment, e.g., in an earthquake zone?
- Do the team know which regulations and guidelines (that apply locally, nationally and internationally) need to be complied with?
- Have structured safety risk assessments [19, 20] [adapted from industry guidances on layers of protection analysis (LOPA), bow-tie, failure modes and effects analysis (FMEA), structured what if technique (SWIFT), hazard and operability analysis (HAZOP) etc.] been performed, documented and reviewed for biocontainment, including biosafety and biosecurity, using subject matter experts?
- Do the layout, HVAC design, cleanroom construction system, utilities design, etc. enable the biocontainment needed for (a) routine operations, (b) non-routine operations (e.g., contaminated cell culture disposal, maintenance shutdowns), (c) abnormal situation (e.g., equipment breakdown, integrity failure)?
- For new facilities: Does the cleanroom fabrication team, including sub-contractors, understand the criticality of their work for the manufacture of vaccines/handling of classified organisms? Can they provide mock-ups/samples for testing and inspection?

Finally, a common question that is often asked is if existing facilities can be used for higher containment operations; generally, the answer is no. Vice versa, a high containment facility can be used for less hazardous organism handling, but this is not cost-effective and adds unnecessary operational constraints. As such, facility design needs to be 'fit for purpose intended' to address the critical biosafety and biosecurity aspects.

BIOGRAPHIES

FAYE LITHERLAND and **RANNA EARDLEY-PATEL** are both chartered principal process engineers who have designed, commissioned, remediated, validated or operated high-containment facilities used for the manufacture and testing of vaccines and other biologics.

AFFILIATIONS

Faye Litherland, CEng, CSci, FIChemE
Director/Principal Consultant
Blue Sky Engineering Ltd

Ranna Eardley-Patel, EngD, CEng, FIChemE
Sustainable Manufacturing Lead, CEPI, formerly Director/Principal Consultant, PTF UK Ltd

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VACCINEINSIGHTS

ADVANCES IN VACCINE MANUFACTURING
PART 1: UPSTREAM ADVANCES &
INTENSIFYING PRODUCTION

SPOTLIGHT

Leveraging modernization of the US influenza vaccine manufacturing base to make better vaccines: a work in progress

Robert C Huebner, PhD
Principal Consultant, Latham Biopharm Group,
a part of Sia Partners

"The time is right to leverage our newly demonstrated manufacturing platforms to design and develop the next generation of influenza vaccines."

VIEWPOINT

Vaccine Insights 2023; 2(4), 77–80

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When highly pathogenic avian influenza emerged in Hong Kong in 1997, killing 6 of 18 people with confirmed infections [1], US public health and national security experts realized the vulnerability of the US and global populations to pandemic influenza. At the time, there was a single US manufacturer of influenza vaccines, Sanofi Pasteur, which relied on seasonal supplies of embryonated eggs to grow the influenza viruses used to make their split virus vaccine.

In response to the 1997 outbreak, the US Homeland Security Council released two documents that laid out plans to improve public health preparedness for pandemic influenza: a national strategy in 2005 [2] and a national strategy implementation plan in 2006 [3]. A key aspect of the preparedness pillar of the national strategy was: "Establish domestic production capacity and stockpiles of countermeasures to ensure… sufficient vaccine to vaccinate the entire US population within 6 months of the emergence of a virus with pandemic potential" [2]. Starting in fiscal year 2004, Congress began supplying funds to address this aspect of the national strategy, with funding through the US Department of Health and Human Services (HHS) and the Department of Defense (DoD). This effort, a several billion-dollar investment, resulted in part in the creation of the Biomedical Advanced Research and Development Authority (BARDA) in 2006 [4] to be the point organization for leading the development of the domestic influenza vaccine manufacturing infrastructure.

Initial efforts to build up domestic vaccine manufacturing started in 2004. HHS funded contracts to bolster supplies of embryonated eggs so they were available year-round [5] and to develop a cell-based influenza vaccine with a provision to build a domestic facility for vaccine production [5]. BARDA followed these contracts with additional cell-based influenza vaccine [6], adjuvant [7], recombinant influenza vaccine [8], and influenza vaccine production facility [7,8] contracts. In parallel, the DoD funded the development of alternate platforms for influenza vaccine production [9].

These efforts have resulted in the licensure of new cell-based, recombinant, and adjuvanted or dose-sparing influenza vaccines [10]. Other improvements include an enlarged domestic capacity to produce adjuvants and influenza vaccines using egg-based, cell-based, and recombinant vaccine platforms [7,8]. The US now has the domestic capacity to produce enough influenza vaccine to provide pandemic influenza protection within six months. But even with improved manufacturing infrastructure and more types of vaccines, is the job of preparing for pandemic influenza finished? Do we have better vaccines? I would argue there is still work to be done to achieve pandemic preparedness with better vaccines.

The majority of influenza vaccines use egg adaptation for egg-based vaccine manufacturing which has been shown to alter how closely a vaccine matches circulating influenza viruses [11–13]. Recombinant and cell-based vaccines, which do not require egg-adaptation mutations for efficient manufacturing, are more effective than egg-based vaccines [14,15] because they avoid egg adaptation and more closely represent viruses circulating in the population. This has led to the committees that select strains for influenza vaccine production recommending two different strain formularies depending on whether a vaccine is to be egg-based or non-egg-based (cell-based, recombinant).

While the use of non-egg-based vaccines is growing, the field effectiveness data in the years since their licensure suggest that we are still being served by mediocre vaccines. The CDC influenza vaccine effectiveness data [16,17] from 2004 to today shows the overall average effectiveness at 41%. Between 2004 and 2012, before any new vaccines were licensed, the average effectiveness over this period was 41%. Between 2016 and 2023, after the last of the new vaccines were licensed, average effectiveness only increased to 42%.

Why is vaccine effectiveness not improving? The tremendous improvements to our influenza vaccine manufacturing capacity and expanded vaccine manufacturing platforms have not expanded into the design and manufacture of better vaccines. We are still largely

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making injectable influenza vaccines focused on making antibodies to the virus hemagglutinin (HA), which appear to only provide 60% protection in the best of years. McLean *et al.* [17] report the mid-season effectiveness at 71% for the 2022–2023 influenza season but since it is known that vaccine effectiveness declines over time through the influenza season [18] it is expected that the final effectiveness percentage will be lower by the end of the season.

I argue that in order to design and manufacture better influenza vaccines, focus is needed on three areas that leverage our expanded platforms and manufacturing capacity to improve influenza vaccines:

1. Incorporating more conserved antigens (neuraminidase (NA), M2 protein) into influenza vaccines would broaden immunity and increase baseline protection, especially in years of a vaccine mismatch;
2. Designing vaccines to stimulate mucosal immunity to protect the initial route of infection and;
3. Designing vaccines to stimulate T cell immunity to limit and control infections. Ideally, we will design improved influenza vaccines that incorporate all three of these improvements over current vaccines.

Manufacturing lessons from vaccines against SARS-CoV-2 may have paved the way for influenza vaccines with improved effectiveness. The capacity for the manufacture of mRNA-based vaccines has been clearly demonstrated by the hundreds of millions of doses of SARS-CoV-2 mRNA vaccines produced. These mRNA-based vaccines were shown to stimulate T cell responses [19,20]. Influenza vaccines based on this technology, designed to incorporate both HA and NA targets into a single vaccine, could offer broader protection with improved T cell responses to control infections when they occur.

Although not as widely used as mRNA vaccines, vectored adenovirus vaccines could demonstrate even greater promise as a future platform for more effective influenza vaccines. Vectored adenovirus vaccines can be delivered by mucosal immunization [21]. Adenovirus-vectored influenza vaccines incorporating both HA and NA targets could stimulate mucosal immunity to protect the initial route of infection along with immunity to a more broadly protective set of antigens, and stimulation of T cell responses to influenza virus.

The time is right to leverage our newly demonstrated manufacturing platforms to design and develop the next generation of influenza vaccines. The improved designs will not only be rapid to manufacture but more effective in combating seasonal and pandemic influenza infections. These steps are needed to ensure we have established and built the rapid development capabilities and manufacturing infrastructure to respond to future pandemics.

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AFFILIATION

Robert C Huebner, PhD,
Principal Consultant,
Latham Biopharm Group,
a part of Sia Partners

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VACCINEINSIGHTS

ADVANCES IN VACCINE MANUFACTURING
PART 1: UPSTREAM ADVANCES & INTENSIFYING PRODUCTION

SPOTLIGHT

Rapid manufacturing of vaccines for pandemic response & personalized cancer: parallels to leverage for common pathways to expedite clinical development?

Antu K Dey
Senior Vice President, Vaccines R&D, GreenLight Biosciences Inc.

"...the paradigm shifts required to substantially condense timelines could come from the field of neoantigen-based personalized cancer vaccines."

VIEWPOINT

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In recent years, multiple viruses have caused outbreaks that threatened a worldwide pandemic, with one virus in particular, SARS-CoV-2, causing the worst human pandemic in 100 years. The first coronavirus outbreak of the 21st century, caused by SARS-CoV-1, appeared in November 2002 and after spreading to 29 countries, came to a halt in mid-2003 [1]. In 2009, the H1N1 pandemic presented a public health emergency of uncertain scope and effect, with reporting of laboratory-confirmed cases and loss of lives in all countries [2]. The second coronavirus outbreak, caused by MERS-CoV, appeared in 2012 and caused deaths in 27 countries, despite its primary localization within the Arabian Peninsula [3]. The third and most deadly coronavirus outbreak, caused by SARS-CoV-2, appeared in 2019 and rapidly spread to cause an unprecedented global pandemic that has already killed over 15 million people worldwide and continues to impact human lives through emerging viral variants [4] despite the tremendous contribution of vaccines in greatly reducing the risk of severe illness and death [5,6]. In addition, there have been other threatening viral outbreaks in the last two decades [7–9]. These 20 years of numerous outbreaks and pandemics have reiterated the need for rapid manufacturing and deployment of prophylactic vaccines and therapeutics to avert the spread of global infection and death.

The speed of COVID-19 vaccine development, particularly of the two mRNA vaccines produced by Moderna and Pfizer/BioNTech, was unprecedented. Within a year of the pandemic starting, two entirely new vaccines based on the mRNA technology were authorized for emergency use that allowed for billions of doses of vaccines to be administered globally, saving millions of lives [10,11]. mRNA holds great promise as a rapid-response manufacturing platform technology to support the production of billions of doses in a small manufacturing footprint and low capital cost facility [12]; however, that promise had to be rapidly translated to reality during a global health crisis. This was made possible by public–private partnerships to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. In addition, transformative clinical trials, strong regulatory agency and manufacturer interactions, and swift and adaptive regulatory strategy in emergency use authorization (EUA) of the two mRNA vaccines [13,14], followed by their full approvals, were pivotal.

Considering the lessons learned from the COVID-19 pandemic and the need to avoid future global outbreak catastrophes, a pandemic prevention plan has been launched to lay the groundwork to develop, test, and approve preventative vaccines against new pandemic pathogens in 100 days [15,16]. It is clear that compressing vaccine development timelines further will require substantial shifts in the current development process, supported by scientific advancements and regulatory agency support.

I believe the paradigm shifts required to substantially condense timelines could come from the field of neoantigen-based personalized cancer vaccines. Neoantigens refer to patient-specific unique short peptide epitopes that are found in tumor cells (and not in healthy tissues) that can be identified using bioinformatics methods [17]. Once the bioinformatic methods for identifying neo-epitopes in cancer genomes are well-validated and accepted by regulatory agencies, the rate-limiting step will be the speed with which these identified neoantigens are manufactured and administered to patients. mRNA can suitably support the speed and manufacture of the vaccine in days; however, it will require the demonstration of rigorous process control because, in this case, 'process' is the 'product'. Application of Quality by Design (QbD) principles [18] will allow mRNA platform manufacturers to install critical process parameters to identify the critical quality attributes and overall control strategy in a target-agnostic manner. This will give regulators the understanding and confidence in vaccine manufacturers' risk

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assessment and ability to implement a robust overall control strategy, including process and analytical test controls that can consistently support the manufacturing of safe and high-quality mRNA products [19].

Once the platform is consistently demonstrating the production of safe and high-quality products, it is plausible to assume that a limited set of testing agreed upon by the regulatory agency through prior consultation may be acceptable to allow vaccine administration first, followed by provision of the remaining test panel results during the clinical trial. This could include reduction or non-requirement of repeated *in vivo* safety pharmacology evaluations for each clinical product candidate. These, taken together, can dramatically condense the needle (biopsy) to needle (vaccine administration) timeline and allow timely access to these precision immunotherapies for patients in experimental medicine studies. This pre-establishment of the safety and quality of mRNA personalized cancer vaccines can in turn support the rapid vaccine manufacturing and regulatory approval process required during a pandemic or outbreak situation.

Although the indications are very different, by sharing knowledge and platform-specific standards acceptable to regulators, manufacturers of personalized cancer vaccines and infectious disease vaccines can contribute to get their products faster to the people who need them.

BIOGRAPHY

ANTU DEY is the Senior Vice President of Vaccines R&D at GreenLight Biosciences Inc., where he oversees the integrated research and development of viral vaccines through the use of the company's messenger RNA (mRNA) platform technology. Before joining GreenLight Biosciences, Dr Dey led the product development and cGMP manufacturing of multiple recombinant vaccine and monoclonal antibody (mAb) candidates at IAVI's Product Development Center (New York, NY) for 6 years. This included development of over a dozen candidates in HIV-1 vaccines and mAbs against HIV-1 and COVID-19 for evaluation in Phase 1–3 clinical studies in the USA, Europe and Africa. Before joining IAVI, Dr Dey worked at Novartis Vaccines & Diagnostics and then at GSK Vaccines for 7 years, in various R&D roles of increasing responsibilities. Dr Dey serves as a scientific advisory board member to various academic and government organizations on vaccines R&D. Dr Dey completed his DPhil. in Biochemistry from University of Oxford (UK) and completed his post-doctoral training at Weill Cornell Medical College (New York, NY).

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AFFILIATION

Antu K Dey
Vaccines R&D, GreenLight Biosciences Inc., Lexington MA, USA

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