7 Vaccine manufacturing and quality control

GAPS AND CHALLENGES

Vaccines are large, complex often hybrid biological molecules. They are produced through multiple steps of production and formulation for which the end product (vaccine or combination vaccine) is often a combination of many component products (antigens or vaccines). As a result the final product cannot be characterised in the same way as a small molecule medicine. The structure, consistency and integrity of the final product is assured by ensuring that the production process itself is as reproducible and consistent as possible, thereby ensuring a reproducible and consistent end product. This requires a production system that can be very tightly controlled and a team able to consistently implement such processes. The manufacturing also encompasses a set of well characterised quality control tests that document the process parameters and agreement with regulators and product release authorities on the best tests to use and parameters of acceptability. The end result is a product that is defined more by its production process than by the final output.

The resulting production process takes between 6-36 months of which 70% of the time is consumed by control testing. As a result anything that can be done to standardise the production process, modernise and standardise release tests and ensure a streamlined process and standardised regulatory and release requirements, will allow shorter cycle times and faster and more predictable production of vaccines. This is urgently needed as today, global demand outstrips supply for all but a very few vaccines. This gap between supply and demand is a result of the complexity, cost and duration of production and the paucity of producers able to meet the demanding standards and costs.

The main areas of focus of the consultation were:

- How to innovate vaccine production and release, to address the global shortage of almost all vaccines
- How to increase production capacity and shorten cycle times
- How to minimise costs and minimise unpredictability of development and production

Achieving better global vaccine supply

One of the key needs identified during the consultation on manufacturing and quality control was the need to support **technologies** that will address the current **global vaccine supply shortage. Overarching principles that could increase production speed, production yields and production predictability** were Quality by Design (QbD) approach and improvements in process analytical technology (PAT) mechanisms. After a decade of development, PAT has become a reality for small molecule production, and has proven its ability to increase process robustness and reduce costs. However, this concept is still emerging for bio manufacturing, and technologies and know-how need further development to be applied in vaccines. Currently the specificity and reliability of these tools are lower for vaccines and cannot be used for quantitative purposes. Therefore, very basic in-process assays are not yet established. Further work is also required to better monitor impurities as well as measuring the 3D structure of the vaccines. This would allow better characterisation of the folding of the antigen being presented and thereby allow better predictability of its potency.

The panel of experts consulted emphasised that innovative technological approaches are also desirable to make **vaccines easier to deliver and administer**. This should include work to develop **thermostable vaccines** to overcome the need to keep vaccines in a cold chain[27] [28]. Participants also agreed that new delivery systems could enhance the ability to deliver vaccines and thereby increase vaccination coverage.

Increasing production capacity and improving timelines especially in epidemic or pandemic settings

The need to be able to rapidly produce large quantities of vaccine in a very short time is essential to the ability to respond to future epidemics and pandemics. This is already a priority in a number of countries (e.g. BARDA[29] in the US), but should become a priority throughout Europe.

[27] IFPMA. The complex journey of a vaccine. 2014
[28] Karp CL et al. (2015) Evaluating the value proposition for improving vaccine thermostability to increase vaccine impact in low and middle income countries
[29] Biomedical Advanced Research and Development Authority. https://www.medicalcountermeasures.gov/barda.aspx

This will require innovation in the process, in disposable technologies and in the approval and release process. Progress made for epidemic and pandemic preparedness is likely to be rapidly transferable to the production of routine vaccines.

The main need identified by the participants was for modular facilities, combining **platform technologies flexible** enough to manufacture a multitude of candidates and **processes/ facilities that are easy to switch and scale up**. Modular facilities would allow the facilities to be used for routine vaccines and then switch rapidly to production of epidemic and pandemic vaccines as was done for the flu vaccine during the H1N1 pandemic. Alternative models include disposable technologies or the combination of warm-based production and stockpiling as is done for the smallpox vaccine.

Today, most current facilities are at or close to full capacity. There is, therefore, the need for a global increase in vaccines production capacity[30]. Approaches such as insect cell culture-based vaccine production may offer greater flexibility with lighter **infrastructure, which could in turn reduce costs by** 80-90% compared to traditional approaches[31].

Disposable bioreactors and downstream equipment also offer the ability for flexible production in BSL2 environments. However, these approaches are not currently possible for all vaccines and work is required to extend their use and develop other novel approaches.

Other production goals include the need to develop scaffold-based technologies able to express a large range of antigens in a highly stable form, and as close as possible to native conformation, that could be combined with other antigens in combination vaccines with minimal risk of conflicting formulations.

Improving affordability and reducing development risks

There are also human and organisational facilitators to vaccine production process optimisation. For example, early and continuous collaboration between the manufacturing teams, process development teams and early research teams is essential. There is also a need to develop tools that allow researchers and companies to better predict from a mL scale production to how a candidate vaccine will behave at commercial scale. Improved understanding in this area will help to de-risk the scale-up phases, identify early potential production bottlenecks or constraints and thus accelerate the time to market of vaccines as well as optimise vaccines affordability.

Lastly, novel **expression systems** such as algae or plants offer the potential for high capacity production in cell lines that are easier to work with and represent a far wider species gap. This would provide a further strategy for addressing the global supply shortage. However, these approaches have yet to prove themselves fully and further development is required.

There are other technologies, such as fully synthetic biology, whereby proteins, DNA or mRNA molecules could theoretically be synthesised chemically rather than biologically. Such an approach would bring huge benefits but would require significant advances in chemistry and associated adaptation of production facilities and regulatory and release requirements[32].

RECOMMENDATIONS FOR EU LEVEL ACTION

The recommendations of the manufacturing subgroup were predominantly on the need for more focused research priorities and associated funding that would drive forward a vaccine production and formulation R&D agenda that would allow:

- Better translation of innovative research into applied production innovation as a result of **better connection of research, process technology and regulators**. This would be in order to promote closer collaboration among scientists, engineers and regulators.
- **Supporting the continuity of funding beyond concept demonstration**; this is especially crucial in the context of emergencies:
  - e.g. by setting up a task force (TF) of regulators and policy-makers to support procedures based on scenario planning. This will allow a better assessment of cost-effective ways of handling emergency situations through establishing appropriate infrastructures in a pragmatic way.
  - Funding innovation for easier administration and delivery to increase vaccine coverage.

With regards to **funding priorities**, the following research areas were mentioned:

- Funding directed at flexible manufacturing systems
  - Investigate/research how to decentralise manufacturing capacity through a more localised supply base to avoid supply interruption in case of issues and shorten transport/delivery timelines.

[30] Vaccines Europe. (2013) Advancing health through vaccines innovation, accessible at www.vaccineseurope.eu
[31] Presentation: Rahul Singhvi, (2010) Manufacturing Enabled Global Influenza Vaccine Solution; cited in T. Mukhopadhyay presentation 2015)– IPROVE R&I workshop
[32] T. Mukhopadhyay presentation (2015), IPROVE R&I workshop

- To support the adoption of single use systems and technologies should help minimising variations between sites.

- Bridging technology and science: collaboration between engineers and biologists

Move away from the constraints of the cold-chain through investing in thermostability. This will enable technologies that ease the vaccine supply process, preventing the problem of deviation from the required temperatures, particularly in the context of low and middle income countries.

- Test alternative delivery devices: increasing vaccine stability and new fill-in allowing to avoid volume loss
- More investment in formulation expertise in the research process
- Develop and validate improved potency assays that better link potency and safety attributes of the product, in order to increase relevance while simplifying the testing
- Develop assay platforms allowing for rapid characterisation in different manufacturing systems
- Develop robust assays for in-process control for both up-stream and down-stream processing
- Improve manufacturing operations and identify new purification techniques to achieve better resolution between impurities and product, e.g. through improved chromatographic techniques adapted to adenoviruses or particle-based vaccines, since current techniques remain limiting being primarily based on mono-clonal antibodies.

Innovative processes for vaccine manufacturing and quality control

GAPS & CHALLENGES	Recommendations
Achieving better global vaccine supply	**Translate innovative research into applied production innovation:** + Promote closer collaboration among scientists, engineers and regulators + Offer continuity of funding beyond concept demonstration (especially in the context of emergencies) + Set up a task force of regulators and policy-makers to support plans based on scenario planning
Increasing production capacity and improving timelines especially in epidemic or pandemic settings	**Develop flexible manufacturing systems** + Investigate how to decentralise manufacturing capacity through a more localised supply base to avoid supply interruption in case of issues and shorten transport as well as delivery timelines + Support the adoption of single use systems and technologies to minimise variations between sites
Improving affordability and reducing development risks, by assessing early enough vaccines candidates in terms manufacturing efficiency potential at commercial scale with large tithers in a cost-effective way	**Bridge technology and science: collaboration between engineers and biologists** + Investing in thermostability enabling technologies + Test alternative delivery devices: increasing vaccine stability and new fill-in to reduce volume loss + Investment in formulation expertise in the research process + Develop and validate improved potency assays to increase relevance while simplifying testing + Develop assay platforms allowing for rapid characterisation for different manufacturing systems + Develop robust assays for in-process control for both up-stream and down-stream processing **Improve of manufacturing operations and identification of new purification techniques** + Improved chromatographic techniques adapted to adenoviruses or particle-based vaccines