Facilities for Personalised Medicine in the Most Personal Form – Today and Tomorrow

When redoing the batch is not an option

There is a paradigm shift underway in which big pharma mass production of products for specific diseases is deviating towards the 'batch of one.' These autologous therapies are patient-specific and there may only be one chance to harvest the patient's cells and return the personalised drug to the same patient, making the process exceptionally personal. Consequently, the overall perspective pivots from process and manufacturing reliability to product and patient safety – and redoing the batch is not an option.

Until now, the research and development as well as the first commercial manufacturing of these types of therapies has been based on a traditional platform with manual handling in facilities with stringent good manufacturing practice (GMP) classifications. As the number of open clinical trials in late clinical stages increases rapidly, so does the need for efficient and reliable commercial manufacturing capacity. As a result, these new and targeted therapies pose new manufacturing challenges, which require flexible and more robust solutions.

Thus, the question is: are we moving away from a traditional cleanroom approach to more flexible Advanced Therapy Medicinal Product (ATMP) facilities in the future? Manufacturers of targeted therapies must consider different production concepts and technologies, automated solutions, innovation and other enablers that are likely to drive the concepts for future stem cell facilities and other types ATMP facilities. With this reality, we are faced with another question: what is the ultimate vision for the ATMP manufacturing facilities of the future?

Henriette Schubert
Global Technology Partner
NNE A/S

Henriette Schubert is Global Technology Partner at NNE A/S. As an expert with 20 years of experience within consultancy within the biotech, life science, pharmaceutical and biopharmaceutical industry, Henriette focuses on consulting assignments related to front end studies and facility design.

At NNE, Henriette is heading Laboratory and Biocontainment Engineering standards, Development, and sets direction in projects globally.

Qualified as an Architect (Cand. Arch/Architect MAA) in 1992 with a master degree from the Royal Danish Academy of Fine Arts in Copenhagen, Henriette has spent most of her professional career within Pharmaceutical, Biopharmaceutical and Biocontainment consulting. The main consultancy types for this experience is GMP manufacturing facilities, Vaccine Facilities, laboratories, and animal research facilities. Henriette his in addition working within ATMP facilities for tailored therapies, including the synergies and conflicts between GMP and biocontainment.

Member of EBSA, ABSA, Nordic Biosafety Group and the IVBWG (International Veterinary Work Group).

Henriette is a regular Speaker at conferences and symposiums at ISPE, PDA, EBSA and ABSA.

The long tail of future treatments

The new pharma marketplace can be compared to the long tail[1] concept. Until recently, the pharma industry has focused primarily on drugs for common diseases with larger patient groups. Now, the tailored and orphan drugs[2] for the treatment of rare diseases, very small patient populations and even single patients are triggering an industry paradigm shift towards a broader focus involving both commercial manufacturing of tailored therapies, personal drugs as well as new drugs for the more common diseases and larger patient groups.

Today, the number of FDA-approved open clinical trials in cell therapies is three times higher[3] than open trials for antibodies. So far, only 13 cell therapies are approved but the number of open trials combined with a favourable regulatory climate[4] indicates an increased and rapid need for commercial manufacturing capacity. Now, the task is to determine which type of platform the tailored therapies should be based on to satisfy capacity, patient safety, product robustness and compliance.

The past: traditional concept based on the 'manual way'

Until now, the traditional way of development and clinical material for tailored autologous therapies has been based on high GMP classified cleanrooms at GMP Grade B as the surrounding room environment for open product manipulation in Grade A laminar air flow (LAF) cabinets. This is a proven concept but also includes well-known challenges and constraints such as:

- Need for dedicated cleanroom suites for specific patient material (one patient, one batch)
- High cost for facility construction
- High operational cost
- Deriving high cost per therapy (per patient)
- cGMP compliance at high GMP classifications (high workload, training etc.)
- High GMP classifications and work environment constraints
- Manual product and process operations and handling (product risk)

The case for 24/7 operations

As an example of this concept, the cell and gene therapy facility at Oslo University Hospital in Norway was established in 2009 for the Department of Cellular Therapy[5] working within leukaemia and solid tumours. The facility is based on a traditional lab scale cleanroom concept of a number of dedicated GMP grade B suites with Grade A LAF and Biosafety Cabinets for open handling of a dedicated patient product. The facility concept and operations are driven by a high focus on product segregation, product traceability throughout the process steps and an overall focus on product and patient safety. Lastly, the driver from the department management of a creating a great workplace in the complex and challenging framework of a high classified GMP environment has been a high priority. Since the most important factor of manufacturing reliability is the ability to provide consistent, high quality cell therapies whenever patients need them, the facility concept and design includes features to minimise operational shutdown time for maintenance to offer 24/7 operations support (e.g. a robust HVAC concept, high quality cleanroom wall/ceiling system with low level of maintenance, etc.). The design drivers are summarised in figure 1.

One of the project-specific constraints included a limited facility footprint and deriving challenges of fitting the programmed functionalities into a layout that must be cGMP compliant in following the game rules of cleanroom classifications ('Chinese box concept'). In order to fulfil functional adjacency requirement, it was concluded to have a pass box principle between GMP grade B and D classified areas as shown in figure 2. This is in principle not GMP compliant but was solved with a double chamber pass box, which was validated and approved by the medicine and health authorities.

Another challenge was the nature of the starting material (stem cells) as a human deriving material. By regulation it is required that handling and manipulation of the cell material must be done under BioSafety Level 2 (BSL2) conditions. It turned out that most of the BSL2 conditions were already fulfilled via GMP requirements and only the type of cabinet for open handling of cell material needed to change from a LAF cabinet to a BSC (BioSafety Cabinet). The remaining part could be handled via standard operating procedures (SOPs).

The example case based on a traditional GMP concept at laboratory scale is similar to those used by a number of global pharma manufacturing companies who have cell therapy candidates for commercial manufacturing in their pipeline. Using this concept involves the aforementioned constraints and challenges, thus the use of this concept does not seem to be a sustainable, robust concept for tailored therapy manufacturing going forward. What seemed to be an obvious concept to use only 10 years ago now indicates a need to move away from a traditional cleanroom concept into more flexible and agile concepts.

Furthermore, the reality is that pharmaceutical

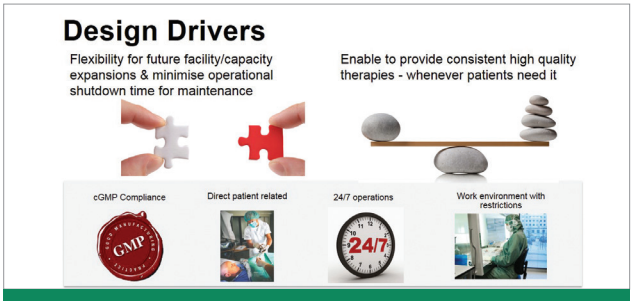

Figure 1

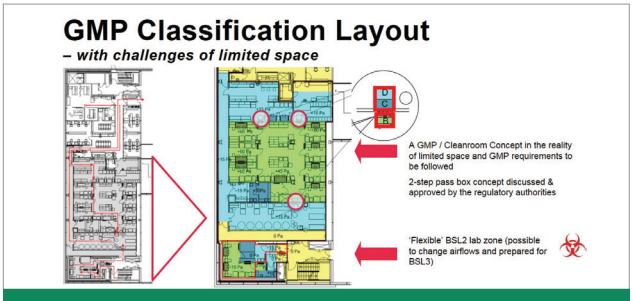

Figure 2

cleanrooms for aseptic areas practically seem to have reached their limit of evolvement. When this limit has been reached there is only two other factors left:

Operators (including gowning and behaviour) and Equipment (including operations). Gowning is also seen to have reached it's limit of development so what is left is really the equipment technology and the processes.

Disruptive innovation and the pharma industry

Looking into other industries' disruption and innovation and further into the pharma horizon, we foresee a changed paradigm filled with smarter solutions. Struggling to think of an example of disruptive innovation? Consider the music industry. Who would have thought the standard of music distribution would evolve from the LP, over the CD to MP3s and later to streaming on an iPhone in less than 20 years?

As shown in figure 3, disruptive innovation within pharma in the latest 20 years of history in pharmaceutical product technology has shifted our focus on small molecules (before 2010), over Biopharm (2010-20) and the relevant question is personalised drugs including tailored therapies will be dominant after 2020? First, it is clear that the efficacy of therapies continue to rise and personalisation of medicine accelerates this trend. Secondly, efficacy will drive demand for personalised therapies and drugs as manufacturing technologies will be developed further. Will traditional pharma as we know it today, be fully replaced by personalised drugs and therapies?

The trends within big pharma involves a number of technology enablers that will impact and benefit areas of operations, GMP classifications, efficacy and product risk as shown in figure 4.

The present and near future concept – 'the missing link'

The evolution of technology for example with robotics is seen as a technology enabler for innovation and disruption in pharmaceutical manufacturing. Technology development within robotics specifically developed for aseptic environments like filling equipment systems, enables the automation of difficult and complex procedures and can dramatically improve product safety and manufacturing reliability. Another example of how fast technology evolves is the microchip. In 2005, the microchip had a 128 Megabyte capacity, whereas the same microchip had a 128 Gigabyte capacity of data storage in a smaller physical size less than a decade later.

Further development is expected to take place within the tailored therapies and personalised drug segment as well. One example is the vision of 'off-the-shelf' therapies using cells from one patient donor to treat multiple patients, where the perspective is getting a little less personal with the possibility to treat more than one patient in a 'batch.'

Few examples exist with process equipment in a small scale, using a closed system and a semi-automated concept with immediate labour savings and decreased product risk. Since current manufacturing is based primarily on a traditional concept of manual handling in high GMP classified cleanrooms and LAF cabinets, development in equipment and processing is necessary – urgently.

Development of 'off-the-shelf' equipment for tailored therapies is key to allow a move away from the manual handling and towards a concept of fully closed and fully automated process, using isolator technologies for continuous processing. Currently, the available process equipment systems still include manual transfers with automated processing steps ('semi-automated' handling).

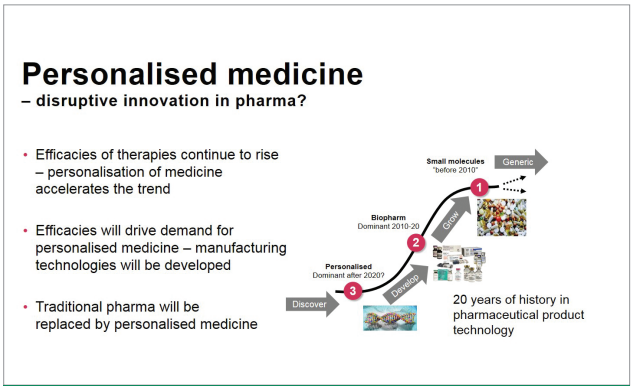

Figure 3

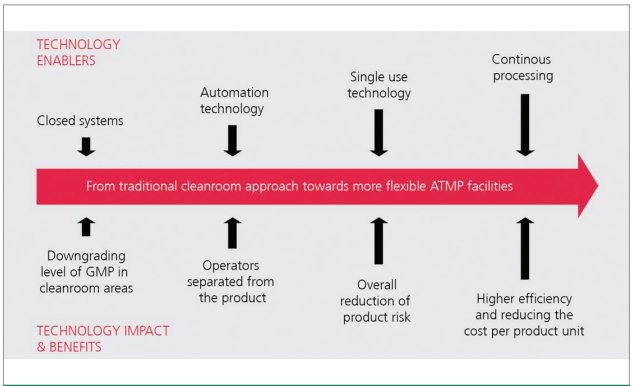

Figure 4

A future concept based on closed and automated processing is expected to more or less replace operators for the majority of personalised medicine manufacturing where it is also expected that very few tailored therapies will stay with the traditional GMP cleanroom concept and manual handing in LAF cabinets.

To take it to the next level, there are a couple of missing links in the development towards a more sustainable concept:

- The main challenge is really how to design the process to enable commercialisation of tailored therapies when neither the processes nor the equipment is fully developed
- There is the lack of cooperation between pharma/biotech companies and equipment suppliers

The vision for future ATMP facilities

The outlook for a more sustainable concept for ATMP facilities includes the vision of a commercialised process based on automated processing in a fully closed and integrated system. The equipment would be a line of linked isolators with integrated robotics, all equipment placed in a controlled, not classified GMP environment with only few operators to control and follow a few process parameters from a remote control room and with only sporadic work activities related to the process itself. This concept would be a tremendous improvement for product and patient safety as well as improving operator work environment and the overall facility construction and operational cost. In the end, this would be a more robust and sustainable concept for commercialised personal drugs.

In many ways, this vision is linked closely to the big pharma trends in aseptic processing where the current and coming GMP regulations focuses on keeping the operators away from the product to increase product and patient safety. The coming EU GMP, Annex 1 is expected to include exactly this focus as well, as there are regulator expectations to the use of fully closed barrier systems. The US FDA[6] goes a step further in their guidance for aseptic cGMP processing, stating specifically: 'Automation of other process steps including the use of technologies such as robotics can further reduce risk to the product.' Therefore, it is fair to say that the big pharma trends can be expected to trigger personalised drugs and ATMP facilities for the future.

Disruption of pharmaceutical cleanrooms

The development of cleanroom technology and pharma facility design is directly linked to the current trends in big pharma including closed processing and barrier systems in lower GMP classified room surroundings with the overall purpose of reducing product risk and increase patient safety.

Looking back at the last 60 years of pharmaceutical cleanroom technology for aseptic manufacturing (as shown in figure 5), it more or less started with a now outdated concept of open handling in a type of 'controlled' area. And a covered process in a semi-open process filling line where operators were only partially covered and even allowed to have bare legs. The evolution of cGMP and an increased focus on product and patient safety took the concept to the present, which is based on open handling in a closed primary barrier system within a monitored cleanroom environment of positive pressure regimes, filtered air and a high level of air changes. The present cleanroom concept still involves manual manipulation via a glovebox technology and product risk and potential impact is reduced but not eliminated even though the cleanroom gowning principles have improved significantly.

Considering the newest and most innovative aseptic filling isolator systems, the principle involves integrated robotics and fully automated processes in a truly full closed barrier system. Thus, the future pharmaceutical cleanroom concept is expected to be much simpler, running at very low GMP room classifications (controlled but may not even be a classified environment), with only few operators who will conduct checks on data screens and look through a sealed window to the automated filling process sporadically and with no glovebox functions needed or integrated in the filling isolator. This may be the state-of-the-art reality in big pharma as well as for tailored therapies in the not too distant future.

But not all big pharma trends can be directly transferred to the tailored therapies segment since a number of specific challenges and constraints exist in this segment that calls for focus and innovation.

The supply chain of tailored therapies

The supply chain for tailored therapies includes a number of extra 'process' steps compared to manufacturing

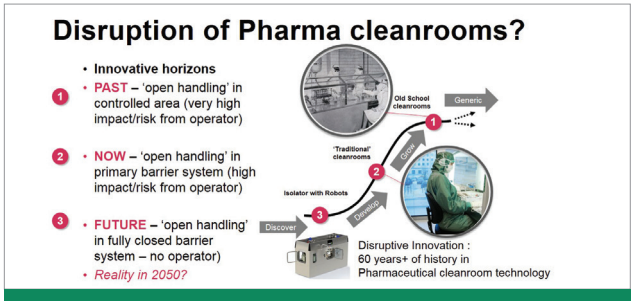

Figure 5

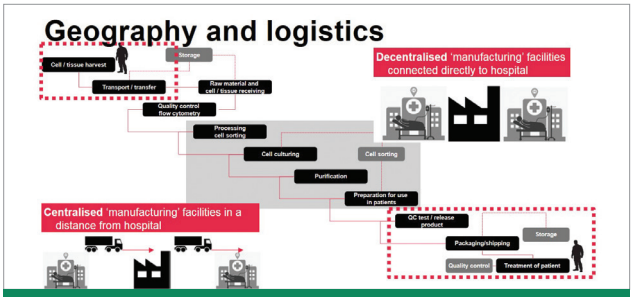

Figure 6

a traditional pharmaceutical product. The extra steps illustrated in figure 6, includes the cell harvest, which is typically within scope for the tailored therapy manufacturer since it is directly related to the patient. In addition, the first steps involve quality control of the starting material, transport and storage of the cells and by nature, and these steps are very critical due to vulnerability and short shelf life of the cells. The other extra step is post processing, which typically involves a hand-over of the tailored therapy ('drug') from a manufacturer to a hospital or clinic where the patient will receive his manipulated cells back. This step includes transport, quality control and potentially storage before the transfusion is conducted. Again, considering the product vulnerability and the 'redoing the batch is not an option' reality, these are very critical steps.

Determining which is the most sustainable concept is in terms of centralised or decentralised ATMP manufacturing facilities and hospitals/clinics is an ongoing discussion. By definition, the therapy manufacturers are the experts within cGMP compliant pharmaceutical manufacturing including whereas the hospitals and clinics are the experts in the direct patient-related processes. The interface between these two areas links directly to the success of a tailored therapy and must be seamless to ensure product and patient safety.

Logistics is one aspect, quality control and segregation strategy is another interface of key importance. Product (cell) vulnerability and short shelf life is driving the concept of keeping the shortest possible distance between the location of cell harvest and cell preparation and the tailored therapy manufacturing processes. This calls for local clusters of tailored therapy units. One example of development in tailored therapies that can change this philosophy is the usage of additives that can prolong the cell and therapy shelf life and can de-risk and allow longer transportation time. This enables another principle of local and decentralised hospital and clinics for the direct patient related processes and decentralised tailored therapy manufacturers that could even be located in another country.

Taking this philosophy further, the fact that cancer and other diseases do not limit themselves geographically indicates it may not be feasible to have a high number of local, decentralised facilities. A one-global centre of manufacturing principle would have a number of benefits but would also include some challenges and prerequisites:

- Combining all competences in one place ensure a better general quality of therapies
- This principle requires stable products and removal of the product vulnerability is a prerequisite
- Requires that multiple doses can be manufactured at the same time

In the end, it will take a number of development steps to really make this concept work efficiently and seamlessly. It is likely that several stakeholders must make an effort to realise a local/global concept to benefit both patients and to constitute a realistic manufacturing supply chain.

Tailored therapies and GMP's

Compliance with GMP is essential to ensure the quality of any medicinal product. The intrinsic characteristics of personalised medicine products e.g. ATMP's such as variability of the starting materials, small batch sizes, short shelf-life, etc. pose specific challenges for the manufacturing process. Additionally, early phases of the process that may take place in a hospital setting operating under a quality system different from the quality system typical of the pharmaceutical sector (as given in the ICH Q10). One challenge here is e.g. the lack of adequate systems in place for evaluation the quality of starting and raw materials. In this way personalised medicine is a game changer in the healthcare industry - not only in the way many severe diseases are treated, but also in the way medicine is developed, approved, produced and marketed.

GMP for e.g. ATMP's has therefore been a huge focus and challenge point for as long as ATPMs have existed, both within research, as well as within development and manufacturing. The topic has had a lot of attention during the last couple of years. However focus has changed during the last couple of years - where the main focus in 2015 was GMP regulatory and compliance, the main

Figure 7

focus in 2016 was primary Manufacturing of ATMPs and secondly GMP regulatory topics, although GMP challenges was still hot. And here in 2017 the key focus and trends are expected to be more on manufacturing, new concepts and technologies than focus solely on GMP.

Getting ready for commercial manufacturing – a joint effort

Some of the enablers for the future vision of a sustainable concept for tailored therapies include regulators and a continued favourable regulatory climate. But this alone will not do it. Moving from development and clinical phases towards commercial manufacturing is a huge step, considering the described challenges in process and process equipment development.

For developers and manufacturers, the step toward commercial manufacturing is costly and for some manufacturers, the better solution might be to have a CMO as the enabler to take an approved clinical trial therapy to commercial manufacturing. This would then require a number of ready CMO companies and process equipment suitable for the specific process – ideally with ready off-the-shelf equipment.

The benefits of CMOs is that they can specialise within tailored therapies and can use money and skills efficiently in manufacturing. Still, manufacturing of the tailored therapies is not simple. To take the manufacturing of the tailored therapies to the next level of commercial production with the vision of future-proof ATMP facilities is a unique challenge, which calls for unique partnerships.

Enablers as illustrated in figure 7 that should take part in and contribute to process and process equipment development include:

- pharmaceutical manufacturers
- hospitals and academia
- process equipment vendors
- equipment developers
- regulators
- pharma engineering consultants
- CMOs

Already these types of partnerships involve some of the mentioned enablers and this is where evolvement and innovation is seen to move faster in the direction of the future vision of efficient and safe manufacturing of tailored therapies.

Conclusion

As commercialisation of tailored therapies is expected to be increasing fast, manufacturing capacity, reliability and efficiency is needed soon. To facilitate these drives, ATMP facilities are foreseen to move away from the traditional approach with the previous pharmaceutical cleanroom 'gold standard' (manual handling, operators handling the products in GMP grade A benches with grade B background). A movement towards a more seamless process and automated manufacturing is developing.

Trends from the general pharma industry will likely trickle down to the ATMP segment and regulator expectations of fully closed barrier systems and use of new automated technology (like robotics) are expected eventually in order to streamline the ATMP segment too. The overall safety for the patient focus is driving this concept.

Moving from the current situation to the future vision for ATMP facilities will take an effort that no single entity can do on their own. The unique challenge of concept development for tailored therapy manufacturing can be enabled and boosted via a joint and coordinated cooperation between A&E consultants, university hospital/academia, equipment developers and pharma manufacturers/CMOs and regulatory bodies.

Considering the previous concept of research and development of tailored therapies – what seemed unrealistic only 10 years ago now seems to be a realistic concept in the foreseeable future. Though the market uptake may delay the big break through, the future vision of ATMP facilities is within sight.

References

1. *Chris Anderson, Wired Magazine 2006 (www.longtail.com)*
2. *Orphan Drugs Catch Fire in Big Pharma, PM360 July 2015*
3. *OutSourced Pharma, Guest Column February 2017*
4. *FDA regenerative development review of cell therapies for life threatening diseases (https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf*
5. *Angle Magazine, NNE, April 2014, http://www.nne.com/Global/Angle/PDF/Angle-2014-04-Personalised-Medicine.pdf (Page 18)*
6. *US FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice, September 2004 https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf*

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