NorthX Biologics

QC IN ATMP PRODUCTION: SAILING A STORMY SEA, WHAT'S THE KEY?

Getting aboard

Medicines based on genes, cells, or tissue engineering i.e. Advanced Therapy Medicinal Products (ATMPs) are a rising star shining brighter and brighter in the horizon for any CDMO operating in life-science. It is natural that many reconsider strategies and set a new course toward this brand-new reality. However, it is neither an easy destination to get to, nor is the route smooth sailing.

Rough seas are expected as each manufacturer bear the responsibility to put in place appropriate measures ensuring the quality of these unique products is maintained and simultaneously comply with the GMP prerequisites, and all under extremely strict timelines.

So how to keep sailing under the one universal flag: "patient safety above all" and keep the quality guidelines? How do we assure proper Quality Control (QC) in the production of ATMPs given the requirements above?

Here is a reflection upon what are the lessons learned from the first steps NorthX took on the QC-journey in becoming a full-fledged ATMP producing facility.

Setting sail

As defined by the Oxford languages dictionary, QC is "a system of maintaining standards in manufactured products by testing a sample of the output against the specification". Hence being an essential aspect of the development and manufacturing to all biopharmaceuticals in general, and to this emerging new class of therapeutics: ATMPs.

Breaking down QC into its main constituents, it relies on five core aspects:

1. **Raw and start materials testing & characterization**
2. **In-Process controls**
3. **Product testing**
4. **Quality management system**
5. **Compliance with regulatory guidelines**

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The five core aspects

1. **Raw and start materials testing and characterization:** All materials used in production need to be qualified meaning that the purity and identity of each material employed must be confirmed whether they are cells, vectors, or reagents.

2. **In-Process controls:** This critical step consists of supervising and controlling the various steps of the manufacturing process which could include cell culture, vector production, and/or product formulation.

3. **Product testing:** Aiming to test the final product for safety, potency, and consistency, this stage includes testing for the presence of contaminants, determining the activity of the product, and certifying that the product meets the required specifications.

4. **Quality management system:** Crucial to maintain the consistency and quality of the ATMPs is to establish a well-rounded and robust quality management system (QMS) and to have strict and phase appropriate GMP. It is imperative that it i.a. contains and employs standard operating procedures (SOPs), training of personnel, and maintains current and actual data on all actions associated to the production steps.

5. **Compliance with regulatory guidelines:** Of paramount importance for manufacturers is to comply with recognized regulatory guidelines and standards for the quality control of ATMPs which in the European Union are published in the EudraLex (Volume 4 part IV).

Weigh anchor

The statements listed above about QC-processes are easier said than done. Time is critical in the production of ATMPs and the demands for rapid turnaround times for QC activities is often incredibly high due to comparatively short shelf lives of the products and the intended use is often for patients with serious and/or life-threatening conditions.

Also note that ATMP is a designation for a broad, complex, and diverse group of therapeutics which means that the inherent production risks, manufacturing processes and correspondent quality requirements is just as complex. In fact, the phrase "the Product is the Process" used by industry insiders is quite descriptive of the relationship concerning the manufacturing process and the characteristics of the resulting product. This tangled bond between process and product is represented in the fact that even minor changes in the production process could have unpredictable and possibly profound effects on the final product. Furthermore, the inherent intricacy of an ATMP makes the complete characterization very tenuous. Therefore, the best option to safeguard that "batch-to-batch" consistency is attained is often to perform a complete characterization of the production process and then rigorously repeat all production stages without discrepancies. Based on these facts, the conceptual idea that the process of producing an ATMP is such a genuine part of the product itself, leads to that the production process often is as patented and protected as the product itself.

Making waves

Being an innovation hub and a CDMO that specializes in the manufacturing of biopharmaceuticals, we understand that this production processes often make use of non-traditional types and sources of materials, require cutting-edge technologies and often calls for the identification of new control parameters to test - all of which bring challenges for the developers, staff, authorities and other regulatory instances. We are also very conscious about the fact that added to Quality, each ATMP needs to be coined with the two most critical requisites associated with all therapeutics: Safety and efficiency.

Pondering on the scenario described above and being mindful about our own path in the dawning of this business, we decided to contemplate the road QC has taken so far and reflect upon the main challenges faced: What were our own strengths when hurdles were found? What lessons have we learned?

We started by doing our homework: further preparing and optimizing our already established QC processes prior to production:

1. Existing guidelines specifically relevant to the QC of ATMPs were meticulously discussed among our SMEs and when need be, with customers and regulatory authorities.
2. Eventual new analysis methods were taken in by our Analytical Development (AD) Unit and introduced in our own QMS by the QC-department.
3. We identified the most critical steps of the specific manufacturing processes and quality control testing and gave them priority.
4. Training of concerned personnel handling critical steps was undertaken and/or updated accordantly.
5. New starting materials were qualified prior to production.
6. All needed documentation framing our QMS was reviewed and prepared in advanced according to identified new needs.
7. When shipping was necessary, all processes handling sample transportation were re-assessed with focus on suitability and speed.

In a sense, what we did was taking a practical risk-based approach to the complete QC processes involving identifying, assessing, and prioritizing potential risks to the quality of the product being manufactured. Adequate controls and monitoring procedures were implemented to mitigate those risks. This approach allowed us to do a tailored risk management plan focusing on the areas of highest risk to guarantee that the appropriate level of quality control was applied to the manufacturing process, and that suitable actions could be taken if deviations occurred. These actions also helped to ensure that, when need be, resources were allocated effectively and that the overall quality of the product was maintained.

Sea of contemplation

Looking back to the very beginning of this voyage, we realized that we have learned several key lessons from back in the day when we started the QC journey in the production of ATMPs:

First and foremost, this is an enterprise that will stress and put your system through a thorough challenge. A good system in place will make you able to deal with this and having knowledge, skills and experience in your team will not only give you a good head start but also prepare you for eventual pitfalls and deviations that will inevitably occur.

Another important lesson was that communication and collaboration were vital to the flow of the process. Direct communication with the customer and close collaboration with other teams and departments, such as AD, Production and QA, helped to ensure that all activities were well coordinated and completed in a timely manner.

A third lesson was that, when needed, using outside help, and therefore outsourcing some of the analysis to well-known and reliable partners can be a way to efficiently perform specific analyses.

A fourth lesson is that the QC process should be flexible. It needs to be adaptable to changes in the production process or the product itself. This includes being able to respond quickly and efficiently to changes in the product or the manufacturing process and making the necessary adjustments.

Finally, it is important to have a very strong quality culture within the organization. Being a CDMO with over 30 years performance history in biological GMP manufacturing has given us an edge on designing and keeping a solid streamlined QMS in place. We have always seen Quality as a top priority and have it integrated into all aspects of our production processes. A reality that gave us a considerable advantage in those early days.

Seeing the port in plain sight

We learned that ATMPs are quite challenging to produce, requiring a deep knowledge of all aspects of the starting materials, production processes and product to achieve strict and proper QC with a well-designed and validated QC process, but at the same time allowing close monitoring and review of the manufacturing process and adaptability to eventual changes.

The cornerstone of QC is to have a well-oiled QMS in place managed by multidisciplinary team with a wide range of expertise. Although compliance with existing regulatory requirements is of utmost importance, they are not intended to place any restrain on the development of new concepts and approaches to QC systems - if the capability to ensure the quality, safety and efficacy of the ATMP is assured.

Along with our own experience of being a CDMO within advanced biologicals, the vertical and horizontal communication flow turned out to be the golden key to the success of applying QC to these processes. All parts involved must be on the same page and understanding all targets of each step of the production process to be able to achieve established goals by working effectively as one.

What are your thoughts/opinions on the QC process applied to ATMP production?
Do you agree with us? We would love to hear from you. Feel free to email us at: *contact@nxbio.com* so we can start a conversation!

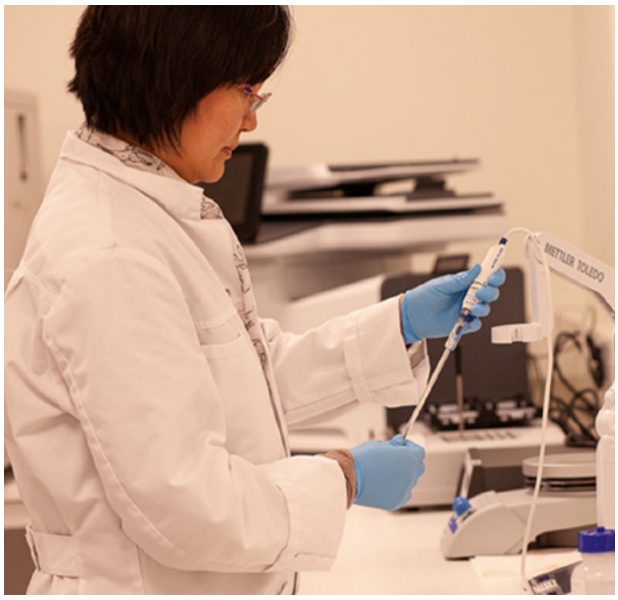
Footnote

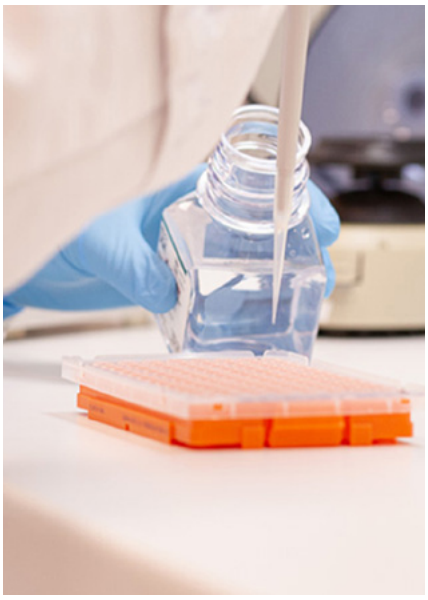
If re-visiting our initial analogy of comparing the QC in ATMP production to sailing a stormy sea, what have we learned?

Well... the journey may indeed be quite tough, and even made harder by the fact that each product is so unique that you will need a brand new map for each destination (production).

To have 1) a sturdy and solid ship tested in all waters, along with 2) the knowledge on the anchor's location and where the compass and guardrails in the system are and 3) having a well-seasoned experienced crew will help you all the way through.

We realize that we can navigate with (and because we have) stars in our company. We certainly welcome the winds of change in the Life-science business.





Abbreviations

QC: Quality control

ATMP: Advanced therapeutical medicinal products

CDMO: Contract Development and Manufacturing Organization

GMP: Good Manufacturing Practice

QMS: Quality Management System

SME: Subject Matter Experts

AD: Analytical Development

QA: Quality Assurance

NorthXBiologics

A leader in new technologies

NorthX Biologics provides process development and manufacturing services with expertise in plasmids, proteins and other advanced biologics. We sit in the heart of Sweden, and our team has been manufacturing biologics to GMP since 1992. In 2021 we were recognized as a national innovation hub for advanced therapeutics and vaccines.

We take pride in adapting new technologies and different innovative platforms to our GMP processes. This enables development, upscaling and finally GMP manufacturing of innovative clinical material and supports our collaboration partners to help patients. We work closely with our staff and clients to provide solutions for biologics and ATMP's.

Learn more at nxbio.com

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