REVIEW OF EU ATMP GMP GUIDANCE

by Robert Smith

On November 22, 2017, the EU Commission adopted the Guidelines on Good Manufacturing Practice specific to advanced therapy medicinal products (ATMPs), as Part IV of EudraLex Volume 4. These guidelines come into force on May 22, 2018. When these GMP guidelines for ATMPs were first drafted, most of the manufacturers of ATMPs were critical of the guidelines being a separate guidance document rather than being an annex to the existing guidelines in EudraLex Volume 4. There were also criticisms from smaller academic and hospital units that the new guidelines place too much burden on these units in their rigid application of industrial type GMPs, which they argued was not practicable to these highly innovative products. Concern was also expressed that as the initial draft stood, the innovative research that was going on with ATMPs would be hindered in the EU.

Now that we have the final guidance document, it is interesting to see how these various concerns have been reconciled by the EU Commission.

The new guidance is 90 pages long and consists of 17 sections plus a glossary of terms. There are several sections in the guide that will be familiar to anyone working in the pharmaceutical industry.

It is clear that in these sections, the authors have taken concepts that already exist in many of the chapters and current annexes and tweaked them for ATMP use. Therefore, one can argue that the authors could have pointed the readers to the existing GMP. However, these sections contain some very specific advice that is pertinent to the manufacture of ATMPs.

In the section Pharmaceutical Quality System, the guidance gives much more emphasis on using a risk-based approach, which is understandable given the nature of ATMPs which have highly variable starting materials and can be complex to manufacture. There is also a recognition that the manufacturing technologies are rapidly advancing, which means flexibility is required. The guidance does make it clear that patient safety must be the goal, even though a risk-based approach is being used.

Another major element of this section is the guidance given for investigational ATMPs. Key areas the guide concentrates on are patient safety and product quality and the need for data from early phase clinical trials to be used in later clinical trials. As with non-ATMP investigational product, the guide does accept that the

These sections include:

- Pharmaceutical Quality System
- Personnel
- Premises
- Equipment
- Documentation
- Production
- Qualification and Validation
- Qualified Person and Batch Release
- Quality Control
- Outsourced Activities
- Quality Defects and Product Recalls

levels of GMP will increase as the knowledge of the ATMP increases.

In the section Personnel, the guidance does state that a QP can be responsible for quality control (QC) or production, but not both. The guidance allows individuals in small organizations to perform both the production and QC role, though individuals are not allowed to QC test batches that they have manufactured. This is a clear divergence from the norms that we see in EudraLex Volume 4, Part I, Chapter 2.

The section on documentation places a lot more emphasis on the bidirectional tracking of cells and tissues from the point of donation, through manufacturing, to the delivery of the finished product to the recipient, as well as the requirements to keep data for 30 years.

The Production section of the guide concentrates heavily on the aseptic processing requirements for ATMPs, as this is seen to be a key requirement to patient safety. There is an acknowledgement of the fact that these products may have a very short shelf life. For example, manufacturing an ATMP can take place in an operating theatre where the time between donation and administration is very short.

The section on qualification and validation is another area of divergence from established GMP practice. The guide recognizes that there may be a shortage of starting material so when validating processes, there is an allowance to use surrogate materials and concurrent validation can be performed, provided this can be justified.

Another area of divergence from the current GMP guidance is around the QP and batch release. Section 11.10 states that there is no exclusion for the same QP to work for two or more sites, provided the QPs can provide their services to each site in a continuous fashion. There is a waiver for marketed ATMPs that are imported into the EU to forgo the testing on import, if there is limited ATMP or the ATMP has a short shelf life. Another area of divergence is the allowance for decentralized manufacturing, where

"fresh cells" means that part of the manufacturing process needs to take place close to the patient. Under such circumstances, there is a requirement to have a central site in the EU that has oversight of the decentralized sites.

The ATMP document also provides some specific guidance for ATMPs that is not found in other EU GMP guidance. One such area is starting and raw materials. There is a requirement that if antibiotics are used, they must not be in the final product. Guidance is also given on using cells that come from outside of the EU, as well as the use of xenogeneic cells and tissues which could transmit pathogens to humans. There is also guidance on the processing of starting materials and it's clear that the guide sees that final product quality is closely linked to the quality of the starting materials.

The guidance documents also provide specific information on seed lots and cell banks. These must comply with GMP and be established under appropriate conditions. There is a need for appropriate documentation to ensure traceability. Seed lots and cell banks must undergo safety testing to ensure they are free from adventitious agents. The guide also provides information on how seed lots and cell banks must be stored, which includes continual monitoring and alarm systems. The guide also states that is it desirable to split cell stocks and store them in different locations.

Reconstitution of product after batch release is also covered. The guide defines reconstitution activities and clearly states that they do not need to take place in a GMP environment. The guide also requires reconstitution activities to be justified and specifies that they can only take place at the administration site. The guide also requires the reconstitution process to be fully described with solvents and other materials being provided if they are required.

Another important section of this guide covers environmental control measures for genetically modified organisms that are ATMPs. In keeping with other aspects of the guide, the use of risk management is a key part of the strategy for ensuring these ATMPs are appropriately controlled and not released into the environment. There is an expectation that emergency plans are in place to deal with any accidental release.

The final section of the guide covers the automated production of ATMPs, which is becoming a common way of manufacturing ATMPs. There are clear requirements for equipment to be qualified and for there to be suitable operating instructions, regular calibration and maintenance of equipment and appropriate training of personnel. The guide also expects these automated processes to have a defined start and end and an expectation that where possible, critical process parameters should be continually monitored.

This new publication is a very comprehensive guidance document to companies and individuals manufacturing ATMP products. There is heavy reliance on utilizing a risk-based approach to manufacturing, which is not surprising as rapid advances are being made in this area. For example, therapies are now being developed where only parts of a cell are being administered to patients. The guide provides a pragmatic solution for small research institutes where the operational reality is that lines between production and quality control can be blurred, while retaining one of the fundamental principles of EU GMP, the role of the QP in the certification and release process. The guide also provides some pragmatism with respect to the fact that not many QPs are currently working with ATMPs. The one question that remains is how far the ATMP GMP guide will diverge in the future from the other GMP guidance as there is currently a lot of overlap.

Have a question on the article? Contact Robert at **robertsmith@nsf.org**.

ABOUT THE AUTHOR

Robert Smith is a qualified pharmacist, Qualified Person and vice-chair of the Royal Pharmaceutical Society's QP Eligibility Panel of Assessors. During his 25-year career in the pharmaceutical industry, he has worked in both clinical trial supplies and the commercial sector. His current interest is in biological products including vaccines and advanced therapeutic medicinal products.

For more information, contact **pharmamail@nsf.org** or visit **www.nsfpharmabiotech.org**

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NSF INTERNATIONAL | PHARMA BIOTECH

The Georgian House, 22/24 West End, Kirkbymoorside, York, UK YO62 6AF
T +44 (0) 1751 432 999 | **E** pharmamail@nsf.org

2001 Pennsylvania Avenue NW, Suite 950, Washington, DC 20006 USA
T +1 (202) 822 1850 | **E** USpharma@nsf.org

www.nsf.org | **www.nsfpharmabiotech.org**

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