Designing a CMC strategy for advanced therapy medicinal products in the EU

Valerie Pimpaneau and Anne Dupraz Poiseau discuss the latest EU guidelines on ATMPs and explain how to develop a solid chemistry, manufacturing and control strategy for such products.

The field of cell and gene therapy has developed tremendously over the past few years, not only in terms of scientific and technological advancement, but also in shaping a regulatory pathway that provides more clarity and predictability with regard to clinical development and marketing authorisation.

Since the EU regulation governing advanced therapy medicinal products (Regulation (EC) No 1394/2007) was adopted in 2007, the European Medicines Agency has issued multiple technical guidelines to help guide ATMP development and provide a better defined regulatory framework for these products. Several products are now approved in Europe (for example, ChondroCelect from Tigenix and Glybera from AMT) and in the US (for example, Apligraf from Organogenesis, CarticeI and MACI from Genzyme, and Provenge from Dendreon).

The very nature of cell, tissue and gene therapy products imposes major constraints on the chemistry, manufacturing and control (CMC) aspects of their development that deserve attention and anticipation early on. Compared with small molecules or protein-based drug products, ATMPs comprise extremely complex structures and often include living organisms or cells. The finished ATMP is also often based on living starting materials that can differ from batch to batch and its quality may even change between batch release and patient delivery. Quality of ATMPs may therefore evolve over time, resulting in strong variability, complicating the setting of specifications and adding a unique set of CMC challenges.

Current and forthcoming guidelines

In this context, the established quality paradigm that applies to other types of medicinal products may not fully apply to ATMPs, and the development of a defined CMC strategy early on in the programme is strongly recommended. Quality assessment and CMC development of ATMPs are likely to rely heavily on risk assessments, detailed process knowledge and strong qualification of raw materials in addition to specific release criteria.

The implementation of the International Conference of Harmonisation’s new quality paradigm (ICH guidance documents Q8-Q11), which integrates the notion of strong process knowledge, and the preparation of new technical guidelines (existing or forthcoming) suggest that the quality requirements are evolving to adapt to the constraints of ATMPs. The recent revision of Annex 2 of the EU guidelines on good manufacturing practices that captures requirements specific to ATMPs (which will come into effect on 31 January 2013) and the draft EMA guideline describing a risk-based approach for ATMPs provide an opportunity to adapt development plans and integrate the specificity of each product.

There is also ongoing reflection at the agency level focusing on issues such as comparability, as well as on the topic of quality and non-clinical requirements at various stages of clinical development for cell based medicinal products (CBMP). In addition, the European Directorate for the Quality of Medicines & HealthCare recently created the RCG working group to discuss the issue of standardisation for key raw materials utilised in the production of ATMPs and better define expectations in terms of quality for materials such as antibodies, growth factors, cell culture media, serum and cytokines.

All these activities reveal an effort by the regulatory bodies to adapt the quality requirements to the constraints of ATMPs. The possibility of developing a science-based approach driven by risk assessment and quality management would forge the foundation of a strong ATMP development plan. This plan would, in turn, support the rationale and provide a justification for the strategic choices that the sponsor may select along the way and build a strong CMC backbone for all regulatory submissions.

An evolving quality approach

Adapted control strategies

In many aspects, the quality assessment approach considered for ATMPs is very much aligned with some of the concepts of quality by design (QbD) that are defined in ICH Q8 as: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Indeed, as part of the QbD roadmap, the first step is to set development goals, namely the specification or “quality target product profile” (QTPP) that consists of a summary of the characteristics that a given product must have to achieve the desired quality. Then, the critical quality attributes (CQA) of the product should be defined; these include physicochemical, potency and microbiological characteristics. Finally, all the variables (process parameters, raw and starting material characteristics, etc) that may impact quality attributes should be exhaustively listed and a risk analysis carried out. To a certain point, a similar systemic approach can be applied to the development of ATMPs.

The above may appear to be a cumbersome and overwhelming exercise at first, with sponsors fearing that they might generate an endless list of risks that are difficult to rank or integrate into their overall plan. The key to a successful quality risk assessment will be to use a pre-defined methodology that allows a 360° view of all the potential risks, their ranking and their translation into an adapted control strategy. All subject matter experts covering process development, manufacturing, analytical development, quality control, transfer and industrialisation aspects will need to be involved in order to provide a consolidated view of product and process characteristics.

As we described in a road map to QbD, in practice, risk assessments involves first identifying what can happen (risks), followed by an evaluation of the probability of the occurrence of each risk and of the impact on product quality. The evaluation of the risk level is often described qualitatively (low, moderate, high) or numerically. Risk analysis should be undertaken at the beginning of the development and should, in principle, be repeated when more knowledge/understanding of the process and product is gained, as this is an iterative process. The exercise provides an opportunity for all subject matter experts to build a common view and reach the same understanding of the product and process specificities, the risks involved and how to best mitigate them in an agreed upon development plan. In practice for process design, this may consist of identifying the steps most likely to affect the quality of the end products and optimising their development accordingly. This can translate into minimising manipulations during the process; streamlining certain steps or adding in process controls at key steps, for example.

For release testing, in many cases it is impossible to use the traditional approach with ATMPs and, therefore, an alternate control
strategy based on process knowledge and identified risks is necessary. This is particularly true for autologous cell therapy for which sample size for release testing represents a constraint. Indeed, the product’s volume is usually small, limiting test samples availability, and its shelf life is so limited that it often has to be used prior to the availability of all test results. Quality assessment for ATMPs will rely, therefore, on two key aspects: firstly, on the availability of adapted analytical tools capable of measuring quality with limited sample size; and secondly, on detailed process knowledge to strengthen the overall control strategy by integrating starting materials quality assessment and appropriate process controls. This, together with strong validation studies, will help demonstrate process consistency and quality, and build a control strategy that may even allow for a reduction in end product testing.

Comparability
ATMP processes will evolve drastically between the research and industrialisation stages and it is critical to anticipate process changes and scale up needs together with the design of the associated comparability strategies that are to be used throughout development. This highlights the importance of having sensitive analytical tools and an adapted potency assay available early on in development in order to build the foundation of a strong comparability plan.

Side-by-side end product testing may not always be feasible due to sample limitation or product stability. A comparability strategy should be designed specifically for each product and may include different elements such as comparison of key process step capabilities, use of lot history to build statistical comparability acceptance criteria, etc. For autologous cell therapy, there may be additional hurdles relating to such things as different starting materials and the impossibility of performing side-by-side comparability studies for which adapted approaches will have to be designed and adjusted.

Regulatory agencies acknowledge the difficulties of establishing comparability for ATMPs and have identified the need for further guidance on the matter. During clinical development, establishing comparability while process evolves will focus on understanding the links between product after each change and the impact of process change on product quality to ensure patient safety throughout clinical studies. With comparability as the centerpiece for the development of ATMPs, sponsors are strongly recommended to anticipate a comparability strategy and confirm the acceptability of their plan with the authorities prior to its implementation to ensure that it will cover expectations at each stage of clinical development.

Key elements of CMC development
We have identified the following three main building blocks of a CMC strategy for ATMPs based on feedback we have received from the EMA after filing for marketing authorisation or during scientific advice: product definition; product characterisation; and control strategy.

Product definition
The first point to carefully address involves clearly defining the following three elements of the ATMP: the starting material; the drug substance; and the drug product. This is particularly important as in certain cases processes are continuous leaving unclear definitions of each of these three elements, which will be subject to different quality requirements depending on their definition within the process. This first exercise is critical not only for anticipating quality expectations overall, but also for optimising the quality sections of subsequent submissions (ie for clinical trials, marketing authorisation and subsequent lifecycle management). As illustrated in Figure 1, the structure and content of the quality sections will be influenced by the breakdown of each specific product and process. Sections 3.2.S.2.3 of the common technical documents (CTDs) for ATMPs – which deal with “control of materials” – are often extremely lengthy as starting materials can be as complex as living cells and activating or modifying agents (proteins or viral vectors, for example). These complex starting materials will require the submission of detailed information related to their production and specifications.

EMA guidance on human cell-based medicinal products is very helpful in defining these different elements of an ATMP. In particular, it states that:

The active substance of a cell-based medicinal product (CBMP) is composed of the engineered (manipulated) cells and/or tissues. Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin. [Emphasis added]

Therefore, in case of a continuous manufacturing process, the difference between drug substance and drug product will be small, drug substance being the engineered cells and/or tissues and drug product being these cells or tissues in their final packaging.

This exercise is also key to determining how to position a device incorporated in an ATMP, either, as mentioned in the EMA guideline, as a...
starting material if it is combined as an integral part with the manipulated cells (for example, when used to make the cells grow) or as a delivery system only (with no or very limited cell-device interactions). In the latter case, related data can be embedded in the Regional Information Section (R) of the CTD Module 3 of the marketing authorisation application and only a certificate of CE marking (when available for the intended device destination) is required; this very often simplifies life-cycle management in case of device change.

If biomaterials, scaffolds or matrices are used as starting materials in the preparation of the ATMP, they should either be CE-marked devices for the intended use or they should meet the essential requirements laid down in Directive 2007/47/EC (the amending medical device legislation) and Directive 90/385/EEC on active implantable medical devices, respectively, and this information should be provided in the marketing authorisation application.

Product characterisation
Once all the elements of a given product are clearly defined, the next critical step is to characterise the drug substance and the drug product in detail. It is necessary to identify all the components that contribute to the mode of action – as they will represent the foundation on which the potency assay is to be designed. Components that do not contribute to the mode of action will be considered impurities on which specifications are to be set.

The product characterisation step relies on multiple development studies that will help support the developer’s understanding of the product. It will also provide the scientific baseline for the control strategy and help justify the tests selected for release testing of the product.

Control strategy
The control strategy aims to show through the use of appropriate analytical tools the ability to reproducibly manufacture a safe product that is sterile, free of adventitious agents and unwanted contaminants. As mentioned earlier, ATMP products release testing can be challenging due to product sample limitation and limited stability. Specific challenges for tissue-engineered products include the need to maintain the (structural) integrity of the end product but still provide sufficient verification of its quality. To avoid jeopardising the integrity of the drug product, it may be necessary to prepare a tissue sample in parallel during production that will be used solely for quality control testing.

The need to develop and validate new analytical tools also represents a challenge for developers as most assays must be specifically developed and adapted to each product.

It is crucial, therefore, to build a multidimensional control strategy that will rely not only on end product testing but also on control of starting and raw materials, process validation and in-process control.

The characterisation studies described above, together with the risk-based approach, will help confirm and justify the critical quality attributes that should be monitored during the production and release.

Release testing, potency and purity
Parameters evaluated as part of the release of a cell-based therapy product should include identity markers, cell count and viability, potency, product-related impurities (such as undesirable cells, cell debris), process-related impurities (residual process components) and microbiological examination. For a gene therapy product, in addition to general pharmaceutical tests (for example, sterility, endotoxin, appearance), release testing will be influenced by the nature of the product and whether it is a viral vector, a plasmid or a genetically modified cell, for example. Identity testing for both the transgene and the vector or cell is to be performed, along with verification of the integrity and sequence of the transgene, purity (absence of production residues) and potency (including gene expression). For viral vectors, the particle to infectivity ratio is also required. Genetically modified cells will be tested as for a CBMP and they should also undergo tests to gauge the percentage of transduced cells. The vector/plasmid copy number per cell should also be tested on each batch of the final product.

When replication defective integrating vector is used, the absence of a replication competent vector (RCV) should be demonstrated.

The assessment of potency is essential for the development of ATMPs and, ideally, a test should be developed prior to the initiation of the first clinical trial and validated prior to pivotal studies. Process will evolve over time and adapt to the increased needs of clinical development, with process changes, scale up and industrialisation. Potency measurements make it possible to assess the impact of process evolution on one of the most critical quality attributes and will be at the core of any comparability study necessary to evaluate changes implemented throughout development. Hence, it is important to develop potency assays early on.

The demonstration of biological activity should be based on the mode of action and the intended biological effect and should, ideally, be related to the clinical response. Composite assays are often required to evaluate potency including the combination of specific identity markers and measurement of functionality in vitro. Alternatively, when no rapid functional assays can be developed, potency assessment may be based on identity markers only if a strong correlation to in vivo biological activity in animal models or in human is demonstrated. The availability of solid assays at the early stages of development will contribute to building a strong correlation with clinical efficacy that may in turn be used to develop surrogate markers for quality assessment.

A key hurdle to potency assay development is the high variability encountered with bioassays, making specification setting difficult and challenging the accuracy of the dose delivered to each patient. The use of orthogonal approaches is therefore recommended to assess potency overall.

Purity also requires strong development efforts, particularly for products consisting of a mixture of cells. It is necessary to perform characterisation studies that demonstrate that specific cell populations are needed to maintain the desired efficacy and justify their presence. Indeed, any cells not involved in the mode of action may have to be removed unless there is strong evidence that their removal would impact efficacy. Process-related impurities such as reagents (antibiotics, enzymes, growth factors, etc), feeder cells and dimethyl sulfoxide (DMSO) are all considered impurities for which a testing strategy should be defined with, if necessary, specifications at end product testing. The testing strategy and, particularly, as it relates to purity can in fact be highly influenced by process knowledge. Indeed, if specific impurities are removed efficiently by the process and validation confirms consistency of their removal, impurity testing at the end-product stage may not be necessary for routine lot release. This provides an opportunity to reduce depleting the drug product for testing purposes.

Process knowledge and IPC
Process characterisation initiated early on in development can help clearly identify or confirm the role of each step and their functionality. This exercise can integrate elements of QbD, described above, such as a risk assessment to identify the critical steps and help define a validation strategy to build a strong “in process control” approach which together will contribute to the overall product quality assessment.

A well understood and controlled process may also help sponsors develop and justify a reduced testing approach at release and limit sample usage.

Raw material testing
The production of ATMPs involves the use of complex raw materials including media, growth...
factors and cytokines. Quality requirements for raw materials should be in line with the new Annex 2 of the EU GMP guidelines that will come into operation at the end of January 2013. This includes a documented raw material management programme that may start with a risk assessment to identify the appropriate quality requirements of each raw material based on their potential impact on product quality.

Wherever possible, compendial grade and characterised materials should be used. A thorough vendor qualification programme should be established. The programme should include audits that will allow sponsors to track the production and control strategies employed at the supplier site and the implementation of quality agreements. It should ensure the availability of certificates of analysis for each lot and certificates of origin should also be available for animal derived materials. Finally, an in-house quality control system for all raw materials is needed that includes verifying their identity and, in the case of critical reagents, verifying their biological suitability. For some of the materials, monitoring of their stability is also recommended.

Biological reagents should be free of adventitious agents and comply with transmissible spongiform encephalopathy/bovine spongiform encephalopathy risk minimisation requirements. The use of recombinant source material is recommended over animal-derived material and, if blood products such as human plasma-derived materials are used, they should be obtained from an authorised source (i.e. they should be a licensed medicinal product). In situations where no qualified source of material is identified, an extensive quality characterisation and qualification package will be required. This package should include process information, complete testing including biological suitability, viral safety information, etc. This will require the implementation of internal monographs describing the quality requirements and specifications as well as a qualification programme for the introduction of new lots. It is critical for sponsors to ensure long-term supply consistency as they move through the later phases of clinical development.

Regulatory agencies have identified the need for further guidance on the standardisation of raw materials for ATMPs to clarify what suppliers and users should focus on and identify the appropriate characterisation approach. European Pharmacopoeia monographs are already in place for certain compounds such as granulocyte-macrophage colony-stimulating factor, erythropoietin, etc., but describe requirements for substances used as active pharmaceutical ingredients.

Acceptable quality requirements criteria for raw materials may be different from those expected for active ingredients but have yet to be defined. Suppliers are now making an effort to provide GMP grade material, but it is also important to bear in mind that using a GMP grade material does not necessarily address all characterisation requirements. Discussions are currently ongoing at the EDQM’s RCG working group to better define the appropriate raw material characterisation requirements for ATMPs.

Adventitious microbial agent and viral safety
The quality of raw materials will also be important to ensure viral safety, since it is often the case that no terminal sterilisation, viral removal or inactivation steps can be integrated as part of the process. A multifactorial viral safety approach that includes donor testing; risk management to avoid cross contamination; characterisation of cell banks; removal and inactivation studies, when feasible; raw material control; and release testing will all contribute to the assessment of biosafety.

Introducing rapid microbiological methods will allow for the assessment of microbial contamination for products with short shelf life. These rapid methods are recognised by health authorities, with guidelines prepared by agencies, and by chapters of the European Pharmacopoeia and the United States Pharmacopoeia Convention. This again illustrates how ATMPs are creating a need for the development of adapted analytical tools.

Conclusion
The design of a well thought out CMC strategy for an ATMP will provide a solid baseline to support product development throughout. It will motivate forward thinking to anticipate future scale up and process industrialisation needs. It is important to keep industrial adaptation in mind while developing a process, with a scale aligned with the anticipated dose and number of targeted patients, and limited manipulation to minimise the risk of contamination. It is important to aim for a simple process where possible, using raw materials that can be adapted to the constraints of a controlled GMP environment later on. All these aspects will have an important impact on the overall cost of development and on the definition of the regulatory road map and associated quality requirements. They will also put sponsors at an advantage during partnership or licensing deals.

The complex nature of ATMPs requires very specific and adapted assessment of quality using newly developed methods. The regulatory authorities understand the need for technical guidelines to frame product development. The evolving regulatory environment and new quality paradigm all provide an opportunity to design a suitable development pathway for ATMPs to ensure safe and efficient products are available to the patients. Several questions remain, however, such as the ethical issues concerning “out of specifications” results for autologous cell therapy products, for example, and whether there may be opportunity to mitigate risk depending on the nature of the out-of-specification and the assessment of safety.

It would also be interesting to see whether a solid CMC strategy, based on science and risk assessment, together with strong process knowledge and a comparability plan could in the future lead to the use of post-approval change management protocols for ATMPs. This would consist of a step-wise approach for assessing changes, with an early evaluation of the strategy intended to assess the impact of the change, followed later by a separate evaluation of the data produced based on the agreed strategy. This would perhaps provide an opportunity to validate upfront with the agencies the acceptability of the change management plan once the product is approved and avoid unexpected heavy and complex life-cycle management.

References

More references for this article are available on the scripregulatoryaffairs.com website.

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