

Design and optimisation of a quality target product profile for ATMPs

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Abstract

The quality target product profile (QTPP) is an inherent part of product development and provides an overview of all the elements that have an impact on the quality, safety and efficacy of the product in a given clinical indication. The concept is defined in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline Q8 and may be more familiar for those developing conventional pharmaceuticals. However, it also provides an excellent tool for advanced therapy medicinal product developers and should be used to consider all elements that have an impact on the ultimate quality of the product and, consequently, the safety and efficacy in clinical and commercial use. Building up the QTPP should start at the research phase and continue up to the marketing authorisation application (MAA) phase; if it is put together properly and regularly updated, it provides the skeleton for the entire chemistry, manufacturing and control module of the MAA.

Introduction

Advanced therapy medicinal products (ATMPs) include a variety of different cell-based medicinal products (CBMPs), gene therapy medicinal products (GTMPs) and tissue engineered products (TEPs) with unique characteristics and challenges when developed for commercial use.^{1,2} In particular, the manufacturing processes and quality control for CBMPs have proven to be challenging, requiring novel manufacturing technologies and analytical tools.³ At the same time, the legal and regulatory landscape for ATMPs has matured and the requirements for different product types have become clearer. However, from the technical requirements⁴ and available guidelines⁵ it is difficult to anticipate what the chemistry, manufacturing and control (CMC) information for an individual ATMP would entail.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q8 (Rev. 2)⁶ provides high-level advice on pharmaceutical development and, as one tool, the quality target product profile (QTPP) is

described. The QTPP is an overview of all the elements during the product development process that have an impact on the quality, safety and efficacy of a product in a given clinical indication (see Table 1). The QTPP does not only focus on manufacturing and quality control issues, but should also cover the specific product design, mode of action of the product, intended clinical use, dosing, route of administration, etc.

According to the guideline, the QTPP is based on the quality-by-design (QbD) ideology, where the process inputs (materials and processing parameters) and critical quality parameters define a “design space” for production. As a result, the QbD approach may be difficult to employ for many ATMPs. However, the QTPP also provides an excellent tool for ATMP developers and could help significantly with identification of the studies and the data required for entry into clinical studies and, ultimately, for a marketing authorisation application (MAA). If it has been put together properly and is updated when more data are accumulating, the QTPP should provide a systematic and enhanced understanding of the product and process under development.

Specificities of ATMPs

CBMPs and TEPs often suffer from high inherent variability of the cellular starting material, which may have a further impact on the consistency of the production process and of the final product. In addition, variable production processes and raw materials are utilised in manufacturing of products for clinical trials.⁷ In such circumstances, the final specifications of the product tend to be wide (eg, autologous products) resulting in variable product efficacy and safety results. Therefore, even for autologous cell products, it is important to establish a link between quality and the clinical performance of the product. GTMPs (viruses and plasmids) are closer to standard biological medicinal products, but the manufacturing processes for these products can also be complex and challenging, involving, for example, multiple helper viruses or plasmids and thus requiring careful control strategy. For all ATMPs, it is important to identify the critical quality attributes (CQAs) for the product and the critical process parameters (CPPs) early in the development to understand which materials and process parameters potentially have an effect on product safety and efficacy. It is also important to follow the product performance in patients and retain both product and patient samples in case of an emerging need to analyse possible reasons behind non-responses and to identify additional quality attributes or response determinants in order to improve the success rate.⁸

How QTPP is built

New product development always begins with the disease to be treated and information on its pathophysiology. For ATMPs, the starting materials and complex manufacturing processes have direct impact on structural and functional characteristics of the product and

Table 1: Quality target product profile for advanced therapy medicinal products.

QTPP elements	Target	Source of information
Starting and raw material attributes	Specifications for starting and raw materials, acceptance criteria and limits based on product design and process validation	Product and process development
Manufacturing process	<ul style="list-style-type: none"> ● Product design ● Batch scale ● Production limits (eg, PDs) ● Identification of critical process parameters and IPCs ● Consistency and PV ● Aseptic processing, good manufacturing practice 	Product and process developments
Drug product quality attributes	<ul style="list-style-type: none"> ● Identity ● Purity/impurities ● Potency/functionality ● Genetic stability ● Sterility 	<ul style="list-style-type: none"> ● Characterisation data ● Control strategy ● IPC, release and stability testing ● Comparability testing ● Bioanalytical testing (patient samples)
Analytical methods	<ul style="list-style-type: none"> ● Assays for IPC-, release and stability testing ● Assays for extended characterisation (including PV, comparability testing) ● Validation of release assays ● Qualification of characterisation assays ● Setting specifications with acceptance limits 	Assay development and validation/qualification studies
Stability	<ul style="list-style-type: none"> ● DS and DP stability and shelf life ● In use stability instructions for handling ● Stability of intermediates and validation of hold steps 	Stability studies using relevant DS/DP/intermediate batches
Container closure	Support product stability during transport and storage	<ul style="list-style-type: none"> ● Biocompatibility testing, data on leachables and extractables ● Stability data
Indication(s)	<ul style="list-style-type: none"> ● Product fit for the disease(s) to be treated ● Potency assay in line with mode of action ● Correlation of potency vs efficacy 	<ul style="list-style-type: none"> ● Literature ● Pharmacology studies (human, animal) ● Efficacy studies
Dosage form	Target product form and formulation	DS and DP development studies (<i>in vitro</i> , <i>in vivo</i> assays)
Dosing	Single dose/repeated dosing vs manufacturing scale, DP strength	Process development, dose definition studies
Route of administration	<ul style="list-style-type: none"> ● Impact of route of administration on formulation and product profile/strength ● Impact of additional substances (eg, medical devices) 	<ul style="list-style-type: none"> ● Mode of action ● Biodistribution data ● Safety/efficacy data (animal, human)
Pharmacokinetics	Persistency and functionality of DP vs. product design	Animal and human pharmacology/PK studies; relevant animal species to be justified
Safety	<ul style="list-style-type: none"> ● Immunogenicity profile of the DP ● Toxicity profile of the DP ● Specification limits for impurities 	<ul style="list-style-type: none"> ● Human and animal safety data; relevant animal species to be justified ● <i>In vitro</i> studies (eg, integration site analysis) ● Bioanalytical testing (patient samples)
Efficacy	<ul style="list-style-type: none"> ● Specification limits for potency, correlation between potency and efficacy ● Quality of batches used in clinical studies, comparability towards commercial batches 	<ul style="list-style-type: none"> ● Human efficacy data ● Bioanalytical testing (patient samples)

DS = drug substance; DP = drug product; IPC = in process control; PD = population doubling; PK = pharmacokinetics; PV = process validation; QTPP = quality target product profile.

Throughout the development process, when new data are accumulating, the information should be used to update the quality target product profile in order to assess the need for comparability studies and to evaluate possible gaps that may need to be filled

therefore the CMC, non-clinical and clinical developments have to support each other in an integrated manner. For product design, all known risks of the intended product components and raw materials need to be considered. In fact, the building of the QTPP should begin with a risk assessment about chosen materials, processes, control strategies and intended clinical use of the product.⁶ For commercialisation of ATMPs, there is a possibility of using a risk-based approach (RBA) to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application (MAA).⁹ As a first step, this approach also involves the identification of known and unknown risks and risk factors related to the product and its intended use. If a RBA is utilised, it is expected to start at the beginning of product development and mature over time, the same way as the QTPP. In fact, the QTPP and RBA include mutual elements and the ultimate aim of both is largely similar.

Early research studies should aim to test the functionality and proof of principle of the intended product type in the given indication. When non-clinical disease models are not available or are not feasible, patient cells – or for example engineered induced pluripotent stem cells – could be utilised.¹⁰ Together with early pharmacodynamic studies, the first pilot scale production runs should take place in order to verify production capacity and the product's suitability for development. When moving towards pivotal non-clinical toxicity studies, the production process, product characterisation and quality control should already be advanced so that comparability of pivotal non-clinical batches versus clinical ones can be demonstrated. Here, CQAs play a central role and many analytical methods should be utilised to identify the most useful assays, which could provide predictive information of safety and efficacy of the product in clinical use. When significant toxicity of the product in non-clinical studies is observed, the product or production process may need to be reconsidered.

For cells, CQAs often include viability and purity- and functionality-related parameters, whereas CQAs for GTMPs may entail correct sequence, expression of the transgene, replication competent viruses etc. The CQAs are always specific for each product and should be defined case-by-case using extended characterisation, but also any available published data on similar products should be considered. Acceptance criteria/limits for CQAs will be defined through process validation and finalised with clinical experience. Often, especially for potency testing, multiple concurrent assays may need to be developed and some may appear more useful for characterisation or comparability testing purposes than for batch release testing (eg, if they are time consuming and cannot be performed before release).

Therefore, the QTPP should include an analytical strategy plan – ie, which methods should be validated for release purposes and which ones should be kept for characterisation and comparability testing purposes. The potency assay for release testing should measure biological activity and functionality of the product. However, if a surrogate assay based, for example, on messenger RNA expression is intended for batch release, correlation of the assay with a functional assay is expected¹¹.

For the product, additional topics, such as a suitable primary packaging material or container closure system, the stability of the drug substance (DS) and the drug product (DP) in the chosen delivery method, and storage conditions, need to be explored and defined for clinical and commercial use. The QTPP should also address whether the product is fit for the clinical indication with regard to the product composition, functionality and formulation.

Optimisation and update of QTPP

Together with product development, the manufacturing process should be developed and optimised. This cannot be done without knowing the CQAs because the selection of the process parameters is always based on the target product quality. For example, *in vitro* cell culture of cell products increases variability, as the cell starting materials often have different growth potential, variability in the original cell composition, etc. In addition, the genetic stability and phenotype of the cells may change during the expansion. Therefore, it is imperative to define the limits for the cell culture based on the findings of the structural and functional characteristics of the cells (eg, morphology, phenotypic markers, potency), including genetic stability. It is equally important to define the maximum population doublings (PDs), both for autologous and allogeneic products, because high variability in the product may result in variability of the non-clinical and clinical results.

The same principle applies to process- and product-related impurities. Often it is considered that for autologous products there are no cellular impurities, since the patient's own cells are given back to the patient. However, it must be noted that the administration of the cells does not always follow the physiological place and magnitude; higher cell doses may be given to unconventional places where presence of certain cell types may be harmful or may even lower efficacy (eg, high levels of granulocytes given with mesenchymal stem cells to cardiac tissue¹²).

Another issue is that target and non-target cells may change during the expansion, especially if growth factors and cytokines are used to drive for high proliferation. Therefore, there should be cell selection and isolation step(s) included in the process if the starting material is heterogeneous and the final cell composition is critical. For all processing and manipulation steps, there should be a clear rationale behind the development, based on optimisation and process validation studies. Different processing and manipulation times and conditions should be evaluated and then validated for commercial production. For the validation, CPPs need to be identified because their variability has an impact on CQAs and therefore should be monitored or controlled through in-process controls (IPCs) and release testing to ensure the required product quality and consistency.⁶

When the manufacturing process is changed (eg, for upscaling purposes or if there are changes made to the starting, raw or packaging materials, intermediates, DS or the final product), the first thing to do is to repeat the risk assessment in order to identify whether the given

change is a minor or major one and to consider the possible impact on the safety and efficacy of the product. When only minor changes are introduced, it may be sufficient to demonstrate that the product has not changed on a quality level. For such comparability studies one should utilise not only release test methods, but also extended characterisation and comparison of IPCs. In addition, it is important that the change(s) do not impact stability of the product.

If the quality of the product is changing (ie, there is a need to change DS and/or DP specifications), additional non-clinical and/or clinical bridging studies are usually required to demonstrate unchanged safety and efficacy.¹¹ Throughout the development process, when new data are accumulating, the information should be used to update the QTPP in order to assess the need for comparability studies and to evaluate possible gaps that may need to be filled before further clinical studies or the MAA.

Non-clinical and clinical aspects

Often, non-clinical studies are overlapping with CMC development and provide important information for product design and formulation development. Sometimes, non-clinical models/assays may provide tools for characterisation (eg, animal models used for proof of concept and mode of action studies). Such assays may be valuable for demonstrating correlation between assays (eg, functional vs marker-based potency assays), but may also be used to demonstrate unchanged functionality and safety as part of a comparability exercise.

Non-clinical toxicity studies should also address the design of product safety; for example, whether the vector used in a GTMP has integration potential, which could possibly lead to integrational mutagenesis and would therefore require integration site testing. Overall, each component of the product that is found to be of high risk (vectors, pluripotent cells, antibiotic resistance genes, etc) need to be justified and the risks mitigated via suitable studies or testing on the product level.

In addition, the dose, persistency of the product, production of therapeutic molecules from ATMPs, and impact of the route of administration on the product profile are areas where the CMC and non-clinical studies overlap and should together support the QTPP. In principle, the same applies for CMC and clinical studies; the findings at the patient level should guide further product design, especially in the case of safety findings and poor/variable efficacy.

It is usually only possible to evaluate the immunogenicity of certain products and product components during human exposure and the initial risk assessment should demonstrate if development of immunogenicity assay(s) are required prior to the first in man study. Overall, it is important to retain samples both from the product and from treated patients in order to make look-back testing and product/process improvements possible in case of any unexpected clinical findings.

Conclusion

The QTPP is an inherent element of product development for an MAA, yet it is perhaps more familiar for those developing conventional pharmaceuticals. However, it also provides an excellent tool for ATMP developers to consider all elements that have an impact on the ultimate quality of the product and, consequently, the safety and efficacy in clinical and commercial use. Building up the QTPP should start at the research phase and continue up to the MAA phase; if it is put together properly and regularly updated, it provides the skeleton for the entire CMC module of the MAA. ■

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References

1. Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *OJ L* 2007;324:121–137.
2. T Boran, M Menezes-Ferreira, I Reischl *et al.* 'Clinical development and commercialization of advanced therapy medicinal products (ATMPs) in the EU: how are the product pipeline and regulatory framework evolving?' *Hum Gene Ther Clin Dev*, 2017;28(3):126–135. doi: 10.1089/humc.2016.193
3. A Mizukami, K Swiech. 'Mesenchymal stromal cells: from discovery to manufacturing and commercialization'. *Stem Cells Int*, 2018:4083921. doi: 10.1155/2018/4083921
4. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. *OJ L*, 2009;243:3–12.
5. European Medicines Agency. Scientific guidelines applicable to ATMPs. Available at: <https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products> (accessed 3 December 2018).
6. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: pharmaceutical development Q8 (R2). 2009. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf (accessed 29 November 2018).
7. C Trento, ME Bernardo, A Nagler *et al.* 'Manufacturing mesenchymal stromal cells for the treatment of graft-versus-host disease: a survey among centers affiliated with the European Society for Blood and Marrow Transplantation'. *Biol Blood Marrow Transplant*, 2018;S1083–8791(18):30402–30406. doi: 10.1016/j.bbmt.2018.07.015
8. JA Fraietta, SF Lacey, EJ Orlando *et al.* 'Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia'. *Nat Med*, 2018;24(5):563–571. doi: 10.1038/s41591-018-0010-1
9. European Medicines Agency. EMA/CAT/CPWP Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83, EC applied to Advanced therapy medicinal products (EMA/CAT/ CPWP/686637/2011). Available at: <https://www.ema.europa.eu/en/risk-based-approach-according-annex-i-part-iv-directive-200183ec-applied-advanced-therapy-medicinal> (accessed 3 December 2018).
10. MJ Greenberg, NJ Daily, A Wang *et al.* 'Genetic and tissue engineering approaches to modeling the mechanics of human heart failure for drug discovery'. *Front Cardiovasc Med* 2018;5:120. doi: 10.3389/fcvm.2018.0012
11. European Medicines Agency. EMEA/CHMP/CPWP Guideline on human cell-based medicinal products EMEA/CHMP/410869/2006. Available at: <https://www.triskel.com/3%20Guideline%20human%20cell.pdf> (accessed 3 December 2018).
12. M Schüssler-Lenz, C Beuneu, M Menezes-Ferreira *et al.* 'Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints'. *Eur J Heart Fail*, 2016;18(2):133–141. doi: 10.1002/ejhf.422