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Committee for Advanced Therapies (CAT)

Questions and answers

Comparability considerations for Advanced Therapy Medicinal Products (ATMP)

Introduction

CHMP scientific advice questions are often related to the suitability of comparability proposals following changes to ATMP manufacturing processes or due to introduction of additional manufacturing sites. Manufacturing process changes may encompass improvements/change in equipment, raw materials and critical starting materials such as the cells or the vector or their suppliers, manufacturing process scale or product stability. Such changes are frequent, especially in the early stages of development of ATMPs.

Every change in manufacture should be done in accordance with GMP. The criticality of the changes and the estimation of their impact on the characteristics of the product should determine the amount of comparability data needed. Where applicable, the Variation Regulation[1] (for authorised ATMPs) or the clinical trial framework (for investigational ATMPs) should be followed.

A suitable comparability program is required to support the introduction of changes during the development stages of an ATMP. The acceptable level of flexibility is progressively reduced from the non-clinical stage to the pivotal clinical use. Comparability is also an important tool to support changes after marketing authorisation where the process and the product are expected to be well defined and appropriately controlled by quality specifications and characterisation tools.

Cell-based advanced therapy medicinal products are complex in terms of composition and dynamic nature (e.g. different function, different differentiation stage, presentation in 3-dimensional forms). Also, the manufacturing process often depends on the combination of multiple biologically active reagents and manufacturing conditions that require careful consideration to ensure that the product remains the same for all patients treated. Changes are often necessary and include renewal of cell lots for production, modifications in the manufacturing process, changes of process scale, change of a raw material supplier, or proposals for additional manufacturing sites sharing the same manufacturing process. In all such cases the comparability exercise becomes a relevant tool to demonstrate that safety and efficacy data with a given preparation is also applicable after the change was introduced. The comparability program for these complex products cannot be based solely on the characterisation of the phenotypic markers related to purity confirming a heterogeneity profile. The dynamic nature of the product reflecting its metabolism, differentiation stage, structural organisation and interactions should be part of the comparability assessment. Functional / biological properties of the product are

[1] Commission Regulation (EC) No 1234/2008 ('the Variations Regulation')

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key to define the level of comparability attained as well as to define the extent of non-clinical and/or clinical data to be generated.

Vector based gene therapy medicinal products can be considered products more closely related to biotechnology in terms of manufacturing process and process controls. In this regard, ICH guideline Q5E can be more extensively considered and the comparability exercise can be focused on the capacity to address the changes with a careful analytical strategy.

The present Q&A aims to address specific issues pertaining to the demonstration of comparability at the level of quality aspects for ATMPs.

Regulatory consideration

Changes to the manufacturing requirements registered as part of an ATMP marketing authorisation must be submitted and reviewed through variation procedures, as appropriate. This concept applies also to clinical trial authorisation of an investigational ATMP, for which substantial amendments must be presented.

Q1: What do "comparability" and "comparability exercise" stand for?

A: Comparability is the conclusion of the comparability exercise demonstrating that no adverse impact on the quality, efficacy and/or safety profile of a product has occurred when a manufacturing process change/transfer is introduced for the drug substance/product. Comparability is not a demonstration of similarity as for a biosimilar approach.

The comparability exercise is a set of activities including both the generation and analysis of data in the context of a study/studies suitably designed and conducted with identified batches and analytical tools at the quality level. Additional study/studies at the non-clinical and clinical level may be needed to investigate comparability of the batches pre- and post-change/transfer of the manufacturing process.

Demonstration of comparability through a suitable exercise is a fundamental part of the evolving manufacturing process to ensure that the safety and/or efficacy data gathered as well as the benefit/risk balance of a product is valid throughout development, for marketing authorisation and beyond.

Q2: How does ICH Q5E guideline that addresses comparability of biological/biotechnological medicinal products, apply to ATMPs?

A: ATMPs are outside the scope of ICH Q5E guideline. ATMPs in general are characterized by starting materials of inherent variability (for cell/tissue-based products), complex biological features and manufacturing processes. The ICH Q5E guideline concept of 'highly similar (and thus comparable) products' on the basis of quality attributes is therefore particularly challenging for cell/tissue-based ATMPs.

Overall, the general principles of ICH Q5E can be applied to ATMPs:

- The comparability exercise should be conducted stepwise, starting with the physico-chemical and biological properties of the product. This will be based on analytical testing e*.g.*, routine batch analysis, in-process controls, process validation/evaluation data, characterization and stability studies, as applicable.
- The investigation should focus on the manufacturing process steps most appropriate to detect a change. This may require an evaluation on all critical steps/in-process controls/materials of the manufacturing process downstream of the change.
- Analytical methods should be suitable for purpose and sufficiently sensitive to ensure the detection of differences/modifications. Any observed analytical difference should be evaluated in relation to its impact on the product quality, safety and efficacy.

- If required due to non-comparable results that can have impact on the relevance of the safety and/or efficacy data gathered so far, the comparability exercise should proceed with the generation and evaluation of comparability non-clinical and/or clinical data as necessary to contribute to the conclusion of comparability of the product.

Q3: How does the risk-based approach (RBA) apply to comparability exercises for ATMPs?

A: The potential impact of the proposed change should always be evaluated for its risks to the quality of the final product and the impact on the efficacy and safety profile of the product. The overall extent of the comparability exercise for ATMPs should therefore be driven by a risk-based approach (RBA). Namely, the RBA should be used to determine an appropriate amount of comparability data and to select a suitable set of relevant critical quality attributes (CQAs) to be compared, taking into account the stage of product development and the number of batches available.

Changes that are considered to have a high risk/impact will require an extensive exercise of comparison at the in-process control level, characterization and release. Whenever relevant, the generation of additional/new validation data has to be taken into account. On the other hand, low risk/impact changes may entail a more limited amount of comparability data. A more comprehensive data package is required to support manufacturing changes in pivotal clinical trials or to the marketing authorisation.

Q4: How should process comparability be addressed?

A: A comparability exercise should not only cover evaluation of equivalency of manufactured products but should include also comparison of processes themselves, if relevant. Comparison of processes is particularly important when a new manufacturing site is introduced. Data from process parameters and results of in-process controls should be evaluated to understand better the impact of any introduced changes. Especially for some attributes, it is more suitable to monitor them at a specific step during the manufacturing process than at the level of drug substance or drug product. These are for example expansion profiles during the cultivation phase, yields of individual steps, monitoring of product or process related impurities etc. The specific strategy should be established based on knowledge gained during the process development.

Q5: At what timepoint during the product life cycle should comparability be demonstrated?

A: It is of importance that the changes implemented in all stages of development are fully evaluated, justified and tracked. Different kinds of changes may be introduced at different phases throughout development. The evaluated risk associated with the change and possible impact on the finished product impact also the focus and level of the expected comparability exercise (see Question 3).

At early stages of development, characterisation and analytical tools to support future needs for comparability demonstration should be explored and gathered as early as possible. At this stage, batches are manufactured often at laboratory scale. In this scenario, changes are frequent and can be quite extensive and, as such, comparability is not expected. What is required is to present relevant analytical data that can support data filiation, i.e. to demonstrate representativeness of the non-clinical safety profile of the batches studied to those to be used in the exploratory clinical trials.

In later stages of development, when more product knowledge is gained, the manufacturing process evolves and pivotal clinical studies take place, a full comparability exercise is required, encompassing a series of in-process tests and parameters, release tests as well as extended characterisation assays.

The introduction of substantial changes to the manufacturing process and the final product during pivotal clinical studies are not recommended due the complexity of the comparability exercise and the possible impact of its results on the acceptability of the clinical data. In cases where late stage changes in the manufacturing process are unavoidable, it is recommended to seek for EMA scientific advice.

A comparability exercise is equally needed when a new manufacturing site is introduced (see Questions 4 and 12).

Q6: What are the analytical tools to consider in a comparability exercise?

A: For a comparability study of pre- and post-change materials, analytical methods used for release testing are the starting point. Extended characterization tests are needed to demonstrate the comparability of these types of materials at a quality level. Methods related to the functional and biological characteristics of the drug product are of particular interest and should therefore be developed for characterization/comparability purposes early in the development.

The analytical methods should be qualified for the analyte and sufficiently specific, robust, and sensitive. See also Question 2.

In the undesirable and complex situation when pre-change material is no longer available and side-by-side testing is not possible, the emphasis should be on the used analytical methods. Insufficient information on the analytical methods will cause doubts on reliability of the recorded data. If, in addition, the used analytical methods differ, it will be difficult to establish a link between the pre- and post-change material on the basis of quality. Therefore, bridging of methods used during development needs to be considered to support the comparability claim.

Q7: What is the preferred approach for demonstrating comparability?

A: In general, there are two main approaches for comparability study:

a) Side-by-side testing of products in the same analytical run. Due to the complexity of ATMPs, it is very important to focus on the effect of the introduced change(s). To reduce the source of variability, it is also advisable that both the pre- and post-change processes should be performed with the same batch of raw materials.

Furthermore, to eliminate the effect of variability of a cell starting material a split-based approach is highly recommended. This is important especially for patient-based (e.g. autologous) cell-based products where the intrinsic patient to patient variability can represent a confounding aspect for the demonstration of comparability.

b) Comparison of post-change data to historical data obtained from pre-change process. This approach is not recommended but it can be acceptable if a side-by-side study is not possible. In this case, potential impact of all variable parameters (analytical methods, personnel, used equipment and materials, …) need to be evaluated.

It is advised that historical data ranges or different statistical approaches (*e.g.*, for control of attributes with a recognised impact) that are utilized for comparability assessment, should be thoroughly selected and justified. In this context, comparability acceptance criteria should always be clearly provided and justified to assure product consistency and therefore comparable efficacy and safety. It should also be considered that acceptance criteria depend on the available data and on the statistical approach/methodology chosen, *e.g.*, a proper interval based on historical data if the approach is based on ranges for post-change individuals/mean, a p-value if the approach is based on inference statistics, etc.

For further statistical aspects, see Question 11.

In case comparability studies are performed using stored (starting) materials, drug substance, or final product, the impact of storage should be considered.

In the comparability exercise at the time of the MAA, comparability acceptance criteria should always be reported along with the results of the comparability exercise runs.

In both approaches, historical data, if representative, can be used to provide insight into potential "drifts" in quality attributes with possible impact on safety and/or efficacy.

Q8: For cell-based products, can the comparability exercise be conducted with healthy donor materials to minimise the use of patient materials?

A: The use of healthy donor material is acceptable due to patient's material scarcity and/or ethical concerns, but depends on a justification of its representativeness (*i.e.* do the patient's cells behave in the same way as the healthy donor's cells e.g. regarding transduction efficiency). The representativeness of the manufacturing scale used needs also to be justified.

In case of authorised products, justification of representativeness between healthy and patient starting materials can be leveraged using additional concepts such as concurrent validation/ongoing process verification (see GMP for ATMP[2], sections 10.40-10.44).

Q9. To what extend should stability studies be used in comparability exercises?

A: In general, full real time stability studies are not required to support comparability. Nevertheless, stability data are very relevant to understand the impact of changes. Many ATMPs have specific storage conditions (such as cryopreservation) and a relatively long shelf life. In this regard, it is more reasonable to focus on dedicated stability studies under accelerated or stress conditions that can be of value to identify possible differences. For cells with a very short shelf life, real-time stability studies are expected.

If relevant, the in-use stability study after the product's thawing and/or preparation before its administration should be also included as a part of comparability exercise. For example, the cells' sensitivity to the introduced changes could be displayed at the phase of their recovery after storage or additional reconstitution/preparation steps.

Even if not routinely included in the shelf-life specifications, addition of relevant characterisation parameters should be considered for comparability purposes. (see also Question 6)

For statistical aspects, see Question 11.

Q10: Is there a minimum number of batches that should be included in a comparability exercise?

A: There is no 'one size fits all'. For considering the required level of comparability demonstration, the intrinsic variability of the product needs to be evaluated and taken into account.

Depending on the type of change introduced, while a small number of batches can serve to demonstrate comparability for a given analytical method where intrinsic variability is minimal and precision and sensitivity is high, other methods such as biological characterisation methods may require more extensive testing of significant numbers of samples as the inherent variability is high. The number of batches included in the comparability exercise needs to be evaluated case by case, and the approach taken requires careful consideration and justification based on the type of change, product and manufacturing process understanding, overall control strategy, sensitivity of the methods and the level of risk.

The higher the variability between batches, the higher the number of batches required to conclude the comparability exercise.

Q11: Are statistical approaches appropriate to show comparability of ATMPS?

A: Statistics may provide useful information to support comparability even though any statistical approach has its own limitations and strengths, and those should be well understood and documented before conduct of the comparability exercise and in order to make informed decisions on the comparability utilizing the statistical results.

[2] Guidelines on Good Manufacturing Practices specific to Advanced Therapy Medicinal Products (C(2017) 7694 final). Eudralex volume 4 Good Manufacturing Practice.

In any case, it is essential that an appropriate pre-specified plan with a justification is provided for the statistical approach chosen and the comparability acceptance criteria proposed for the relevant quality attribute selected according to a risk-based approach. In this regard, it is emphasized that solely meeting specifications is not considered sufficient to conclude on comparability.

A risk-ranking of CQAs can be performed to drive the selection of the preferred statistical methodology. A combination of various methodologies can be used to understand the robustness of the chosen statistical approach.

Inclusion of side-by-side analysis of individual values with accompanying descriptive statistics to summarize data (*e.g.* min-max and 3*sigma ranges) is recommended, particularly when comparing a limited number of samples/batches (*e.g.*, in earlier development phases). Likewise, suitable graphical representations (*e.g.*, individual values scattergrams) could be provided, allowing the identification of possible shifts within the acceptance criteria.

Further consideration should be given to the reflection paper on statistical methodology for the comparative assessment of quality attributes (EMA/CHMP/138502/2017).

Concerning stability aspects, evaluation of comparability between pre- *vs.* post-change degradation/"time change" rates may be performed *e.g.*, by comparison of the slopes of the time-based regression lines, when applicable. (See also Question 9)

Q12: What is the comparability exercise needed when a new manufacturing site is added to an existing authorisation?

A: When several manufacturing sites are introduced under the same authorisation procedure, a high degree of comparability is expected to be demonstrated. The comparability of the product manufactured at different sites should be comprehensively substantiated. The first step should be to perform a comparability assessment of the manufacturing process and equivalence of the analytical methods on both sites by evaluation of process parameters and in-process control, to validate the process transfer. Secondly, the comparability of the product itself through release and suitable characterisation testing should be demonstrated. (See also Questions 4, 6 and 9)

Q13: Is a comparability exercise needed when changes are made in the manufacturing of starting materials?

A: An evaluation of the criticality of the change to the manufacturing of the starting material need to be conducted, taking into consideration current process and product understanding.

When critical changes are made in the manufacturing of starting materials for ATMPs having an impact on the manufacturing process or the finished product, a comparability demonstration is required to ensure the consistent quality of the product and to ensure that the change does not have an adverse effect on the safety or efficacy profile of the product.[3]

[3] Reference is made to the section on comparability studies in the *Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells* (EMA/CAT/GTWP/671639/2008 Rev.1)