What are the quality challenges regarding comparibility considerations of Advanced Therapy Medicinal Products?

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INTRODUCTION

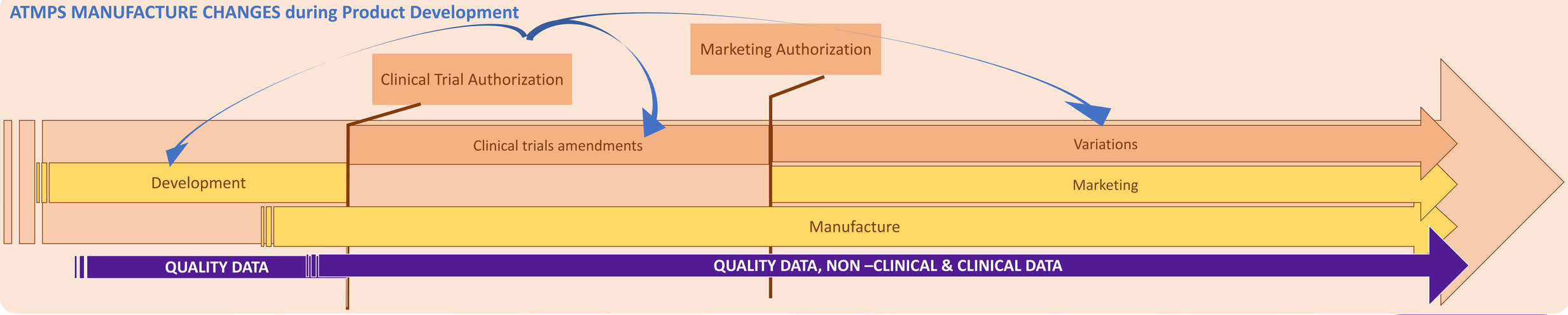
The question of comparability for Advanced Therapy Medicinal Products (ATMPs) is very often asked during Scientific Advice Meetings at the European Medicines Agency. Indeed, changes to ATMPs manufacturing processes, improvements/changes in equipment, raw materials and critical starting materials, or process scale are frequent in the early stages of development or even after marketing authorization. Quality comparability is the first step in the review of variations procedures of a medicinal product. Indeed, quality information is of major importance with analytical testing, risk-based approach and manufacturing evaluation as it will allow to conclude if non-clinical and clinical data on comparability are also needed or not.

The text of December 2019 of the **Committee for Advanced Therapies (CAT)**, entitled "**Questions and answers, Comparability considerations for Advanced Therapy Medicinal Products**" contains the major questions companies can have when a comparison is needed between the pre- and post-change of the manufacturing process of ATMPs. The answers are based on analytical and statistical tools which are needed in frequent experimental changes situations. Generally, this text addresses the issues linked to the demonstration of comparability regarding the quality aspects of ATMPs. Another important text is the **ICH Q5E guideline that addresses comparability of biological/biotechnological medicinal products**. However, ATMPs are outside the scope of this guideline, except for the general principles that can be applied to ATMPs.

Through of comparative textual analysis of these two texts, this poster will show the complementarity of the information provided, but also the very dynamic impact of the Q&A text targeted on ATMPs in comparison with the large recommendations of the ICH guideline on biotech products.

RESULTS

ATMPS MANUFACTURE CHANGES during Product Development



Assessing the comparability **before/after changes** should start with comparison of quality data.

Changes can happen **during the development phase or after marketing authorization**.

COMMON TOPICS

WHEN?

"comparability exercise" based on the **physico-chemical and biological properties** of the product: **Analytical methods for release testing** can be used; validated methods not necessary.

Even if products are different, **comparison method before/after change** (in the manufacturing process) **is the same**.

WHAT?

1/ **Comparison of quality attributes** with analytical testing, based on active substance & finished product properties;

2/ if not satisfactory, **comparison of non-clinical & clinical data**.

For quality data, comparison integrates all data collected, e.g., routine batch analyses, in-process control, process validation data, characterization or stability.

HOW?

"A comparability exercise should not only cover evaluation of equivalency of **manufactured products** but should include also comparison of **processes themselves**", if relevant.

OF WHAT?

Knowledge of the manufacture and development data are key words for both texts.

Scope

Q&A text: ATMPs, especially cell-based medicinal products

ICHQ5E guideline: proteins, polypeptides, and derivatives, and is recommended for vector-based gene therapy medicinal products.

Types of data

It is mainly in ICH Q5E that confirmatory nonclinical or clinical studies are appropriate, after comparison of quality data.

Characterization

by appropriate techniques (described in ICH Q6B) includes determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity; each "criteria should be considered as a key point in the conduct of the comparability exercise".

ICHQ5E guideline: analytical tests "chosen to define drug substance/drug product specifications alone" and used at release of the product are generally not "considered adequate" to evaluate comparability, &"Modification, elimination, or addition of a test (i.e., in the specification) might be indicated".

Q&A text : "analytical methods used for release testing are the starting point"; "if the used analytical methods differ, it will be difficult to establish a link between the pre- and post-change material" (Q6).

Stability Studies

ICHQ5E guideline: "Real-time/real temperature stability studies on the product potentially affected by the change" should be initiated for proteins.

Q&A text: full real time stability studies not required to support comparability for stable ATMPs; accelerated or stress conditions, and in-use stability studies are only proposed.

SPECIFIC TOPICS

The following subjects are only treated in the Q&A text because they are connected to ATMPs.

Methodology of the comparability exercise:

- Two main approaches are possible for comparability study of ATMPs: "Side-by-side testing of products in the same analytical run", and "Comparison of post-change data to historical data obtained from pre-change process", the latest one is not recommended (Q7).
- "Statistics may provide useful information to support comparability". "Solely meeting specifications is not considered sufficient to conclude on comparability" (Q11).

Cell-based products: the comparability exercise can be conducted with healthy donor materials with justification (Q8).

When a manufacturing site is added for a marketed product, "a high degree of comparability is expected" with "comparability assessment of the manufacturing process", "equivalence of the analytical methods" and "comparability of the product itself" (Q12).

A "comparability exercise" is needed for "critical changes in the manufacturing of starting materials for ATMPs having an impact on the manufacturing process of the finished product" (Q13).

Regulatory consideration: a change in the manufacturing process results in a variation procedure of the marketing authorization or an amendment of the clinical trial authorization

Risk-based approach should be used to determine an appropriate amount of comparability data and to select a suitable set of relevant critical quality attributes (CQAs).

DISCUSSION/CONCLUSION

The Q&A is limited to ATMPs whereas the guideline is for Biotechnological/Biological Products. ICHQ5E coming into operation in 2005 is used as a Reference text for Q&A of 2019. Nevertheless, only the general principles of ICHQ5E can be applied to ATMPs which are considered to be out of the scope of ICHQ5E due to their characteristics.

The Q&A addresses a number of questions that have been brought to the attention of the EMA by marketing-authorisation holders (MAHs) or European Economic Area competent authorities, on matters related to the quality of medicines. It provides a harmonised position on issues which require clarification, typically during assessment procedures.
The Q&A should be red in conjunction with other guidelines.

The comparability considerations of the ATMPs changes are based on Quality data in the Q&A with a lot of work during the Pharmaceutical Development with the use of modern quality tools; the comparability considerations of the Biotechnological/Biological Products changes are based on quality, non-clinical and clinical data.

The obligations to assess changes based essentially on in vitro studies, as in the Q&A, are extremely important for MAHs, because they thus limit in vivo studies on animals or on patients, which are long, expensive and not necessarily ethical.

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