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GUIDELINE ON COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES

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* **The document of 20 September 2001 has been updated to make changes such as 'drug substance' to 'active substance', 'drug product' changed to 'finished product', 'note for guidance' to 'guideline', 'marketed' to 'authorised', etc. The paragraph mentioning the difference between essential similarity and comparability is removed in the light of the reference to similar biological medicinal products in the new annex to Directive 2001/83/EC. This guideline should also be read in conjunction with the guideline on non-clinical/clinical issues.**

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COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE QUALITY ISSUES

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1. INTRODUCTION

1.1 Purpose

It is well acknowledged that medicinal products of biotechnological origin i.e. medicinal products containing proteins derived from r-DNA and hybridoma techniques are often subject to change in their manufacturing process (active substance and/or finished product). Improvement of product quality, increase in production yield and global productivity or improving process economics are the main reasons for introduction of such changes. These changes can be introduced either during the development phase or after the Marketing Authorisation has been granted. Whatever the production step at which the change occurred, there is a necessity to compare the product derived from the modified process to the one derived from the currently used process, essentially to ascertain that introduction of the change did not alter the physico-chemical and biological characteristics of the product. These characteristics (mainly reflected by the current in-process controls and release specifications) are of utmost importance as they are the basis on which quality, safety and efficacy of the product are claimed. A change in these characteristics may lead to a different safety or efficacy profile of the product. As a consequence, a comparability exercise should be considered for a given product following change made in its manufacturing process.

This Guideline does not cover changes introduced at a very early stage of development (namely before pre-clinical studies and initial clinical trials to evaluate preliminary safety are conducted).

In addition, there is a need to consider the necessity for conducting comparability studies for situations where a manufacturer is seeking approval of a Marketing Authorization for a biotechnology-derived product claimed to be similar to one already authorised.

Whatever the situation, the reasoning (step by step approach) as regards the comparability exercise should be identical. In this approach, the following parameters should be considered as key points: i) characterisation studies, ii) validated manufacturing process, iii) release data, iv) stability data, and, in wider perspective v) pre-clinical and clinical studies.

This Guideline has been prepared with reference to the scientific principles already developed, for example in the following documents:

1.2 Regulatory framework

- CPMP Guideline on Production and Quality Control of Medicinal Products derived by Recombinant DNA Technology,
- CPMP Guideline on Production and Quality Control of Monoclonal Antibodies
- CPMP/ICH/365/96 Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B),
- CPMP/ICH/139/95 Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products (Q5B),
- CPMP/ICH/138/95/ Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C),
- CPMP/ICH/294/95 Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products (Q5D),
- CPMP/ICH/295/95 Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products derived from Cell Lines of Human or

Animal Origin (Q5A).

These Guidelines address the key elements on which specifications for quality control of biotechnology-derived proteins should be set. Further guidelines on general quality requirements should also be taken into account.

1.3 Scope

This Guideline addresses the issue of demonstration of comparability for medicinal products of biotechnological origin i.e. containing proteins derived from r-DNA and hybridoma techniques so-called biotechnology-derived proteins. As a consequence the principles adopted and explained in this document should apply to proteins and peptides, their derivatives and products of which they are components (e.g. conjugates). These proteins are produced from recombinant cell-culture expression system and can be highly purified and characterised using an appropriate set of analytical procedures. The principles and arguments outlined in this document may be used as a framework when envisaging similar situations for other biological products not covered by this Guideline.

1.4 Comparability exercise

Comparability is the exercise that will demonstrate that two products have similar profile in terms of Quality, Safety, Efficacy. The comparability exercise should be viewed as a sequential process. The claim of comparability in terms of Quality, Safety and Efficacy can be deduced from quality studies (partial or comprehensive) and may need to be supported by bridging preclinical/clinical studies.

The comparability exercise and the claim of comparability is applicable to the two situations and two different procedures:

- change introduced by one manufacturer (or related manufacturers) into its own process for a given product (variation) either before the granting of a marketing authorisation or after the granting of a marketing authorisation (variation procedure).
- for a product claimed to be similar to another one already authorised (new application).

2. COMPARABILITY EXERCISE FOR CHANGE INTRODUCED IN THE MANUFACTURING PROCESS OF A GIVEN PRODUCT

As mentioned in the introduction, it is frequent for a manufacturer, in the life cycle of a product, to introduce changes in the production process. These changes can be introduced either during the development phase (see also 2.2.1) or after the marketing authorisation has been granted. In all cases, whatever the stage of development where the change is introduced, it is the responsibility of the manufacturer to assess to what extent the change introduced i) modify the quality profile of the resulting product and ii) may potentially impact on safety and efficacy.

In this chapter, the various key elements to be considered in designing the comparability exercise and extensiveness of the required studies are presented.

2.1 Points to consider in performing comparability studies

The comparability exercise should be considered as a whole set of interrelated considerations encompassing the three evaluation criteria of quality, safety, and efficacy.

Indeed, any change or modification made to a production process may impact on the quality, safety and efficacy of the finished product. Many different types of changes can be introduced in the manufacturing process. Annex I lists the most common changes introduced in the manufacturing process. Regulations have classified pharmaceutical variations as minor and major. However this classification may not be appropriate as the basis for designing

comparability strategies since even changes considered as minor may result in relevant modifications of the quality profile of the product. Consequently, it is advisable not to classify *a priori* any changes as minor or major based on the type of change itself, but to consider the potential consequences (which will be major or minor) of the change introduced on product quality, safety and efficacy.

Depending on the consequences in terms of quality, safety and efficacy of the introduced change, various situations with different levels of complexity can be foreseen and thus the comparability exercise:

- will be limited to the strict process validation of the change introduced,
- will be extended to various quality criteria such as in-process controls, stability data, thorough analytical and biological characterisation of the product,
- cannot be fully carried out based solely on quality criteria and needs to be further documented as regards *in vivo* safety/efficacy profile.

Consequently, extensiveness of the comparative studies will depend on:

- the stage of development when the change is introduced
- the quality criteria consideration regarding the potential impact of the change introduced on the purity as well as physico-chemical and biological properties of the product
- the suitability and availability of analytical methods to detect potential modification(s) as regards product characteristics,
- the relationship between quality criteria set with safety and efficacy results, based on the overall pre-clinical and clinical experience (safety and efficacy criteria consideration).

2.1.1 Stage of development when the change is introduced

The comparability exercise should be carried out when change is introduced either during development, i.e. after critical studies (demonstration of product consistency, stability studies, pre-clinical studies, pivotal phase II/III clinical studies) have been initiated or after the marketing authorisation has been granted. Needless to say that where change is introduced at a very early stage of development (namely before pre-clinical studies and initial clinical trials to evaluate preliminary safety are conducted) the basic issue of comparability is not raised.

2.1.2 Quality criteria consideration

The complexity of the concerned molecular entity should be considered as a major criterion in discussing comparability. Indeed, depending on the physico-chemical properties of the molecule (e.g. from primary to quaternary structure, length of the sequence, post-translational modifications such as extent and nature of glycosylation, N/C terminal modifications), it can sometimes be difficult to define precisely the product and there is a need to use an extensive series of analytical techniques exploiting the various physicochemical properties (size, charge, hydrophobicity, etc.) and biological activity of the molecule.

In many cases, due to the inherent variability of the biological process, the end-product consists of a complex mixture of molecules (product-related substances). This heterogeneity, which is taken into account when assessing the in-vivo behaviour of the product, should be characterised to assure batch-to-batch consistency. Heterogeneity contributes to the difficulty of the comparability study due to the complexity of these products. The *Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* stipulates that specifications for active substances and finished products should be considered as the result of a total quality control strategy which includes cloning strategy, expression and genetic stability, thorough product characterisation, validation and consistency

of the manufacturing process (in-process controls, quality monitoring of raw materials and reagents), stability data, as well as quality of the batches used in pre-clinical and clinical studies. It is noteworthy that, in some cases, it may not be sufficient to demonstrate only compliance with the approved specifications and additional studies on protein structure, impurity profile and/or biological activity may be needed.

Consequently, as an initial approach when introducing a change in a given process, the following parameters, on which specifications have been based, should be considered as key points: i) characterisation studies, ii) validated manufacturing process, iii) release data, iv) stability data, and, in wider perspectives v) pre-clinical and clinical experiences. They should be evaluated in a step by step approach when discussing comparability.

2.1.3 Suitability of available analytical methods

Given the complexity of the molecule and its inherent heterogeneity, it is sometimes difficult to guarantee that the set of analytical techniques (even state-of-the-art and acknowledging the huge progress made in the field) selected by the manufacturer will be relevant or able to detect any slight or discrete modifications of the characteristics of the biotechnology-derived product. It is however the demonstration of absence of such discrete modifications which could authorise a manufacturer to declare its product indistinguishable in all aspects pertinent to the evaluation of quality.

Whenever a change is introduced in the production process, manufacturers should provide assurance that a comprehensive quality control program has been developed and an appropriate set of analytical methods have been selected in order to assess the comparability of the product before and after the change have been introduced. The degree of validation of the analytical methods used should be appropriate to the stage of development. Whatever the impact of the change(s), the analytical methods should allow suitable assessment of the manufacturing process as well as specifications regarding both the active substance and the finished product. The main task will be to establish to what extent the analytical methods used are able to detect any slight modification possibly introduced by the change

2.1.4 Safety and efficacy criteria consideration

It should be noted that specifications for active substance and finished product are based on data derived from batches, which have been used in pre-clinical and clinical studies. This means that specifications applied have been validated both by and for the *in vivo* use of the product.

When a change in the manufacturing process results in modifying the specifications (active substance/finished product) and/or in process controls, it should be considered whether the comparability exercise can be restricted to quality aspects or, if quality aspects are not sufficient, it should also include safety and/or efficacy criteria. In situation where differences either are identified or are suspected, appropriate pre-clinical and clinical studies could be considered as the only definite way to demonstrate comparability, at least for some specific features such as immunogenicity.

In this respect, the nature and the extent of the pre-clinical and/or clinical studies to be performed when assessing the potential consequences of the change introduced should be justified and designed taking into account the degree of knowledge of the molecule, its mode of action and the experience already gained as regards *in vivo* behaviour.

2.2. Strategies of comparison depending on the change introduced in the manufacturing process

The manufacturer, when introducing a change in a manufacturing process (active substance or finished product) is confronted with two different approaches as regards the strategy to be

applied:

a) the initial hypothesis considers that the change introduced will not have any impact on the quality criteria of the product. In this case, assurance has to be provided that the in-process control and/or the release data found (active substance or finished product specifications), as compared to those obtained using the previous process, have not been modified. The comparability exercise can be acceptable provided that the methods used are sensitive enough to detect slight differences in the structure of the molecular entity. When routine tests are considered as inappropriate to pick up subtle differences, additional studies, using more powerful analytical methods such as those previously performed in characterisation studies (during the initial development), should also be envisaged. In case the expected quality acceptance criteria are not met, a complete validation program should be carried out (see point 2 here below).

b) the initial hypothesis considers that the change introduced will impact on the quality of the product. In this case, consequences of the change(s) on the characteristics of the product should be investigated using a full set of validation data with particular emphasis on characterisation, batch-to-batch consistency and stability. In addition, the potential impact of the change as regards safety and efficacy has to be taken into consideration.

Depending on the process level where the change is introduced, several controls (monitoring, follow-up) would have to be performed sequentially all along the process leading to the final intended finished product.

2.2.1 Change with no impact on quality criteria (in-process controls as well as active substance and/or finished product specifications)

In this case, the comparability exercise can be restricted to the change introduced. Manufacturer should focus on the modification introduced and illustrate that the change has no impact on the whole set of quality acceptance criteria by the results obtained for a suitable number of consecutive batches (in-process controls and release specifications). However, depending on the change introduced, the need for stability data cannot be systematically excluded. Such change does not call into doubt the quality of the active substance/finished product and thus does not put into question what has already been established dealing with safety/efficacy.

This case could be encountered in situations such as: change in reagent supplier, change in excipient supplier, etc. In such cases, if the quality results for one batch are found different, assurance that these results are directly linked to the specific change introduced (and not linked to any other adverse events) should be provided and the others situations, as described hereafter, should apply.

2.2.2 Change with impact on in-process controls without impact on active substance and/or finished product specifications

Consequent to the change (introduced, although there are no modification with respect to release specifications (active substance and/or finished product), some in-process controls needs to be refined in a way to guarantee reproducibility of the modified process. Data (revised in-process controls but unmodified release specifications) on a suitable number of consecutive batches have to be provided to i) illustrate the consistency of the manufacturing process and ii) ascertain that release specifications remain unchanged. In addition, stability studies should be initiated and data provided on several batches (active substance and/or finished product). In this situation, as for the one mentioned in section (3.1), change introduced does not put into question what has already been established dealing with safety/efficacy.

The comparability exercise can be acceptable provided that the methods used are sensitive

enough to detect slight differences in the structure of the molecular entity. When routine tests are considered as inappropriate to pick up slight differences, additional studies, using more powerful analytical methods such as those previously performed in characterisation studies (during the initial development), should also be foreseen.

2.2.3 Change with impact on quality criteria (in-process as well as active substance and/or finished product specifications) and no anticipated consequences on safety/efficacy

Demonstration of comparability should be based on the following:

- Quality: validation of the process based on results from a suitable number of consecutive batches, and stability data. As a consequence, based on thorough characterisation studies (including analytical state-of-the-art methods/tools used in initial development but not retained as part of the routinely performed tests), the specifications have to be re-discussed and changed.
- Safety/Efficacy: in the light of the identified modifications in terms of molecular identity (including heterogeneity and impurity profile), the argument that there are no consequences regarding safety and efficacy should be discussed and justified by the manufacturer.

2.2.4 Change with impact on quality criteria (in-process as well as active substance and/or finished product specifications) and anticipated consequences on safety/efficacy

If the modification identified as regards quality criteria raise scientifically-based questions in terms of safety/efficacy, additional pre-clinical and/or clinical studies may be necessary to provide assurance about the safety and efficacy of this product.

Considering the degree of knowledge available at the end of pivotal clinical studies or post-marketing as regards the relationship between clinical efficacy and quality characteristics of the product, the manufacturer should provide data, based on a suitable clinical study protocol, on possible consequences in terms of safety and efficacy. These considerations are product specific and consequently, depending on the specific situation the manufacturer is confronted with, the protocol will consist either i) in a suitable and well justified bridging study or ii) in more extensive studies (see Guideline on non-clinical and clinical issues).

3. COMPARABILITY EXERCISE FOR A PRODUCT CLAIMED TO BE SIMILAR TO ANOTHER ONE ALREADY AUTHORISED

In this case the manufacturer, although possessing all the necessary information on his own manufacturing process, would normally not have access to all necessary information that could allow comparison in terms of quality with any other products already on the market. Indeed, the expression/vector system, production and purification process, facility/equipment, analytical techniques, etc. may be different from other manufacturers; the extent of the difference cannot be evaluated by the second applicant.

It should be recognised that, in most cases, comparison can be made against the published data, such as in a pharmacopeial monograph with respect to gross physico-chemical or biochemical characteristics of the molecule such as molecular weight, pI, biological activity, etc. However, as explained in this guideline, comparison based on testing and characterisation of active substance and finished product is not sufficient to establish all aspects pertinent to the evaluation of quality, safety and efficacy for a biotechnology-derived protein.

Consequently, with the above considerations in mind, this situation represents the most complicated case. As such, an extensive comparability exercise will be required. The extent

of the pre-clinical and/or clinical bridging studies will depend on the nature of the active substance and formulation, and the complexity of its molecular structure as well as the possible differences as compared to the reference product (including impurities and stability, and in some cases the finished product formulation).

4. CONCLUSION

The following factors should be taken into consideration in any comparability study:

i) the complexity of the molecular structure,

ii) the type of change(s) introduced in the manufacturing process, and

iii) their impact on quality, safety and efficacy.

For each individual situation, a step by step approach should be used to identify any potential impact consequential to process change(s) on the molecular integrity and consistency. A flexible approach should be adopted taking into account progress in science and technology. For products claimed to be similar to another already authorised, the comparability strategy may require bridging studies to address the underlying issues relating to pre-clinical pharmacology/toxicology, and clinical safety/efficacy. It should be recognised that in cases, where satisfactory comparability may not be demonstrable, a full preclinical and clinical data package will be required.

ANNEX I

Type of changes to a manufacturing process

Many different types of changes can be introduced in a manufacturing process. A non-exhaustive list of changes following the sequence proposed in the Biotech Headings Notice to the Applicants is detailed below.

- Formulation and filling
  - Excipient
  - Equipment
  - Change in the manufacturing protocol
  - Scale
  - Change or additional manufacturing site/facility
  - Shipping conditions
- Finished product
  - Batch definition
  - Shelf-life
  - Container/closure system
  - Shipping conditions
  - Storage conditions
- Expression system
  - Master cell bank:
    - new bank derived from existing cell line or initial clone
    - Raw material change
    - Storage conditions
  - Working cell bank:
    - Manufacturing change: raw material (cf. fermentation), new method of production.
    - Storage conditions
- Fermentation/culture process
  - Raw materials: new supplier, specifications, addition/substitution/elimination of raw materials, media composition
  - Cell culture conditions: pH, oxygen, temperature, time, mode
  - Scale of fermentation/cell culture
  - Equipment
  - Change or additional fermentation site/facility.
- Purification process
  - Column/resin change : size of the column, supplier, cleaning and storage conditions
  - Reagents: new supplier, specifications, replacement of raw materials
  - Purification protocol: addition, substitution, elimination of a specific step
  - Scale of the downstream process
  - Change or additional purification site/facility
  - Equipment

- Active substance
  - Batch definition, pooling strategy
  - Shelf-life
  - Container/closure system
  - Shipping conditions
  - Storage conditions