MENAGEMENT IN HEALTH CARE PRACTICE A Handbook for Teachers, Researchers and Health Professionals	
Title	**LEGISLATIVE BACKGROUND FOR MARKETING AUTHORISATION OF THE BIOSIMILAR MEDICINAL PRODUCT IN THE EU**
Module: 2.9	**ECTS (suggested): 0.2**
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Keywords	Generic, biosimilars, biotechnological and medicinal products, biopharmaceuticals
Learning objectives	After completing this module students and public health professionals should: • be aware of new terminology in the EU pharmaceutical field since 2004, based on Directive 2004/27/EC; • recognise the newly introduced product, which were for first tine submitted via European Evaluation Agency – EMEA; • increase knowledge of comparison of generics and biosimilars; • differentiate the groups and the products which are included; • identified, upon official sources the word market of the biopharmaceuticals where the patent has already soon expired; • improve the knowledge and understanding of the largest group of proteins derived from biotechnology, blood-plasma medicinal products, vaccines, cytokines, interleukins, hormones, gene - and cell - therapeutic and **in vivo** diagnostic allergenic products, where the patent and the data exclusivity is expire and biosimilar product could be authorised.
Abstract	The article presents a legislative overview of the medicinal products from biotechnological source, which are derived from living organisms so called biosimilars. Since 2004, based on Directive 2004/27/EC the term "biogeneric" does not exist any more and the therapeutic proteins including, recombinant human insulin for the treatment of diabetes, human growth hormone for the treatment of hypo-pituitary dwarfism, interferon, erythropoietin for the treatment of anaemia in cases of chronic renal failure, various blotting factors referred to an original medicinal products are called «boisimilars». All these biological medicinal product often heterogeneous so that modern analytical

	methodology could not always characterize them in terms of differences in conformation, heterogeneity and impurity profiles. Since 20 November 2005 the Marketing authorization way for biosimilars is via the Centralized Procedure pursuant Regulation (EC) 726/2004, Annex 1. In year 2006-2007 the number of the submitted medicinal product to EMEA is 14. The survey follows and discusses the issues which are necessary for the marketing authorization of all these medicinal products to prove the safety, efficacy and quality, where appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.
Teaching methods	Lectures, seminars, exercises, individual work and small group discussions.
Specific recommendations for teachers	• work under teacher supervision /individual students' work proportion: 30%/70%; • facilities: a computer room; • equipment: multimedia, LCD projection equipment, computers (1 computer on 3 students), internet connection, access to bibliographic data-bases; • training materials: readings are mainly available in the Internet; • target audience: master degree students.
Assessment of Students	The final mark should be derived from assessment of the theoretical knowledge (oral exam), multiple choice questionnaire (MCQ), contribution to the group discussions, quality of individual work and seminar paper.

LEGISLATIVE BACKGROUND FOR MARKETING AUTHORISATION OF THE BIOSIMILAR MEDICINAL PRODUCT IN THE EU

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THERORETICAL BACKGROUND

Legislative Background for Marketing Authorisation of the Biosimilar Medicinal Product

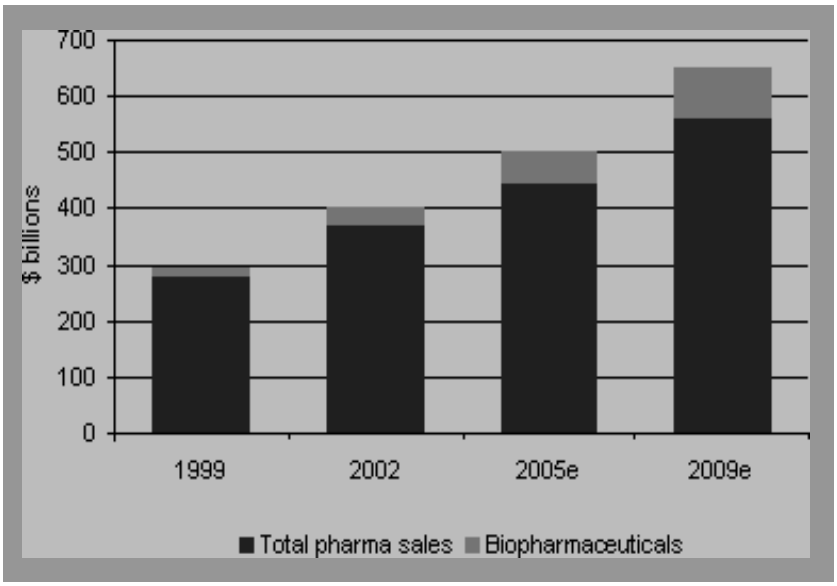
Thanks to the development of molecular biology and genetic engineering, new medicinal products derived from biotechnology are available to healthcare markets, thanks to the recombinant DNA (r-DNA) technology in the last 20 years used to manufacture safe and effective therapeutic medicinal products.

Medicinal products from biological source are derived from living organisms and they are often heterogeneous so that modern analytical methodology could not always characterize them in terms of differences in conformation, heterogeneity and impurity profiles. These therapeutic proteins include recombinant human insulin for the treatment of diabetes, human growth hormone for the treatment of hypo-pituitary dwarfism, interferon, and erythropoietin for the treatment of anaemia in cases of chronic renal failure, various blotting factors and many other conditions.

The largest group of proteins derived from biotechnology are, blood-plasma medicinal products, vaccines, cytokines, interleukins, hormones, gene - and cell - therapeutic and **in vivo** diagnostic allergenic products, these represent and most of them are heterogenic and the contemporary analyses do not provide method for full analyses option. Often the analysis method may have product impact. In the last decade the medicinal products from biological origin are growing extremely and, the forecast till year 2010 will be nearly 50% of all new marketing authorized product will be of biotechnological origin (Fig 1 and Fig 2) (1).

The different patent position for biopharmaceutical is complicated by the fact that "biogenerics" does not exists" with the Review 2005. As the regulation stand, therapeutically similar products must be different to the original and they cannot rely on the original data and must submit full market authorisations via the EMEA' centralised procedure, since 20 November 2005. Many biotech medicinal products are in process or are already patent expiry and they presents serious part of the pharmaceutical world market, where the top ten 10 Biopharmaceutical Companies (Fig 3) (2).

The term „biosimilars" was introduced in March 2004, as the regulations stand, therapeutically similar products must be different to the original. As such, they cannot rely on the original data and must therefore submit full market authorisations via EMEA's Centralised procedure (the obligatory or preferred route to market for most biopharmaceutical products). Most EMEA concept papers for biopharmaceutical medicinal products are directed to the active substance under patent expiry (3).



Source: IMS Health, BioGeneriX(1)

Figure 1. Biopharmaceuticals' share of global prescription sales

Product	Innovator company	Active substance	Patent expiration	Global sales, 2002
Humulin	Lilly	human insulin	2001	$1.0bn
Intron A	Schering-Plough	Alpha-interferon	2002	$2.5bn
Procrit	Amgen/J&J	erythropoietin	2004	$4.3bn
Epogen	Amgen	erythropoietin	2004	$2.3bn
Neupogen	Amgen	filgrastim (GCSF)	2006	$1.4bn

Source: IMS Health, BioGeneriX(1)

Figure 2. Blockbuster biotechnology products with patent expiry before 2007

CASE STUDY

Legislative basis of the "biosimilar" for marketing authorisation in EU

The general requirements for generic products are not sufficient for biosimilar products because any changes in the manufacturing process may generate significant differences in terms of quality, safety, and efficacy. The efficacy and safety of a biosimilar biotech molecule is not necessarily to be the same for all indications. Therefore, according to the pharmaceutical Review 2005, the applicants for biosimilar products will have to provide to EMEA specific preclinical and clinical data for each therapeutic indication and also for new routes of administration (4).

Company	Sales in 2006	
01	Amgen	$13,858
02	Genentech	$7,640
03	Novo Nordisk	$6,526
04	UCB Group	$2,711
05	Biogen Idec	$2,592
06	Gilead Sciences	$2,588
07	Serono	$2,498
08	Genzyme	$2,278
09	MedImmune	$1,221
10	Millennium	$220

Figure 3. Top 10 Biopharmaceutical Companies *based on 2006 biopharma revenues Note: In all Top Company profiles, dollar amounts are in millions (2)*

An abridged registration procedure which allows an applicant for marketing authorisation of a generic medicinal product to provide bioequivalence studies instead of necessary clinical trials. The manufacturer must prove the quality of the generic medicinal product and since the active substance is already well known for its safety and efficacy, the generic must only demonstrate its therapeutic equivalence to the reference product through what are known as bioequivalence studies.

No legal framework has existed for generic medicines derived from biotechnology before 2004. This deficiency was solved during the review of EU pharmaceutical legislation, known as the "Pharma Review 2005". Specific provisions were adopted in the final text under the co-decision procedure by the European Council and the European Parliament establishing a legal base for biogenerics where **"similar biological medicinal products" are possible to be authorised under condition pointed in the** Directive 2004/27/EC.

The Commission published a new Directive 2004/27/EC (4) went into force on 1 November 2005, introduced a legal framework for biosimilar medicines identical to that for generic medicines. Article 10(i) (iii) of the Directive 2001/83/EC together with Part II, section 4 of Annex 1 provided the guidelines for a biosimilar dossier.

Biological medicinal products are defined in Part I 3.2.1.1 b. of Directive 2003/63/EC with replace the Annex 1 of Directive 2001/83/EC. The definition in Article

10 (1) in 2001/83/EC was not applicable for the biological medicinal products and the concept for "Essential Similarity" was not possible to be used. **The medicines legislation from 2004**, amending the Community code on medicinal products for human use (Directive 2004/27/EC) Article 10, paragraph 4 introduces the requirements for biosimilars (4,5).

The **Directive 2004/27/EC** which change the Community Code pointed in Art 15 out what should be covered by the biological medicinal product similar to the referent product. They couldn't be taken as biogenerics because of differences in the manufacturing processes, used substance, molecular properties and the therapeutically efficacy. The final text of this new legislation was approved on 31 March 2004 by the Council and was transposed into national law and in effect throughout the EU by November 2005 (4).

"Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of ***appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.*** *The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided" (4).*

The **Directives 2001/83/EC** and 2003/63/EG changed of specific marketing authorization application requirements, additional Modules 1, 2, 3 of the CTD format; particular the toxicological and clinic profile of Module 4 and 5 shall be provided.

The practical approach depends on the analytical possibility in order to comply with the "biosimilarity" on the respective manufacturing process, on the clinical and regulatory experience. The approach could be used for well characterized biotech medicinal products, all recombinant DNA/Hybridomtechnic and all products with derivate and conjugate. As biopharmaceuticals are defined by their production process, any change can impact safety and efficacy and therefore demands new approval (5).

Both the precise definition and the requirements for this therapeutic category in Article 10 (6) of Directive 2001/83/EC, as amended, have created a number of implications. The process for marketing authorization and preparation of biosimilar medicinal products is clearer and more precise than in the past, where even in case of a positive opinion of CHMP like INN Somatropin – trade name Omnitrop (London, 26 June 2003, CPMP/3184/03) - no marketing authorization on Somatropin (Omnitrop) was granted by the Commission as Omnitrop was not considered to have well-established use and thus was not authorized till the Directive 2004/27/EC had come into force. Omnitrop was authorized later like a first biosimilar product authorized by the Community after Review 2005 was introduced and the Directive was already in place. During 2006 and 2007 the number of submitted biosimilar applications to EMEA is 4 and 10 respectively.

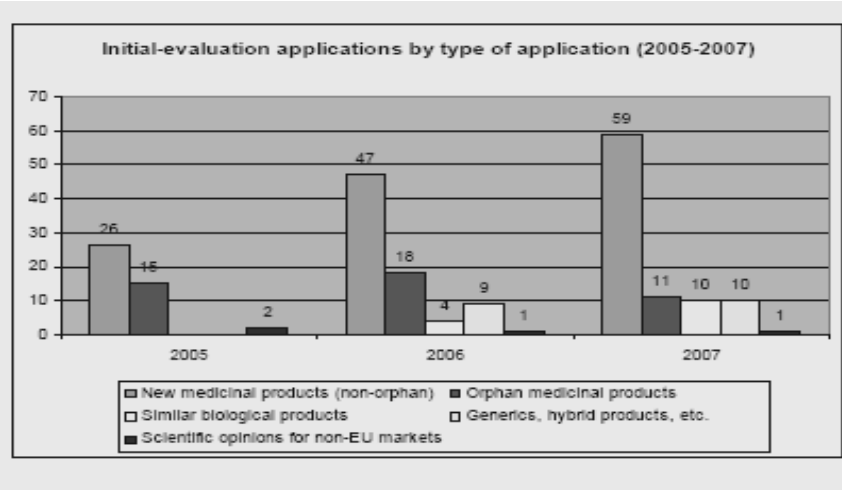


Figure 4. Biosimilar application to EMEA 2006-2007

The FDA legislation for "follow - on biologics"

The U.S. FDA concedes that it has no framework for "follow-on biologics" for the vast majority of therapeutic proteins subject to biologic licensing under the Public Health Service Act. The U.S. FDA concedes that it has no statutory framework for "follow-on biologics" for the vast majority of therapeutic proteins subject to biologic licensing under the Public Health Service Act. The U.S. agency builds a framework for a few large molecule products (human growth hormones, insulin etc.). An abbreviated process for limited types of biologics, types of tests to demonstrate structural similarity and comparability, immunogenicity testing requirements was outlined. Interchange ability for biologics represents a fundamentally more complex issue an approach and many guidelines were published. The FDA has pointed out concern for large comparative crossover studies for interchange ability rating and the acceptance of biosimilars by the medical community (6,7,8).

Approaches dealt with comparability in the EMEA and ICH guidelines

1. The comparability of biotechnical/biological products subjects to change in the manufacturing process in the clinical studies and after the marketing authorisation is subject of ICH guideline - ICH 5QE (10).

The terms "comparability" has two aspects, in the ICH Guidelines 5QE refers to changes in the established manufacturing processes within the same manufacturer of an existing biotech medicinal products. In that case the requirements for demonstrating the comparability are not the same than for demonstrating similarity of biological product (10).

With Commission Regulation 1085/2003/EC and 1084/2003/EC stipulating the need for more costly lengthy and complex Type II variation, where simpler IA or IB procedure would be applicable for small molecule. When manufacturer introduce major changes and then the regulator may view the resulting protein as an entirely new medicinal product with need to demonstrate comparable safety and efficacy.

1.1 The comparability of biotechnical/biological products subjects to change in the manufacturing process in the clinical studies (clinical development)

Determinations of product comparability can be based on quality considerations whether the manufacturer can provide assurance of comparability through analytical studies. Additional evidence from nonclinical or ***clinical studies*** is considered appropriate

when quality data are insufficient to establish comparability. The extent and nature of pre-clinical and ***clinical studies*** will be determined on a case-by-case basis where various factors shall be considered.

1.2. Demonstration of Comparability during Development

During product development, it is expected that multiple changes in the manufacturing process will occur that could impact drug product quality, safety, and efficacy. Comparability exercises are generally performed to demonstrate that pre-clinical and clinical data generated with pre-change product are applicable to post-change product in order to facilitate further development and support the marketing authorisation. Comparability studies conducted for products in development could be influenced by several of factors such as the stage of product development, the availability of validated analytical procedures, and the extent of product knowledge, which are limited at times due to the available experience that the manufacturer has with the process.

Comparability of biotechnological/biological products is required. The comparability exercise should utilise available information and will generally become more comprehensive. Process changes introduced in late stages of development and when no additional clinical studies are planned to support the marketing authorisation, the comparability exercise should be as comprehensive uses method. In that case some outcomes of the comparability studies on quality attributes can lead to additional non-clinical or clinical studies.

Due to the limitations of the analytical steps in early clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability, and therefore, bridging pre-clinical and/or clinical studies, as appropriate, might be needed. In order for a comparability exercise to occur during development, appropriate assessment tools should be used and analytical procedures used during development might not be validated, but should provide results that are reliable and reproducible (10).

1.3. Preclinical and Clinical Considerations

Comparability determination can be based on quality considerations if the manufacturer can provide assurance of comparability through analytical studies and additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability. All non-clinical and clinical studies are determined on a case-by-case basis in consideration of different factors, which include quality findings, the nature and the level of knowledge of the product and existing non-clinical and clinical data, relevant to the product (10,11).

2. The comparability of biotechnical/biological products subjects to change in the manufacturing process after the marketing authorisation (12)

A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted.

Where the relationship between specific quality, safety and efficacy issues has not been established, and differences between quality of the pre- and post-change product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not mean that the quality issues of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge could ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the product. To identify the impact of a manufacturing process change, a careful evaluation of all foreseeable consequences for the product should be performed.

The quality data on the pre- and post-change product are generated, and a comparison is performed that integrates and evaluates all data collected, e.g.,

- routine batch analyses;
- in-process control;
- process validation/evaluation data;
- characterisation and stability, if appropriate.

The comparison of the results to the predefined criteria should allow an objective assessment of whether or not the pre- and post-change products are comparable. The manufacturer could be faced with one of several outcomes, as follows:

- ***No adverse impact on safety or efficacy profiles is foreseen-*** pre- and post-change product are highly similar and considered comparable;
- ***The analytical procedures used are not sufficient to discern relevant differences*** that can impact the safety and efficacy of the product, additional testing (e.g., further characterisation) or nonclinical and/or clinical studies to reach a definitive conclusion should be performed;
- ***Differences*** in the quality attributes of the pre-change and post-change product observed, it can be justified that no adverse impact on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and post-change product can be considered comparable;
- ***Comparison of quality attributes*** and a possible adverse impact on safety and efficacy profiles cannot be excluded and the manufacturer should consider performing pre-clinical and/or clinical studies;
- ***Differences in the quality attributes*** are so significant that it is determined that the products are not highly similar and are therefore not comparable.

Pre-clinical or clinical data allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process. The products should have highly similar quality attributes biopharmaceutical product before and after manufacturing process changes and that there is no adverse impact on the safety or efficacy and immunogenicity, of the drug product occurred, based on an analysis of product quality attributes.

Comparability to reference medicinal products of similar biological medicinal products is subject of the EMEA guidelines

Biosimilar medicinal products are manufactured and controlled according to their own development. An extensive comparability exercise is required to demonstrate that the similar biological and reference products have similar attributes in terms of quality, safety and efficacy. The quality issues relevant for comparability presenting of similar biological medicinal products containing recombinant DNA-derived proteins are addressed in the

"Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: quality issues" (EMEA/CHMP/49348/05) (13).

When an application for biological medicinal product is containing a biotechnology-derived medicinal protein as active substance it refers to a reference medicinal product having been granted a marketing authorisation by an independent applicant after the expiry of the data protection period in accordance with Title III Chapter I, Article 10 as the amended Directive 2001/83/EC (4).

The Marketing Authorisation (MA) application dossier of a biological medicinal product claimed to be similar to a reference product already authorised shall provide a full Module 3 (quality dossier) and equivalent efficacy and safety of the similar biological medicinal product has to be demonstrated as well.

Biological medicines are usually complex and often heterogeneous, no modern analytical methodology may be adequate for full characterisation following process change. This is addressed in the released ICH and CHMP guidelines. The Directive 2003/63/EC and the guideline CHMP /BWP/49348/2005 stress that the impact of any process change need to be considered on a case-by case basis (5,11,13).

This may involve merely testing against the finished product specification but, in many cases, additional extensive characterisation is required which may need to include non-clinical and clinical studies. According to the European guidelines, a manufacturer can claim that a new product is similar to a therapeutic protein already on the market. The claim should be substantiated concerning quality, safety and efficacy, which are the three main parts of a new drug application. For all three parts of the dossier - quality, safety and efficacy of the same innovator product should be used as a reference.

Reference medicinal product is a medicinal product authorised in the EEA, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. The active substance of a similar biological medicinal product must be similar, in molecular and biological characteristic, to the active substance of the reference medicinal product.

The same reference product should be used throughout the comparability program for quality, safety and efficacy studies during the development of a similar biological medicinal product in order to allow the generation of coherent data and conclusions.

The pharmaceutical form, strength and route of administration of the similar biological medicinal product should be the same as that of the reference medicinal product and in case when the pharmaceutical form or the strength or the route of administration differ, the results of appropriate non-clinical/clinical trials must be provided in order to demonstrate the safety/efficacy of the similar biological medicinal product. Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case-by-case basis.

Reference Active Substance - the comparison of the biosimilar active substance to a publicly available standard as a reference (i.e. Ph.Eur, WHO, etc.) is not sufficient to demonstrate biosimilarity of the active substance since this material may not have known and defined safety and efficacy profiles and the manufacturer generally does not have access to the originator active substance, and cannot directly compare his active substance to the one used in the originator's medicinal product. Based on more than one analytical method the biosimilar manufacturer must demonstrate, that the active substance used in the comparability exercise is representative of the active substance present in the reference medicinal product.

Applicant should use various approaches to obtain representative reference active substance derived from the reference medicinal product in order to perform the comparative analysis at the active substance level, where this approach should be

appropriately validated. The suitability of the sample preparation process, and should include the comparison of the biosimilar active substance with active substance material derived from the reference and the biosimilar medicinal products (12).

Comparability exercise for demonstrating biosimilarity - analytical methods for biosimilar medicinal products

Characterisation studies "state-of-the-art" should be applied to the biosimilar and reference medicinal products in parallel at both the active substance and the medicinal product levels to demonstrate with a high level of assurance that the quality of the biosimilar product is comparable to the reference medicinal product.

Analytical considerations - suitability of available analytical methods - Given the e complexity of the molecule and its inherent heterogeneity, the set of analytical techniques should represent the state-of-the-art and should be selected by the manufacturer in order to detect slight differences in the characteristics of the biotechnology-derived product and the selected methods used in the comparability exercise would be able to detect differences in all quality aspects.

Biological activity - the comparability exercise should include an assessment of the biological properties of the similar biological medicinal product and the reference medicinal product. Biological assays using different approaches to measure the biological activity should be considered as appropriate. The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate and these assays should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable (10).

Purity and impurities - the purity and impurity profiles of the active substance and medicinal product should be assessed both qualitatively and quantitatively by a combination of analytical procedures for both reference and biosimilar products. Tithe manufacturer developing biosimilar products would normally not have access to all necessary information that could allow a comparison with the reference medicinal product. Information provides conclusions on the purity and impurity profiles. The impurities in the biosimilar product should be identified and compared to the reference product using state-of-the-art technologies and depending on the impurity it my be necessary to conduct trials in order to prove that there is no adverse impact of the surveyed biosimilar product.

Specifications are defined as described in ICH Q6B: *Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological. (16)* The acceptance criteria should be described and each acceptance criteria should be established and justified based on data obtained from lots used in nonclinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data and data obtained from the comparability exercise (quality, safety and efficacy).

The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

Conclusion

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

Although in Europe a regulatory path for approval of "biogenerics" was no longer possible, before end 2005 the regulatory path of biosimilars is directed to demonstrate considerable quality pre-clinical and clinical data.

The Regulatory authorities are breaking new grounds in regards with the biosimilar products. The balanced approach adopted by EMEA regarding the additionally published guidelines for biosimilars after Directive 2004/27/EC will allow evaluation on a case by case basis and the well defined framework can be built up on the based of the scientific knowledge.

The extent and the nature of non-clinical tests and clinical studies on biosimilar products are determined in consideration of various factors. According to Review 2005, many guidelines specifying the "appropriate pre-clinical tests or clinical trials" clarifying the general requirements for biological products in terms of safety and efficacy are issued. Nonetheless, there are still many questions about the data required to demonstrate biosimilarity with a biological reference product and how companies will manage after having received scientific advice by EMEA and new additional guidelines:

- Immunogenicity assessment of biotechnology-derived therapeutic proteins (guideline) Biosimilar medicinal products containing recombinant interferon alpha (guideline)
- Biosimilar medicinal products containing low molecular weight heparins (guidelines) are available (17).

EXERCISE

Task 1

Please provide the approaches dealt with comparability in the EMEA and ICH guidelines.

Task 2

Please provide where the definition for biosimilar is published and what is the difference between generic and biosimilar product.

Task 3

Please provide the main issues for comparability of biosimilar medicinal products.

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RECOMMENDED READINGS

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