

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Research Article.....!!!

Received: 23-03-2015; Revised: 29-03-2015; Accepted: 30-03-2015

REGULATORY REQUIREMENTS FOR BIOTECHNOLOGICALLY DERIVED PRODUCTS AND MARKETING AUTHORIZATION IN EUROPEAN UNION

Bhavin Trivedi, Krupa C. Thula*, Dilip G. Maheshwari

Department of Quality Assurance and Pharm. Regulatory Affairs, L. J. Institute of Pharmacy, L. J. Campus, Between Kataria Motor and Sanand-Sarkhej Circle, S. G. Highway, Ahmedabad, Gujarat-382210, India.

Keywords:

Biotechnology,
Biosimilars, CTD, European
Union

For Correspondence:

Krupa C. Thula

Department of Quality Assurance
and Pharm. Regulatory Affairs,
L. J. Institute of Pharmacy,
Ahmedabad, Gujarat-382210,
India.

E-mail:

krupathula@yahoo.com

ABSTRACT

Biotechnology revolution has made substantial contributions in the healthcare sector with more than 200 biologic medicines and vaccines profiting millions of patients worldwide and there are still more than 600 products which are under development. These products can now be produced by manufacturers other than innovator, with the expiry of some of patents. These Biotechnological medicines are commonly referred to as similar biological or biosimilars. These medicines offer a great opportunity to provide exceptional access to affordable healthcare for several lifesaving medicines. The prospect behind the attention towards biosimilars is due to its limitless prospectus to serve mankind. Europe's generic medicines companies possess the scientific knowledge and technical experience to produce safe and effective biosimilar pharmaceuticals. The legislative framework exists in Europe for the European medicines agency to evaluate the quality, safety and efficacy of these biological derived medicines. Since, 2006, the European Commission has authorized several biosimilar medicines declaring that each of them has been compared and matched with the reference medicinal products concerning quality, safety and efficacy parameters. These are mostly used medicines these days and it is also concluded that many patents for biotechnology has either been expired or ready to expire in the current era. It is terminated that European healthcare systems are eager for the cost relief and increased patient access to the life enhancing treatments that biosimilars are expected to bring.

INTRODUCTION TO BIOTECHNOLOGICALLY DERIVED PRODUCT ^[1]

A product that is similar to a biological medicine, a medicine whose active substance is made by living organism that has already been authorized that is called as reference medicinal product, is collectively known as biotechnologically derived products

Both similar biological medicinal product and reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same disease conditions. A biological medicinal product is a product that contains a biological stuff. A biological stuff is meant a substance which is produced by or extracted from a biological source and that needs a combination of physical -chemical-biological testing together with the production process and its control for its characterization and the determination of its quality. For example, monoclonal antibodies, medicinal products derived from human blood and human plasma, immunological medicinal products, recombinant proteins and advanced therapy medicinal products should be considered biological medicinal products.

Biotechnologically derived drugs are generic version of off-patent recombinant biotechnological drugs. Similar to generics, they can reduce costs but only by around 20-30% of original drugs price. Since the biotech drugs are highly expensive, even this reduction translates to a huge amount of money and wider availability of these drugs. This will also, in turn, sink health care costs worldwide

Examples of some available Biotechnologically Derived products are:

1. Recombinant proteins- Insulin, Interferon α , Interferon β , Tissue Plasminogen Activator
2. Monoclonal Antibodies- Herceptin
3. Artemisnic acid(Anticancer)- Produced from Yeast [Artemisinin-based combination therapies (ACTs)]
4. Hepatitis B vaccine, Epogen, Neupogen- rDNA derived products.

Other example is Enoxaparin sodium

Name: Enoxaparin sodium

Category: Anti-coagulant

Mechanism of Action:

The mechanism of action of Enoxaparin is anti-thrombin-dependent. It acts mainly by accelerating the rate of the neutralization of certain activated coagulation factors by antithrombin. The antithrombotic activity of Enoxaparin is well correlated to the inhibition of factor Xa. Enoxaparin interacts with Prothrombin, Antithrombin III and Factor X. Enoxaparin straps and accelerates the activity of antithrombin III.

Contraindications:

- Active major bleeding
- Well known hypersensitivity to Enoxaparin sodium

Reference Drug Product: Eparin

TABLE-1: GENERAL INFORMATION OF EPARIN

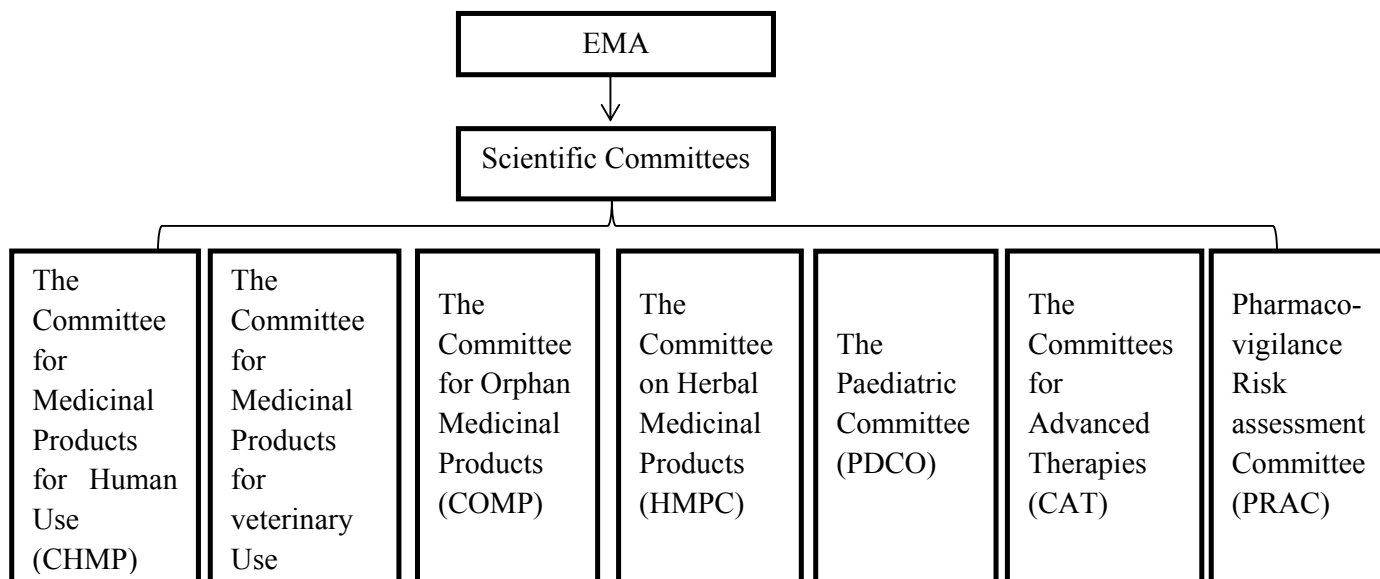
Name	Eparin
Agency product number	EMEA/H/C/000104
Active substance	Enoxaparin sodium
International non-proprietary name (INN) or Common name	Enoxaparin sodium
Therapeutic area	Venous Thrombosis
Anatomical therapeutic chemical (ATC) code	B01AE01

REGULATION OF BIOSIMILARS IN EUROPEAN UNION ^[2, 3]**EUROPEAN MEDICINES AGENCY:**

The EMA began its activities in 1995, when European system for authorizing medicinal product was introduced.

EMA's crucial role is the leadership for the protection and promotion of public and animal health, through the evaluation and supervision of medicine for human and veterinary use.

The EMA is primarily involved in the centralized procedure. In the centralized procedure, companies submit one single marketing authorization application to the EMA for granting marketing authorization in all 27 member states.



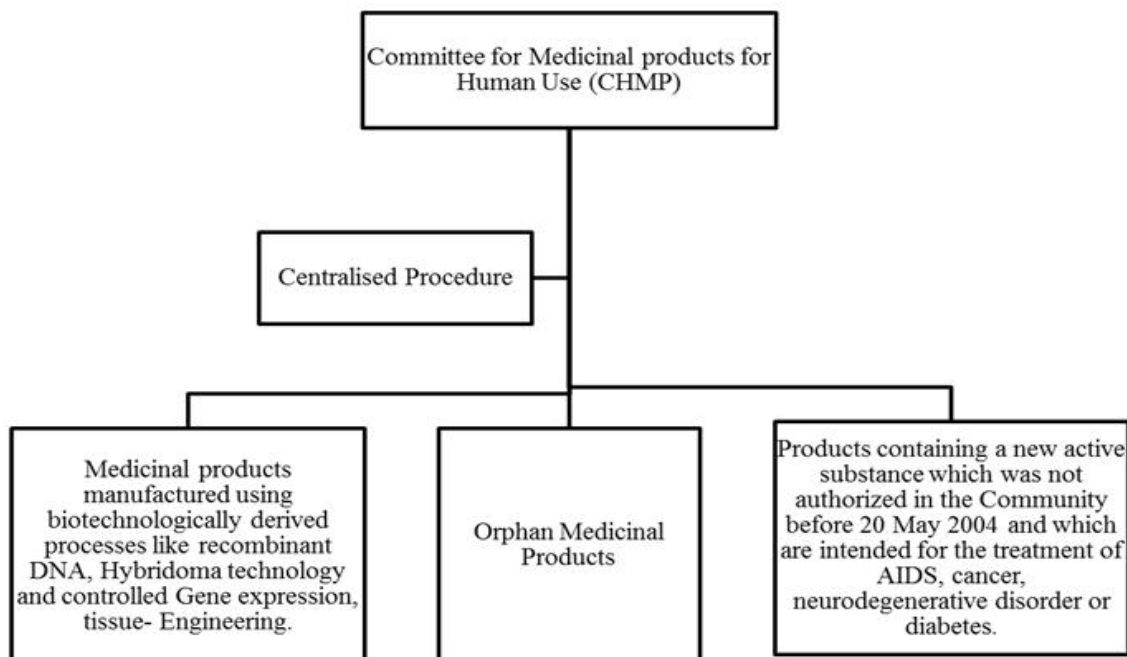


FIGURE-2: CENTRALIZED PROCEDURE

REGULATION PROCEDURE FOR CENTRALISED PROCEDURE ^[4]

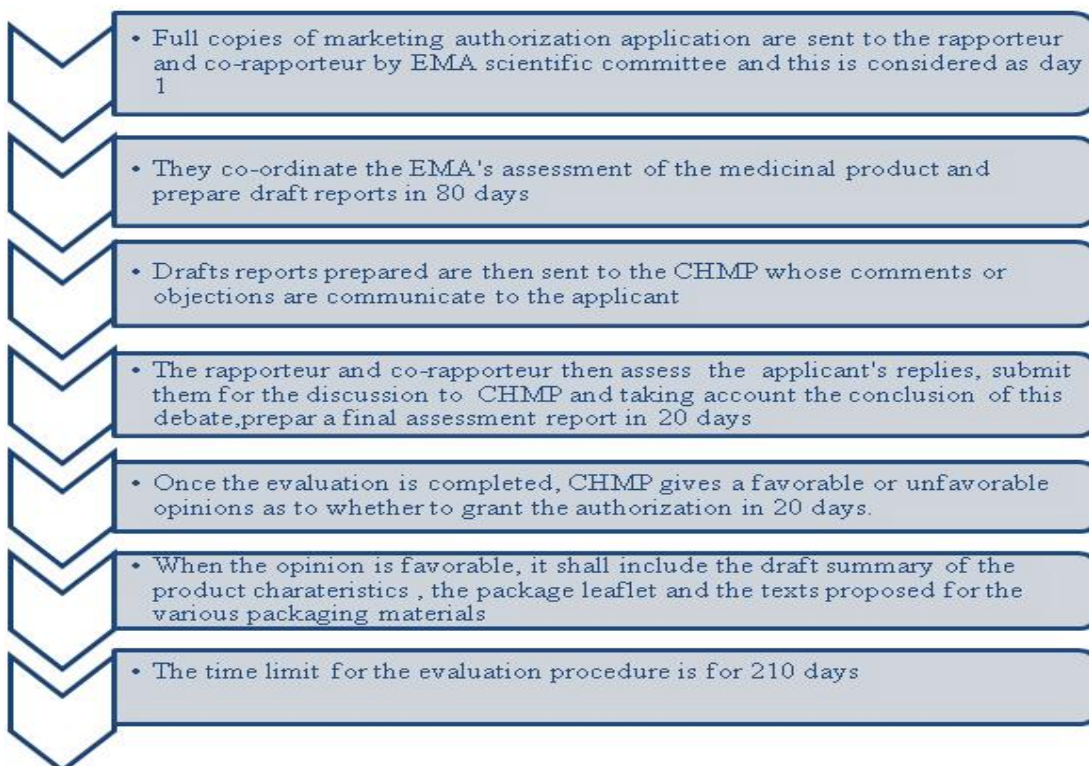


FIGURE 3: REGULATION OF CENTRALISED PROCEDURE

ORGANIZATION OF APPLICATION OF BIOSIMILARS FOR CENTRALISED PROCEDURE^[5]

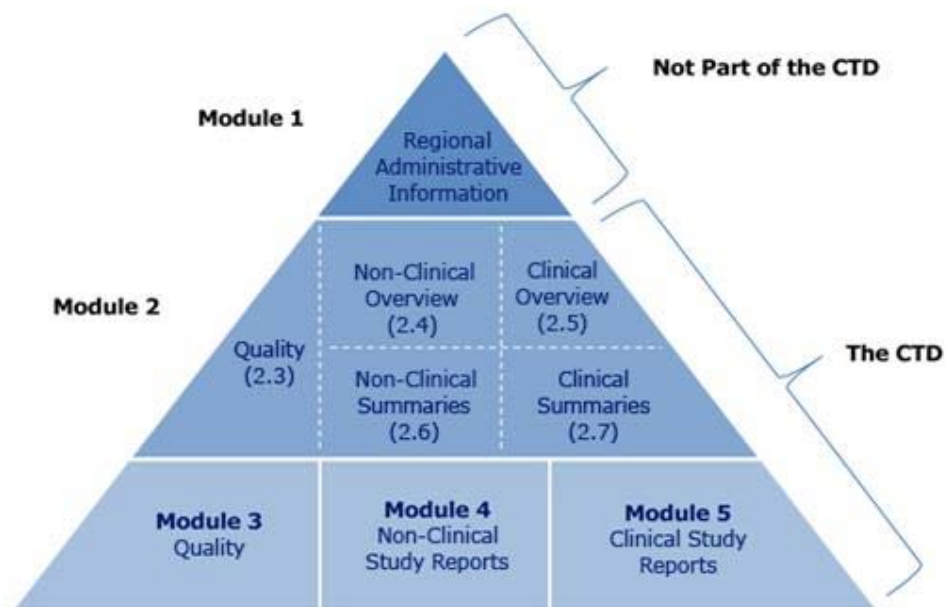


FIGURE-4: CTD TRIANGLE

Module 1: Administrative information and Prescribing Information: Module 1 of the common technical document describes the administrative information and prescribing information.

Module 2: Quality Overall Summary: The QOS should include sufficient information from each section to provide the quality statistics to the reviewer. The QOS should also highlight critical key parameters of the product to be granted and also should provide justification in cases where the guidelines are not given.

Module 3: Quality: Module 3 describes the format and organization of the chemical, pharmaceutical and biological data relevant to the application.

Module 4: Non-Clinical Reports: These reports describe the format and organization of the nonclinical (Pharmaco-toxicological) data relevant to the application.

Module 5: Clinical Reports: These reports describe the format and organization of the clinical data relevant to the application.

COMMON TECHNICAL DOCUMENT (CTD) FOR THE MARKETING AUTHORIZATION APPLICATION IN EUROPEAN UNION

Module 1- Administrative information and prescribing Information

1. Cover Letter:

- Applicant should provide one cover letter along with application. Applicant should request the regulatory authority for the approval of their product through cover letter.
- For paper accession, only the applicable cover letter for the member state concerned/ EMEA should be provided.

2. Application Form:

- Applicant should provide duly filled and signed application form along with application. The relevant application form has to be included, depending on the type of the application.
 - New applications and any extension applications
 - Variation applications.
 - Renewal applications

3. Product Information:

- Applicant should provide the detailed information about the product like product effect, side effect, pharmacology, information about labeling, information about package insert, information about product approval in the market.

SPC, Package leaflet and Labelling:

- Applicant should provide the summaries of product characteristics, draft label for product and should also provide package leaflet of product.
- Application for biosimilars comes under the centralized procedure. For application in the centralized procedure, the templates for product information are given below:
 - Name of medicinal product
 - Quantitative and qualitative composition
 - Pharmaceutical form
 - Clinical particulars like therapeutic indications, posology and method of administration, Contraindications, Special warnings and precautions for use, Interactions with the other medicinal products and other forms of interactions, pregnancy and lactation, effect on ability to drive and use machines and undesirable effects.
 - Pharmacological properties
 - Pharmaceutical properties
 - Marketing Authorization Holder
 - first authorization date/ authorization renewal
 - Date of revision of texts

Storage

Pack size available

Labelling:

Particularly to appear on outer carton

- Name of medicinal products
- Pharmaceutical form and contents
- Method and route of administration
- Special warnings for children

Expiry date

Manufacturing date

Special storage conditions

Name of marketing authorization proprietor and pertinent address of Marketing Authorization proprietor (holder)

Batch number

Mock-up:

- In this part applicant should provide a mock-up of the outer and immediate packaging of the medicinal product must be included with the application.
- A “mock-up” is a copy of the flat artwork design in full color, providing a replica of both the outer and immediate packaging that provides a two-dimensional presentation of the packaging/labeling of the medicinal product that is predominantly referred to as a “paper copy” or “computer generated version”.
- Applicant should also provide print copy of package insert for particular drug

Specimen:

- Applicant should provide actual carton, label, and package insert of product in this part of application. When specimens are submitted, a list detailing the specimens provided should be included.

Consultation with Targeted patient groups (User Testing):

- Applicant can use the different type of method for consultation but mainly used method is “user testing”. This method includes the test the readability of a specimen with a group of selected test subjects. It is not mandatory for generic drug application. Applicant may provide reference to already approved package leaflet. Results of such consultation should be presented in English for the centralized, decentralized and

mutual recognition procedure in the national language to permit the assessment of the test to be undertaken by competent authority responsible for granting the marketing authorization.

Product Information that is already approved in the Member States:

- In this part, applicant should provide the information about product from other member state in which product is already marketed. It is mainly required in case of mutual reorganization procedure but when the application follows the centralised procedure, this part becomes “Not Applicable”.

Braille:

- Applicant should name of medicinal product in the form of Braille format on the packaging.
- It is not mandatory to provide the information in Braille lippie. It depends upon the applicant, whether he is going to provide or not.

Information about experts:

- Applicant must provide detailed report by expert, which is responsible for information included in module 3, 4 and 5. Applicant should also provide brief information on the Qualification, training, and practical experience of the expert.

Quality:

- One responsible person should provide the statement indicating that he is responsible for information of quality part of dossier. If any query related to quality part arises then he is responsible for query.

Report must be provided in following format:

- According to his/her respective qualifications the undersigned expert declares hereby to have performed the duties set out in accordance with Annexure I, Part-I, 1.4 of Directive principle 2001/83/EC in European Union.

Quality:

- Name of the expert authoritative for information of module 1, 2 and 3
.....
- Signature of expert:
- Address:
.....
.....

- Date:
- Report also includes brief information on the educational background, training, and occupational experience of the expert.
- Same in case with non-clinical and clinical

Specific requirement for different types of application:

Information for Generic, 'Hybrid' or Biotechnologically derived drug Applications

- This is generic biotechnologically derived drug application therefore applicant should provide the sufficient information about product (up to approximately 5 pages), which should provide assurance the product is a similar of reference medicinal product.
- This summary should encompass all the details about the similar biological medicinal product, its active substance, raw materials and manufacturing process.
- Applicant should impart the information about any changes in product, which could affect comparability of two products.
- The comparability of medicinal product versus the reference medicinal product for quality, safety and efficacy should be described, and the reference medicinal product used throughout the quality, safety and efficacy development programme (as appropriate) should be defined.
- Applicant should comprehend the table "overview of the chosen reference product for comparability", which is available in full CTD guideline of EMEA.

Extended Data/Market Exclusivity

- This unit is required in the case where marketing authorization holder/applicant wishes to claim (Additional) data/market exclusivity when applying for a new indication or change in product strength or any other change in product.

Environment risk assessment

- In this part the applicant should provide the information that the product has any potential risk to environment or not. Risk included in this part mainly those which are arising from the use, storage and disposal of the medicinal product not for risks which are arising from the synthesis or manufacturing of medicinal product.
- Applicant should provide extensive documentation for the environmental risk assessment in a separate volume as part of Module 1 for paper submission.

GMO:

- This part is applicable to those products, which contain GMO (Genetically Modified Organisms) GMO means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

- Environmental risk assessment means the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs. Applicant should provide the information about any risk associated with the use, storage and disposal of product along with the appropriate risk management's strategy.
- Signature of the author with proper date, information on the author's educational, training and occupational experience (CV), and a statement of the author's relationship with the applicant, shall be provided.

Documentation on orphan market exclusivity of medicinal product:

- This section is required for all new Applications (not only for Designated Orphan medicinal products) as well as for Type II variations for new indications.

Information on pharmacovigilance:

Pharmacovigilance System

- Applicant should provide detail description about pharmacovigilance system, which is available for the purpose of reporting any adverse drug reaction and side effect of the product. Applicant should provide detail information about pharmacovigilance system like information about responsible person. Information about flow of ADR reporting, information about computer system use for ADR monitoring etc.

Risk-management System

- Applicant should provide detail description about Risk Management System, where appropriate. The information should be provided in the form of EU-Risk Management Plan, as outlined in Volume 9A of EUDRALEX i.e.-
 - Empowering EU governments for reciprocity of information and evaluate health events
 - Serving as a debate assembly that advises health ministers
 - Facilitating coordinated crisis response by EU governments.
 - Applicant can provide EU-RMP at any time during product life cycle, mean during both pre-authorization and post-authorization

Documentation related to clinical trials:

- A declaration that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC should be provided, where applicable.

- Statement should indicate that “clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC” together with a listing of all trials (protocol number) and third countries involved. This is applicable to those applications for which clinical trial report are submitted.
- Applicant should provide only the statement, whether trial conducted in other country as per ethical requirements of Directive 2001/20/EC or not.

Information relating to pediatrics:

- This is also applicable for all new Applications for a medicinal product which is not authorized in the EMA for new pharmaceutical forms, new indications and new routes of administration.

Module 2- Overall summaries of Common Technical Document

Introduction

Quality overall summary- Introduction

- Quality Overall summary- Drug substance (S)
- Quality Overall summary- drug Product (P)
- Quality Overall summary- Appendices (A)
- Quality Overall summary- CTD Regional data (R)

Non-clinical Overview

Clinical Overview

Non-clinical recorded written and Systemized Tabulated Summaries

- Introduction
- Pharmacology written summary
- Pharmacology tabulated summary
- Pharmacokinetics written summary
- Pharmacokinetic tabulated summary
- Toxicology written summary
- Toxicology tabulated summary

Clinical Summaries

- Biopharmaceutics summary and associated all Analytical methods
- Clinical pharmacological studies summary
- Summary of clinical efficacy
- Summary of clinical safety
- Literature references
- Synopses of individual studies

Module 3- Quality

Body of data

- Drug substance
- Drug product
- Appendices
- Regional information

Literature references

Module 4- Non-Clinical study Reports

Table of content

Study reports

Literature references

Module 5- Clinical Study Reports

Table of content

Tabular listing of all clinical studies

Clinical study reports

Literature references

DOCUMENTS REQUIRED FOR BIOSIMILARS IN EUROPEAN UNION ^[6]

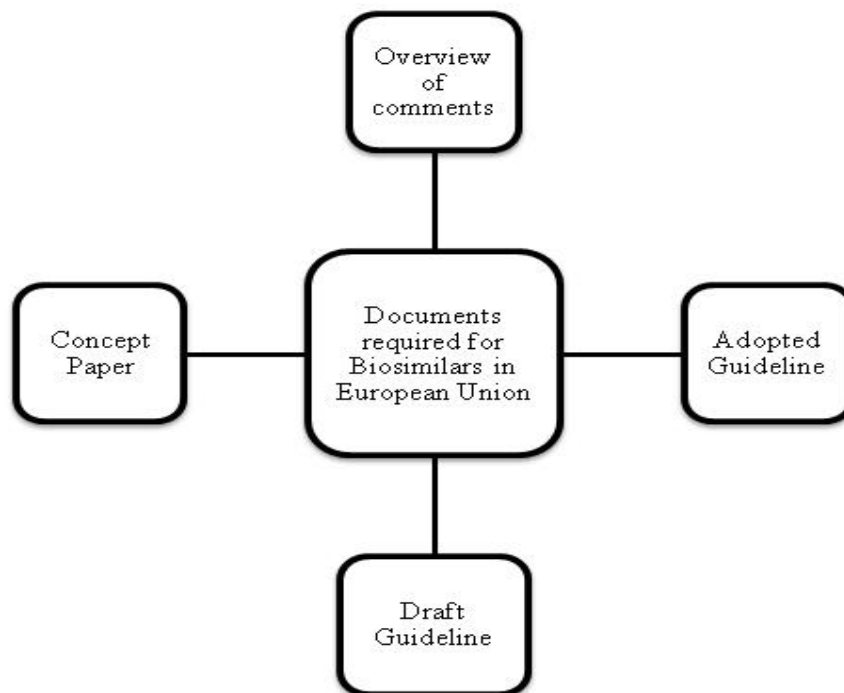


FIGURE-5: DOCUMENTS REQUIRED FOR BIOSIMILARS IN EUROPEAN UNION

1) Overview of Comments:

Interested parties/organizations/individuals that commented on the draft document as released for consultation.

2) Adopted Guideline:

It includes executive summary, its regulatory framework and its scope, its legal basis and relevant guidelines, its application of biosimilar approach, choice of reference product and principles of establishing biosimilarity.

3) Draft Guideline:

It also includes executive summary, its regulatory framework and its scope, its legal basis and relevant guidelines, its application of biosimilar approach, choice of reference product and principles of establishing biosimilarity.

4) Concept Paper:

Introduction: The purpose of this guideline was

- To initiate the conviction of similar biological medicinal products.
- To layout the primary principles to be applied.
- To provide applicant with a “User Guide”, showing where to find relevant scientific information in the various CHMP guidelines, in order to substantiate the claim of similarity.

Problem Statement:

- The proposition of biosimilarity may have to be explained in a clearer way.
- Numerous terms are in use for “biosimilar” or “Similar biological medicinal products”, and often the term “biosimilar” has been used in an inappropriate way.
- Discuss the practicality to produce the generic legal basis for some biological products.
- Some definite features require re-discussion and potentially a refinement.

Discussion (on the problem statement):

- The biosimilarity exercise follows the main concept that clinical benefit has already been established by the reference medicinal product, and that the aim of the biosimilar development programme is to establish similarity to the reference product, not clinical benefit. It may be of the benefit to amend the guideline accordingly to make this principle, and the conclusion clearer to the reader.

Recommendation:

- It is suggested to review the guideline on Similar Biological Medicinal Product (“overarching guideline”) in light of experience gained and to propose changes where necessary.

Proposed Timetable:

- Publicize for external consultation: November 2011
- Time limit for external comments: February 2011
- It is expected that the revised guideline will be released for consultation in the first semester of 2012.

Resource requirements for preparation:

- Experts from BMWP and BWP will develop the revision of the guideline in consultation with other CHMP working parties. Minimum one formal meeting of the drafting group will be required in the margins of the working party meetings.

Impact Assessment (anticipated):

- Expected advantage for industry and assessors of biosimilar products.

Interested Parties:

- The Competent authorities of the member states.
- Pharmaceutical industry.

References to literature, guidelines, etc.

- N/A

CONCLUSION

Biosimilars presents several eccentric policy predicaments in case of their safety and efficacy parameters. Commencing a pathway for the approval that points to the safety and efficacy challenges is a problematic process. This evaluation should inaugurate the key similarities between the two and then after determine the differences between them. The legislation should also identify the level of clinical data that are essential for evaluation and approval of the biosimilars. Legislation for biosimilars also calls for post-marketing safety studies consequently to monitor any potential differences in safety and efficacy between the biosimilar and original drug that becomes apparent once it enters in to the market. Legislation for biosimilars should always define the standards for the compatibility of the biosimilars with the original drug.

European Union biosimilar portfolio is well developed and still continuously growing and its biosimilar related guidelines are also continuously growing for advanced execution. Also, EU experiences important reference for others. Main challenges for the future of biosimilars in EU are like moving towards more complex biosimilars like as monoclonal antibodies and considering the possibility of a global development of biosimilars.

ACKNOWLEDGEMENT

The authors are thankful to Dr. K. Pundrikakshudu, Director of L. J. Institute of Pharmacy, Ahmedabad, India for providing facilities and encouragements to carry out the research work.

ABBREVIATIONS

BMWP: Biosimilar Medicinal Working Party

BWP: Biologics Working Party

CHMP: Committee for Medicinal Products for Human Use

CTD: Common Technical Document

DNA: Deoxyribonucleic Acid

EMA: European Medicines Agency

EU: European Union

GMO: Genetically Modified Organisms

QOS: Quality Overall Summaries

REFERENCES

1. International Conference on Harmonization. Preclinical Safety Evaluation of Biotechnologically Derived Pharmaceuticals S6(R1). [Online]. 2013 Dec [cited 2015 March 2]; Available from: URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf
2. The European Medicines Agency. Structure and Regulatory Procedures. [Online]. [cited 2015 March 4]; Available from: URL: http://www.mbc.unimi.it/Jmonnet/ammannati/locandina_jablonsky.pdf
3. Ministry of Health and Regulatory Affairs. Types of application. [Online]. [cited 2015 March 8]; Available from: URL: <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Typesofapplication/index.htm>
4. European Medicines Agency. Centralised Procedure. [Online]. [cited 2015 March 10]; Available from: URL: http://ec.europa.eu/health/authorisation-procedures-centralised_en.htm
5. International Conference on Harmonisation. Organization of the common Technical Dossier documents for the registration of Pharmaceuticals for human use M4. [Online]. [2015 March 11]; Available from: URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3_organisation.pdf
6. European Medicines Agency science medicines health. Multidisciplinary: Biosimilar. [Online]. [cited 2015 March 12]; Available from: URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp.