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OVERVIEW OF BIOTECHNOLOGICALLY DERIVED PRODUCTS AND VARIOUS REGULATORY PARAMETERS FOR BIOSIMILARS IN EUROPEAN UNION

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ABSTRACT

The prospect and feasibility behind this kind of attention towards biotechnology and biosimilars is due to its boundless prospectus to serve mankind. So far, biotechnology has touched our lives in all directions, such as, health, food and animal life. It is also essential to notice the importance and potential of biotechnology for the improvement of our environment and for better living. We also retire for the day with bedside medicines either to keep us healthy or to control chronic diseases, like stroke, arthritis, diabetes, which makes our life better. So, a strict regulation is required for the biotechnology products and biosimilars in any country because of its safety and efficacy issues. 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. Also the innovator drugs are costly, so regulation of biosimilars has become the necessity. So, the regulation, registration, documents for biosimilars, Aseptic process, labeling requirements, ADR reporting system for biosimilars are some important regulatory parameters which are focused in the article.

Keywords: Biotechnology, Biosimilars, European Union, Labeling, Pharmacovigilance.

INTRODUCTION

Biotechnology[1, 2, 3]

It seems like the word "Biotechnology" has become the "Buzz" in today's world. The word 'biotechnology' has received tremendous importance and significance during last few decades, which is just unrivalled.

Biosimilars

Unlike generic medicines where the active ingredients are identical, biosimilars are similar of originator biologic but not the very same copies of the originator biologic. They are related to original biologics, but not the same. Biologics made by different manufacturers differ from the original product and from each other. The twist of biologics prevents identical copies and is therefore not is same as generic drugs. Due to their complex structure and the processes involved in manufacturing, biosimilars must be determined on the basis of quality, non-clinical and clinical data to be similar to an original biologic in terms of structural characteristics, and safety and efficacy should also be same as that of the original biologics. Minor differences with the active ingredient are expected and granted so long as any such differences are demonstrated not to be clinically significant. A wide range of biologic drugs patents are expired or ready to expire,

which has enlarged interest in the development of biosimilars.

History

The term biotechnology was first introduced in 1919 to describe the interface between biology and human technology for the conversion of raw materials into socially valuable products. At that time, the focus was on food production but by the 1940s early progress in the technology had led to the development of medicines; enabling the production of antibiotics, such as penicillin, which continue to be used to control infectious diseases. An ideal definition of biotechnology was not reached until the United Nations and World Health Organization accepted the 1992 Convention on Biological Diversity and defined biotechnology as "any technological application that uses living organisms, biological systems, or derivatives, to make or modify products and processes for specific use".

Biotechnology in Medicines

Biotechnology has empowered the discovery of treatments for a variety of life threatening diseases. Worldwide, there are over a 350 million patients which get benefit from approved medicines manufactured through biotechnology. Recently, over 650 new biological medicines and vaccines are going to develop to treat most of the critical diseases. As the exclusive rights for these biological medicines expire, similar biological medicines, or "biosimilars", are being developed, with some previously available products which are known as 'reference products'. Biological medicines are comprised of proteins and other substances that are often naturally produced in the human body. In healthcare, biotechnology is being used in three primary areas: therapeutic medicines, vaccines and diagnostics. When compared to chemical medicines, biological medicines are generally more complex and usually much larger in size than chemical medicines. The complexity is predominantly due to the manufacturing process for biological medicine, as they are developed in living system the exact characteristics and properties are highly dependent on the manufacturing process.

Biotechnologically Derived Products

A Biotechnologically derived product is a product that is similar to a biological medicine (a medicine whose active substance is made by living organism that has already been authorized, the so-called 'reference medicinal product'. Similar biological medicinal product and its 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 substance. A biological substance is produced by or extracted from a biological source and that needs a combination of physico-chemical-biological testing together with the production process and its control for its characterization and the determination of its quality. For example, monoclonal antibodies (mAbs), recombinant proteins, medicinal products derived from human blood and human plasma, immunological medicinal products and advanced therapy medicinal products should be considered biological medicinal products.

Biotehnologically 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.

Development of Biologic Medicines

Biologic medicines are made in living organisms to produce proteins for the treatment of various life threatening diseases, mostly by genetically modifying cell lines. DNA technology is often used to position desirable genes or remove undesirable ones within a living cell. Biotechnology has led to the development of most important medicines, including monoclonal antibodies for the treatment of cancer, human insulin for the treatment of diabetes and the cloning of the naturally occurring protein. The genetic code of a chosen protein, like as insulin or an immune system antibody, is recognized and

replicated by combining different segments of DNA to build a functional DNA sequence. Now, the DNA sequence is introduced into the host cell of a living organism, such as yeast, bacteria or altering the cell's genetic makeup and coding it to produce the chosen protein.

Regulation of Biosimilars in European Union[4]

EU Legal and Regulatory Pathway

In the European Union, marketing authorization applications for biotechnology-derived medicinal products, including biosimilar medicinal products, are by law reviewed centrally by the European Medicines Agency (EMA). The resulting marketing authorization is valid in all EU Member States. The EU is the first region in the world to have set up a legal framework and a regulatory pathway for "similar biological medicinal products", commonly called as "biosimilars". The EU regulatory framework inspired many countries around the world e.g. Australia, Canada, Japan, Singapore, USA etc. as well as the World Health Organization (WHO).The concept of a "similar biological medicinal product" was adopted in EU pharmaceutical legislation in 20004 and came into effect in 2005. In the course of 2012, the EMA included a definition of a "biosimilar" in an EMA procedural guidance document "A similar biological medicinal product, also known as "Biosimilar", is a product which is similar to a biological medicine that has already been authorized, the so-called "reference medicinal product". A similar biological medicinal product and their reference medicinal products is expected to have the same safety and efficacy profile and are generally used to treat the same conditions. The reference medicinal product, to which the application for marketing authorization for a biosimilar medicinal product is concerned, "is a medicinal product which has been permitted for marketing authorization by a Member State or by the European Commission on the basis of a complete dossier submission, i.e. with the submission of Quality, Pre-clinical and Clinical data" and in consensus with the provisions, applicable to originator medicinal products.

Comparability and Biosimilarity in European Union

Comparability between the reference and the biosimilar medicinal product is the core principle of a biosimilar development. The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological medicinal product and for development of a biosimilar medicinal product are the same. However, as recognized by Weise et al in a scientific journal, data requirements for biosimilar medicinal products are higher than when assessing a process change for the same product. "It should be noticed that a comparability exercise is also required for originator biological medicinal products when changes to the manufacturing process are made. Indeed, such changes are frequently introduced throughout a product's lifecycle (e.g., to improve the quality or to increase the yield of the product). As an out-turn, the quality profile of the biological product may evolve over its life cycle but would still be considered as comparable to the product before changes were made as long as relevant impact on safety and efficacy has been excluded with sufficient confidence.

"Biosimilarity" is a regulatory term used in the European Union to designate the comparability between a biosimilar and its reference medicinal product. The marketing authorization of a biosimilar medicinal product is based upon a regulatory assessment that the applicant has demonstrated the product's similarity to the reference medicinal product by the means outlined in the Committee for Medicinal Products for Human Use (CHMP)/EMA specific "scientific guidelines on biosimilar medicines". Biosimilar medicinal products are systematically developed to be highly similar to the reference medicinal product with regards to quality, safety, and efficacy.

This is followed by a comparability exercise performed in several steps:

- First step-quality comparability (physicochemical and biological comparability)

- Second step- non-clinical comparability (comparative non-clinical studies)
- Third step- clinical comparability(comparative clinical studies)

Quality comparability is established with regard to the molecular structure as well as with regard to the functionality and must be demonstrated with comprehensive analytical characterization, relevant receptor binding studies and bioassays, all to be performed with the biosimilar and the reference medicinal product in a rigorous comparative manner. The non-clinical and clinical comparability then provides the confidence that any differences observed at the quality level have no impact on the safety and efficacy of the biosimilar medicinal product when compared to the reference medicinal product.

Registration of biosimilars in European Union[5]

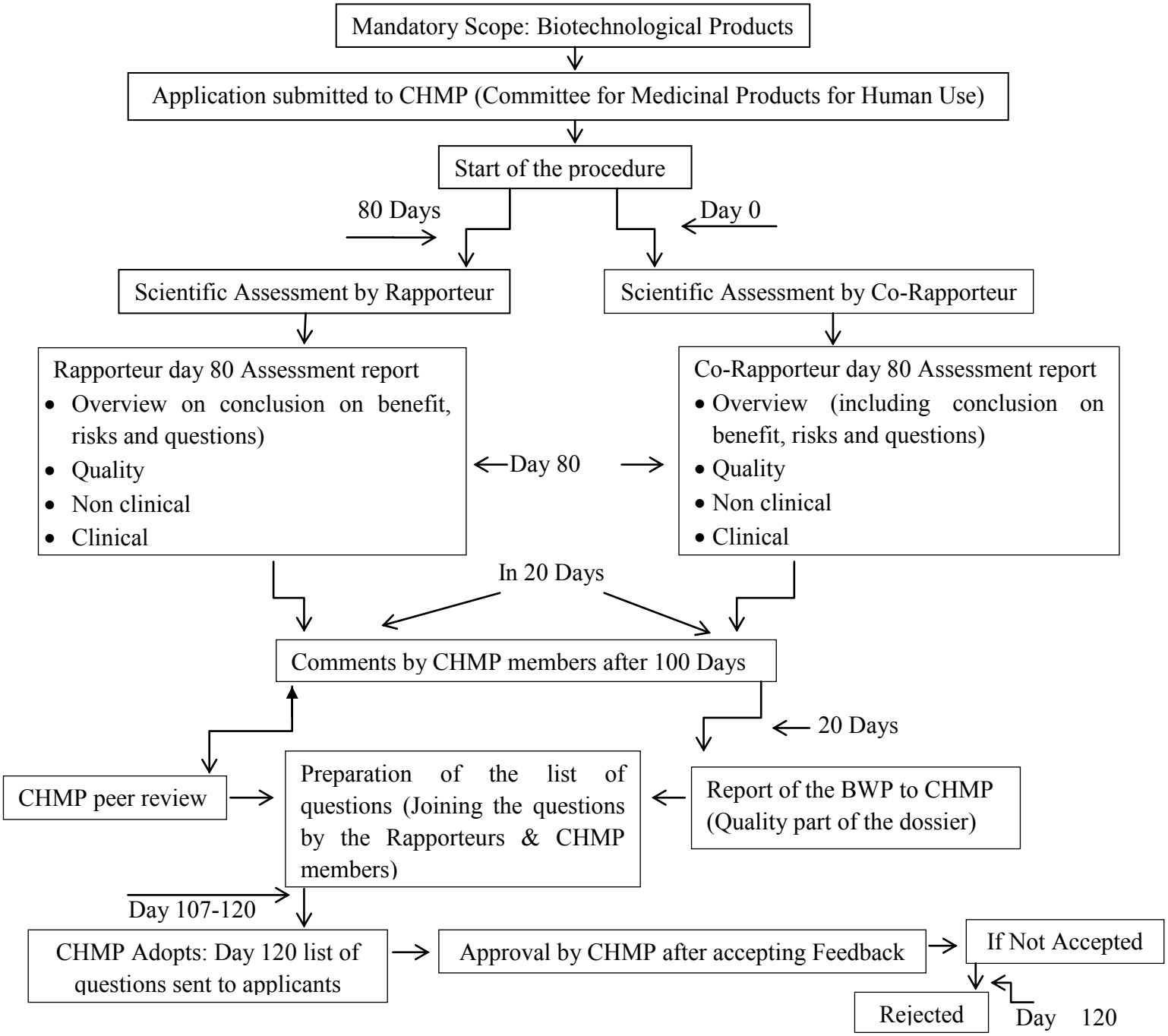

Figure 1: Flow chart for the Registration of biosimilars in Europe

Table 1: Some Europeans Medicines Agency (EMA) approved biosimilars[3]

Name of Product	Active Substance	Therapeutic area	Authorization Date
Abasria	Insulin Glargine	Diabetes	9 September 2014
Accofil	Filgrastim	Neutropenia	18 September 2014
Bemfola	Follitropin alfa	Anovulation (IVF)	24 March 2014

Table 2: Documents required for biosimilars according to EMA[6]

Topic	Documents	Reference number	Publication Date	Effective Date
Similar biological Medicinal Products	➢ Overview of Documents ➢ Adopted Guideline ➢ Draft Guideline ➢ Concept Paper	CHMP/437/04 Rev. 1	October 2014	30 April 2015

- Overview of Documents
- Adopted Guideline
  - Introduction (Background) and scope
    - Regulatory Framework
    - Scope
  - Legal Basis and Relevant Guidelines
  - General Principles
    - Application of Biosimilar Approach
    - Choice of reference products
    - Principles of establishing Biosimilars
- Draft Guideline
- Concept Paper
  - Introduction
  - Problem Statement
  - Discussion (On the Problem Statement)
  - Recommendation
  - Proposed Timetable
  - Resource requirements for preparation
  - Impact assessment (anticipated)
  - Interested Parties
  - References to literature, Guidelines, etc.

Aseptic Manufacturing Process for Biosimilars in European Union

Sterility is best achieved through sterile filtration of the bulk using a membrane filter (0.2 µm or less) in sterile container closure systems and working in a clean area. Drug product, container, and closure are first subjected to sterilization methods separately and appropriately. So this is a complex working procedure, which consists of several consecutive and necessary working steps, each of them contributing its part towards the aim of manufacturing an aseptic product (prevention of microbial contamination). Any manual or mechanical manipulation of the sterilized drug, components, containers or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. Aseptic manufacturing is used in cases, where the drug substance is in stable against heat; hence sterilization in the final container closure system is not possible. Aseptic manufacturing means that the used drug substance and excipients were sterilized appropriately and all materials, equipment and container closure systems were used only after sterilization. All working steps were performed in so called clean areas to avoid contamination.

Flow Chart

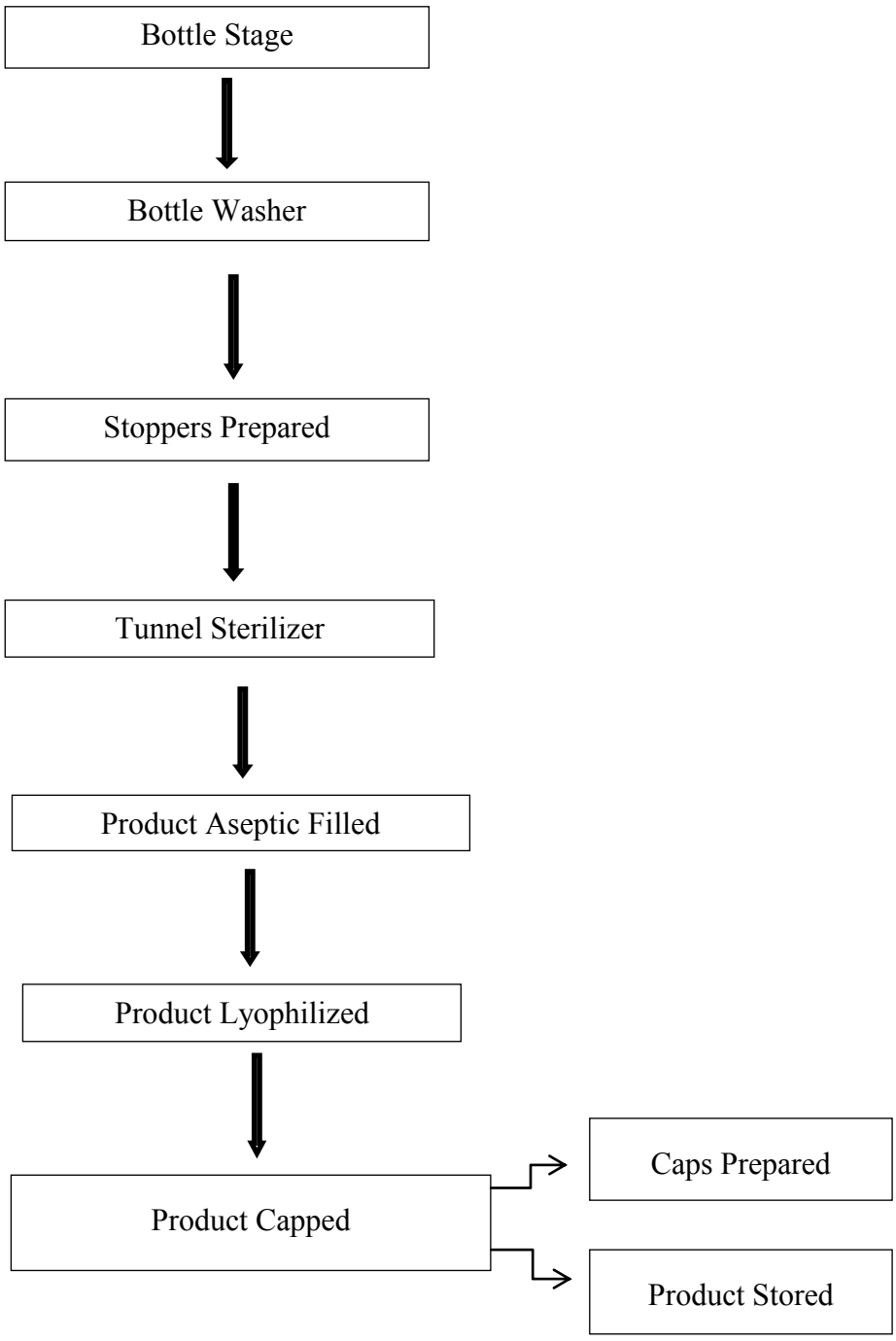

Figure 2: Flowchart for the sterilization of bottles during aseptic manufacturing process

As in the above flowchart, the sterilization process for the bottles during aseptic manufacturing process starts with the bottle stage in which the bottle is kept on the bottle stage from where it is proceed to the bottle washer for washing and cleaning. On the other side, the bottle stoppers are prepared. After washing and cleaning process, the process move towards the sterilization in which the bottle is passed through a tunnel in which the sterilization process is carried out. Then the bottle is treated with aseptic product filling. After the filling of the product, it undergoes the lyophilization that is called as product lyophilization. Once the product lyophilization process completes, the bottle goes through the product capping, where the caps are prepared, capped and stored.

Requirements for Aseptic Filling for Vials

Vial is the packing materials (container) which is used in aseptic filling of dry injectable powder.

Flow of Vial During Aseptic Manufacturing

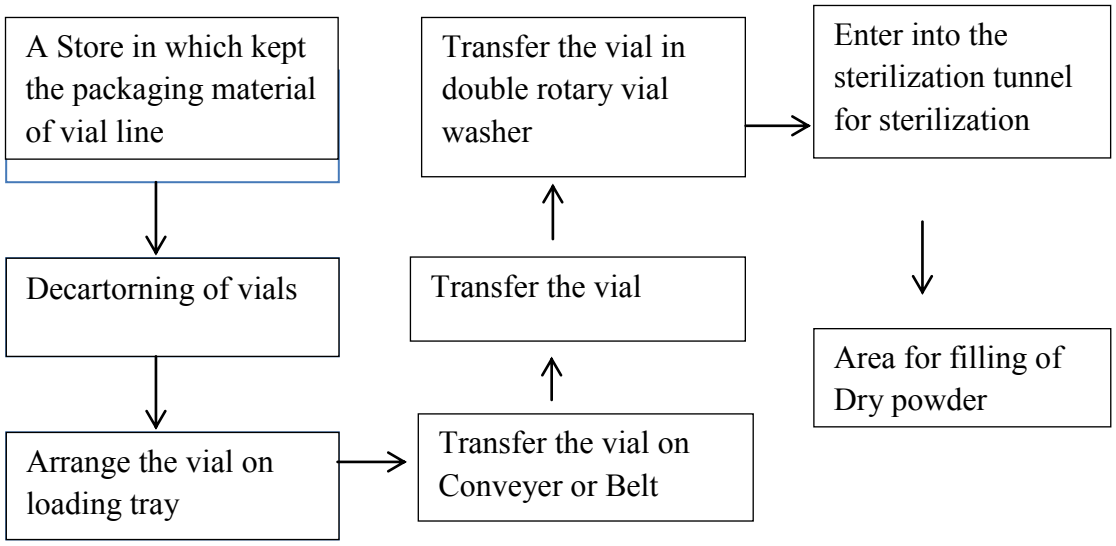

Figure 3: Flowchart for flow of vial during aseptic manufacturing process

Likewise as bottles, vial used for the filling of the dry injectable powder also undergoes the aseptic manufacturing process in which first step is to put the all vial lines for packaging in the appropriate sore and storage conditions. After the completion of first step, second includes the decartorning of the vials from the sterilization. Now the vial to be sterilized is arranged on the loading tray. There, from the loading tray, vials are transferred on the conveyer or belt where these are proceed to the further transfer of vial into double rotary vial washer for proper washing and cleaning. Now after proper washing and cleaning of the vials, these are entered into the sterilization tunnel for the throughout sterilization of the vials. Then after these vials are entered into the area where there filling of the dry powder takes place.

Labeling Requirements for Biosimilars in European Union[7]

As defined by EMA the product labeling, in particular the Summary of Product Characteristics (SmPC) is a key component of the marketing authorization of all medicines in the EU and the basis of information for healthcare professionals on how to use a medicine safely and effectively. The European Biopharmaceutical Enterprises (EBE) welcomes the Biologics Working Plant (BMWP's) acknowledgement that adequate scientific information for biosimilars should be provided and in this regard the product label is the essential component for prescribers. It was concluded that a robust regulatory framework, effective risk management, transparency and continued education would help engender confidence in the appropriate use of innovator biological medicines and biosimilars.

Labeling Standard of Biosimilars: Why A Combined Approach Fits The Purpose

Three possible scenarios for the labeling (including SmPC and PIL) of biosimilars have been briefly described in Table 2, which gives an overview of the approaches and relevant key considerations.

Table 3: Description and key considerations of the proposed labeling options

Labeling Option	Description	Key Considerations	Examples of Key Regulators
Approach A	Generic approach: label to be an identical copy of the reference product	• Biosimilars might have fewer indications than the reference product and generic labeling approach may create confusion. • In this scenario, preclinical/clinical data for biosimilars would be excluded • SmPC needs to reflect the data generated to support marketing authorization • Comparative clinical data are of high relevance e.g. comparative immunology	EMA has used this approach to Remsima. The challenge of how to handle a reduced number of indications listed in the therapeutic indications sections did not arise as all indications were granted in this case.
Approach B	New product approach: Label only includes information on the biosimilars	• Does not take into account the known proof of similarity, e.g. long term safety profile, of the reference product. • Incomplete safety and efficacy information • Impractical for physician to refer back to reference product label • Could imply that authorization of biosimilar should be based on a lower level of evidence as less data would be required.	There is no example where regulators have taken this approach
Approach C	Combination approach: Label to be a combination on information on both the biosimilar mAb and the reference product	• Full and transparent disclosure of all data generated by biosimilar and originator which maps to standard PI sections • Clearly identifies source of data (Biosimilar Originator)	Health Canada has used this approach for Remsima; Swissmedic request, e.g. the information for healthcare professionals must also clearly identify the data that specifically applies to the biosimilar

EMA: European Medicines Agency; mAb: Monoclonal antibody: SmPC: Summary of Product Characteristics

EBE believes that Approach C is best suited. First of all, the unique considerations that apply to biosimilars (as compared to generics) exclude Approach A as a suitable option because it does not include relevant data the biosimilar manufacturer has compiled for its clinical comparison. Yet prescribers may want to see such biosimilar data alongside that for the

originator, as this will explain the basis for which indications have been approved. Furthermore, by using biosimilar data only (Approach B) characterization data is not included, thus neglecting the proof of biosimilarity. This characterization assumes that the long-term safety profile for the reference product should be applied to the biosimilar and that therefore class warnings, etc.; are appropriate for both products. In addition, because Approach B only provides biosimilar data, this also means that the prescriber needs to refer back to the reference product's label to complete their understanding of the product, and this is not practical. Approach C is the more balanced approach that can enable transparent disclosure of all relevant information related to the biosimilar and the reference product. Furthermore, Approach C is an approach that also allows transparency on where the data generated comes from, either from the originator or from the biosimilar.

EMA: European Medicines Agency; mAb: monoclonal antibody; SmPC: Summary of Product Characteristics

Five Points That Show the Need for Detailed Specific Guidance on What a Transparent Label for Biosimilars Would Look Like

EBE identifies that there are five important points for consideration, which arise when prescribers refer to the SmPC of a biosimilar, and these should be considered in any policy guidance related to the matter. They are:

- **Quantity of Data**
  There is the concern that physicians would directly relate similarity to the amount of clinical data provided in the SmPC. However, in accordance with the biosimilar concept the more similar the product is to its reference product, the less clinical data that will need to be generated during its own development. Therefore, only by the SmPC containing a combination of information relevant to the originator and biosimilar could the CHMP conclusions be provided to the prescriber.

- **Extrapolation of Indication**
  In terms of labeling, taking a generic approach, the identical product label, could lead to misperceptions by physicians that these are identical products, which biosimilars cannot be.

- **Switching**
  Decisions around switching require transparent product information so that prescribers can make their choices confidently. As the EMA Q&A document on biosimilar medicines states the following about switching: 'For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist'.

- **Pharmacovigilance**
  In supporting the aims of the Pharmacovigilance Directive reporting requirements for biologics (including brand name and batch number) should be included on the prescription in order to improve traceability and enhance Pharmacovigilance.

- **Drift**
  Once the biosimilar has been approved, there is currently no regulatory requirement for biosimilarity to be re-established at any time. It is well acknowledged that the reference product and its biosimilar will have separate life-cycles which could affect the safety and efficacy profile, while having no change to the other.

Table 4: Sources of product information in the EU

EU Documents	Basic Principles
Summary of product Characteristics	Summarized information to be included, e.g. needed for MA, meant for physicians, to inform them on how the specific product is to be used
Patient Information Leaflet	Summarized information to be included to enhance a patient's understanding of their product
European Public Assessment Reports (EPAR)	Summarized information on the basis for approval of a given medicine, e.g. EPARs is primarily designed to provide information on how a medicine was assessed by EMA and to describe scientific conclusions of the relevant agency committee.

ADR Reporting System for Biosimilars in European Union[3]

Every pharmaceutical company must have a Pharmacovigilance system in place which is used by the marketing authorization holder to monitor the safety of authorized medicinal products and detect any change to their benefit-risk balance. This Pharmacovigilance system is subject to inspections by the regulatory authorities. Every company is required to submit a Risk Management Plan (EU-RMP) together with the marketing authorization application. The EU-RMP also describes the measures the applicant intends to introduce to prevent or minimize any potential risks when using the medicinal product, including the measurement of their effectiveness in clinical practice. Under the new EU pharmacovigilance legislation, a marketing authorization can be granted subject to the condition to conduct post-authorization safety (PASS) and/or post-authorization efficacy studies (PAES).Such studies will be part of the pharmacovigilance plan of the EU-RMP. The aim of a PASS is to identify, characterize or quantify a safety hazard or to confirm the safety profile of the medicine, or to measure the effectiveness of the risk management measures during its lifetime. The EU-RMP for a biosimilar medicinal product is product-specific. Therefore EU legislation requires that for every adverse reaction report of a biological medicine, the name of the medicine, as approved, and the batch number should be included in the ADR report. For the same reason, and as mandated by the new EU Pharmacovigilance legislation, "the Member States shall ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of medicinal product and the batch number. The new EU pharmacovigilance legislation has also introduced a new approach which consists in publishing a list of medicines subject to additional monitoring for a set period. The EMA and the Member States will work together on this public list and further steps have been taken in the course of 2012. Medicinal products subject to additional monitoring are to be identified as such by a black symbol and an explanatory statement will be added to the summary of product characteristics and in the package leaflet.

CONCLUSION

The arrival of biosimilars presents several eccentric policy predicaments. Initiating a pathway for the approval that points to the safety and efficacy challenges is a tricky process. For the proper regulation of biosimilars, a country should have proper legislation which should require a baseline scientific evaluation of original innovator drug and biosimilar. 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. Legislation for biosimilars also should provide the sufficient inducements to the research-based companies. Biosimilars presents significant opportunities- whether for development in the health care sector or for treating patients- mostly in over the long terms. Concurrently, policy makers must ensure that high standards of public safety are maintained to protect patients and that the right IP framework is in place to motivate innovators. If so, we can reasonably expect favourable results from the greater use of biosimilars improving health care standards in both the developed and developing countries.

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