Chapter 6

Scientific and Regulatory Perspective on Monoclonal Antibody Biosimilars

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Additional information is available at the end of the chapter

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Abstract

Similar biotherapeutic products (SBPs), also called biosimilars, exhibit similar biological and clinical properties to authorized reference products. Biosimilars, including small molecules like erythropoietin and complex macromolecules like monoclonal antibodies (mAbs), have been used extensively in disease treatment. Monoclonal antibody biosimilars have gradually become a dominant development in the global pharmaceutical industry since their patents or data protection have been expired or nearing expiration. Since the mAb biosimilars are complex biological macromolecules with various post-translation modifications, it is important to evaluate whether these tiny differences significantly affect the quality. From a regulatory perspective, the comparability study needs to be performed to demonstrate that the quality, safety, and efficacy are similar to the biological reference. Based on these comprehensive comparative results, the indicated extrapolation might be acceptable. Post-market surveillance is also required because of unexpected biological variation caused by slightly different manufacturing processes. This chapter presents the scientific and regulatory considerations for monoclonal antibody biosimilar products for manufactures and for the regulatory authorities to administrate wisely and comprehensively.

Keywords: biosimilar, monoclonal antibody, biosimilar monoclonal antibody, regulatory perspective, comparability study

1. Introduction

The developments of "copies" of drug products, such as generic drugs or biosimilars, have become the trend in the pharmaceutical markets. However, in fact, they are strikingly different in respect of the structure, developments, and approval requirements [1]. Unlike the

generic drug, which is chemically synthesized, the biosimilar is a complex molecule with many post-translational modifications, because it is produced from the complex living cells. In contrast to the generic drug, the biosimilar has immunogenic potentials. Furthermore, only the bioequivalence study is required for the approval of generic drug products in the regulatory requirements; whereas, for biosimilar products, the comparative study to demonstrate the biosimilarity to reference products is required [2–4]. The biosimilar is a biological product, which exhibits high similarities to the products already licensed in terms of quality, safety, and efficacy. However, the exact definition of "biosimilar" itself does not reach the consensus among different regulatory agencies [5]. Despite these differences among regions, the basic principles for biosimilars are similar [6, 7]. For harmonization on the evaluation and regulation of biosimilars, the guideline on the evaluation of similar biotherapeutic products (SBPs) is provided by WHO Expert Committee on Biological Standardization (ECBS) [8].

Monoclonal antibodies (mAbs) are the fastest growing class of biotherapeutic products for treating cancer or inflammatory diseases and they can be found on the lists of the top 10 global annual pharmaceutical revenues. As the patents or data protections have been expired or nearing expiration, many global pharmaceutical industries have turned toward developing similar mAb biotherapeutic products. The similar mAb biotherapeutic products, also called biosimilar mAbs, exhibit highly similar biological and clinical properties to the authorized reference mAbs. The entry of these products into the markets could help to slow the increasing healthcare costs due to its affordability and accessibility. The mAb is a complex macromolecule with several sizes and charge variants or post-translational modifications, including different glycosylation profiles, or N and C terminal heterogeneities. The presence of differences is shown in each mAb due to the structural complexity. Although these differences are seemingly tiny, it is possible to have large impacts on the quality of final products. Therefore, additional guidelines that apply to mAb-derived products are demanding. In 2016, WHO guideline on the evaluation of biosimilar mAb products was adopted by the ECBS [9]. The document provides some critical considerations for manufactures as well as regulatory authorities for characterizing or assessing the quality of biosimilar mAb products. However, until now, there have been no standard analytical methods or clear specifications for defining the similarity in the nonclinical and clinical comparability studies. The manufactures have to develop their own analytical methods to prove similarity in relation to reference products, and these analytical methods are required to be scientifically validated [10].

The quality attributes of biosimilar mAb products might be affected by the manufacturing process. Manufacturers of biosimilar mAbs do not easily obtain the detailed information about the manufacturing process of the reference products or the usage of the active ingredients [11]. In general, the amino acid sequence of the biosimilar mAbs must be identical to the reference mAbs; however, other characteristics, including the structure conformation, biological activity, or contents of impurities, might vary from products to products. To obtain the approval from the regulatory authorities, the comparability studies of structural and functional characterization and process-derived impurities of the biosimilar products and reference products are required [12]. Moreover, one mAb biotherapeutic product might apply to multiple indications and exert the clinical effects through different mechanisms of action (MoA) [13]. Therefore, the comparability studies in the clinical

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trials are also required. If any clinical differences of biosimilar mAbs compared to reference mAbs are found, additional evaluations must be justified to exclude any adverse effects [14]. However, there are many challenges for developing biosimilar mAbs, including the harmonization of analytical methods, development of comparative assay, and exact definitions of biological activity in the clinical trials [15]. Due to the complexity of bioprocess in the biosimilar mAbs, very tiny differences in the manufacturing process might have large impacts on the quality of final products. The development process and critical concerns in each step are described as follows, which would be helpful for manufactures as well as regulatory authorities to administrate with more scientific and regulatory considerations.

2. Framework of development

From the point of product approval, the development of biosimilar mAbs may be divided into the pre-market and post-market stage. In the pre-market stage, to obtain the approval from the regulatory agencies, the biosimilar mAbs must undergo a rigorous development process and comparative study to demonstrate the quality, safety, and efficacy similarity to the reference mAbs. After the product approval, in order to achieve the maximal safety and quality of mAb biosimilar products, post-market surveillance is indispensable. The framework of biosimilar mAb development and critical points for considerations are shown in **Figure 1** [16].

2.1. Manufacturing development

Biosimilar mAbs are developed to show similarity to reference mAbs in terms of quality, safety, and efficacy. The manufacturing development of biosimilar mAb products might be different from that of reference mAbs, because some detailed information of the manufacturing process of reference mAb is not accessible by the manufactures [11]. In order to reduce any unnecessary clinical safety and efficacy effects, the manufacturing process should be optimized to minimize the differences between biosimilar mAbs and reference mAbs. It is advisable that the manufacturing process of biosimilar mAbs should be as similar as possible to that of reference mAbs and the manufactures should understand each manufacturing process. If any differences in the manufacturing process are found, the potential impacts of changing elements on the product quality, safety, and efficacy should be evaluated and justified [17].

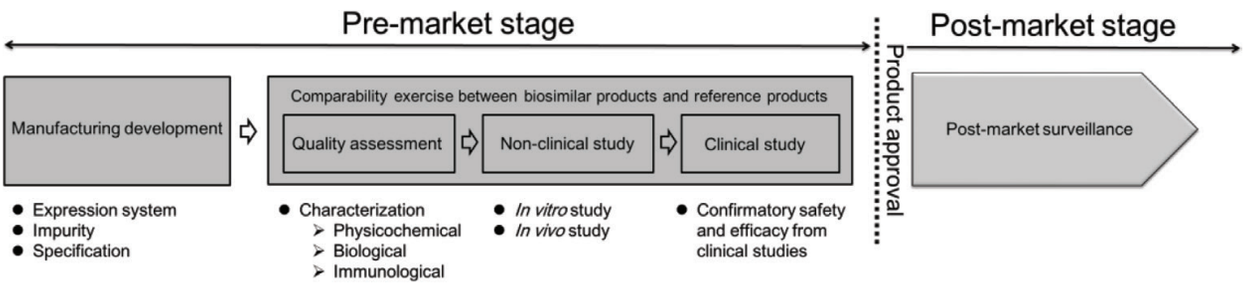

Figure 1. Framework development and critical points for considerations of biosimilar mAbs.

2.1.1. Expression system

Choice of suitable expression system is one of the critical points for the manufacturing process. According to the WHO guidelines, a different expression system is allowed for the production of biosimilar mAb products [8, 9]. Although the primary structure (amino acid sequence) is not affected by different host cell lines, the protein modifications, including N-terminal truncation, C-terminal truncation, or post-translation modification, and process-derived impurities like residual host DNAs or residual host proteins might be affected. These changes might indirectly affect the biological effects in the clinical consequences. In most cases, when different host cell types are used, different glycosylation profiles might be found [18]. For example, the mAb products produced from mouse cell lines, like NS0 or SP2/0 cells, have alpha-1,3-gal in their carbohydrate structure. However, there is no production of such structure in the human cell lines, because these cell lines lack the necessary enzyme to synthesize the alpha-1,3-gal antigens [19]. Moreover, the immune response against this"special" glycosylation structure would be triggered in the human body, which might lead to the adverse clinical effects. This situation could be avoided by using Chinese hamster ovary (CHO) cells [20]. Therefore, to minimize the differences between biosimilar products and reference products, the choice of the expression system for the mAb biosimilar products should be carefully considered. In general, it is advisable for the manufactures to choose the same host cell type as that of reference mAbs to minimize the possible impact on the clinical efficacy and safety of the products when developing mAb biosimilars.

2.1.2. Impurity

Product impurity is inevitable in the manufacturing process. Impurities, the components which are not desired in the drug substance or drug products, might trigger some safety concerns [21]. To ensure the safety of products, the differences of impurity profiles between the biosimilar mAbs and reference mAbs need to be evaluated. For mAb products, the testing of impurity includes the analysis of residual host DNA, residual protein A, or monomer contents in the products. If any differences between biosimilar mAbs and reference mAbs are significantly observed, additional evaluation of the impurity-derived impacts on the product safety and efficacy is required [8, 12, 22].

2.1.3. Specification

The specification (acceptance criteria) needs to be considered in the manufacturing process. The specification of biosimilar mAbs is not actually the same as that of reference mAbs. Sufficient batches of biosimilar mAb products are needed for the collaborative study. The setting of specification of biosimilar mAbs is based on the manufacturing experiences or comparative results of the collaborative study on biosimilar mAbs and reference mAbs. In general, the limit setting of biosimilar mAbs should not be wider than the range of variability of reference mAbs. If the acceptance criteria of biosimilar mAbs are significantly out of the acceptable range of reference mAbs, additional evidence to confirm the safety of products is needed [21, 23].

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2.2. Comparability exercise

From the regulatory requirements, the comparability exercise of biosimilar mAbs and reference mAbs must be needed. According to ICH Q5E, the comparability study should prove that the proposed product is highly similar to the reference product before and after the manufacturing process changes [24]. The comparability data of quality attributes might be the foundation for reducing the requirements of non-clinical and clinical studies. When considering that batch variabilities might affect the results of comparability exercise, products from different batches should be evaluated. What is more, the analytical methods in the comparability exercise should be sensitive to detect the potential differences between biosimilar mAbs and reference mAbs and the parameter ranges for each analytical methods need to be determined by an appropriate statistical analysis [8, 9, 25].

To obtain representative data from the comparability exercise, the choice of a suitable reference mAb is important. Comprehensive information of reference mAbs could be the foundation for the establishment of quality, safety, and efficacy profiles, to which are the biosimilar mAbs compared. Head-to-head comparisons are performed to demonstrate high level of biosimilarity between the biosimilar mAbs and reference mAbs in the comparability exercise [26]. Following considerations are provided for the choice of suitable reference mAb biotherapeutic products [8, 12, 22].

- Whether the reference products have already been authorized based on the integrated set of quality, safety, and efficacy data.
- Whether the drug substance, active ingredient, and the biological function of biosimilar mAbs are similar to those of reference mAbs.
- Whether the dosage form and route of administration of biosimilar mAbs are identical to that of reference mAbs.
- Whether the same reference products are used throughout the comparative quality, safety, and efficacy studies.

2.2.1. Quality assessment

The quality comparative studies are conducted by the state-of-art analytical techniques and appropriate analytical methods. The analytical methods should be sensitive enough to detect any differences between biosimilar mAbs and reference mAbs. For the development of analytical methods, the information of the analytical limitations, like specificity in each analytical technique should be known by the manufactures. The characteristics including physicochemical, biological, and other related properties (e.g., impurities, finished products, and specification) are analyzed by the head-to-head comparative studies [27–30]. For mAb analysis, the common characteristics and analytical methods to ensure product quality are provided in **Table 1**, and these analytical items could also be applied to the comparative study of biosimilar mAbs and reference mAbs [5].

Characteristics	Items	Analytical methods
Primary structure	Intact mass analysis	Mass spectrometric analysis
	Peptide mapping	Enzyme digestion and HPLC
	N-terminal sequence	Edman degradation
	C-terminal sequence	Peptide mapping and intact molecular mass analysis
	Disulfide bond bridge analysis	Peptide mapping under nonreduced condition
	Glycosylation site	Peptide mapping with mass spectrometric analysis
Higher order structure	Structure analysis	Circular dichroism
Post-translational modification	Glycan profiles	Enzyme digestion and mass spectrometric analysis
	Sialic acid content	HPAEC-PAD
Heterogeneity	Isoforms	cIEF
Immunological activity	Binding affinity	Enzyme immunoassay
Biological activity	Potency	Cell-based assay
Purity/impurity	Product-related impurity	HPLC
Process-related impurity	Host cell protein	ELISA
	Residual DNA	PCR
	Residual protein A	ELISA
	Endotoxin	LAL

HPAEC-PAD: high performance anion exchange chromatography with pulsed amperometric detection; HPLC: high-performance liquid chromatography; cIEF: capillary isoelectric focusing; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction; LAL: limulus amebocyte lysate.

Table 1. Analytical items and analytical methods for the analysis of mAb characterization.

2.2.1.1. Physicochemical properties

The characterization of physicochemical properties for biosimilar mAbs is required, due to the inherent complexity of mAb products. The monoclonal antibody is a macromolecule with size and charge variants and different post-translational modifications. The structural heterogeneity should be analyzed by the state-of art techniques. The physicochemical testing should include the determination of the primary structure (e.g., amino acid sequence), higher order structure (e.g., disulfide bond bridges, free thiol functional group, and secondary or tertiary structures), and some physicochemical properties (e.g., charge variants, site-specific glycosylation patterns, or glycan profiles) [12].

The analysis of the primary structure is the determination of the amino acid sequence of products. In general, the primary structure of mAb SBPs should be identical to that of reference

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mAbs, except for the structural heterogeneity in the N-terminus or C-terminus. Peptide mapping is a common analytical method to identify or quantify the abundance of heterogeneous forms. For higher order structures, the conformation stability is critical for functional properties. For example, the differences in intra-disulfide bridges could directly affect the IgG2 affinities in mAb products [31]. The commonly analytical techniques used in the testing include hydrogen-deuterium exchange mass spectrometry (H/DX-MS), circular dichroism (CD), and two-dimensional nuclear magnetic resonance (2D-NMR). H/DX-MS is used to identify the rigid or flexible domain of the protein structure in the formulation conditions, CD is used to assess the content of secondary structure, and 2D-NMR is used to analyze the integrity of protein structure [32]. In some situations, a combination of two or more analytical techniques, like capillary electrophoresis coupled with mass spectrometry, might be powerful in characterizing the physicochemical properties [33].

The comparability exercise on the post-translational modification of biosimilar mAbs and reference mAbs is required in the physicochemical analysis. The comparative glycan analysis includes the N-glycan analysis, site-specific glycosylation patterns, or overall glycan profile [34]. Given that small differences in glycan profiles could cause unexpectedly immunogenic consequences, additional data to support the product safety are required. Moreover, the high heterogeneity of the active ingredients increases the complexity of the structure or other physicochemical properties, which caused it difficult to analyze the different variants in one analytical method. To solve these problems, the combination of the different analytical methods, like ion exchange chromatography, isoelectric focusing, and capillary electrophoresis, is developed. However, the analytical techniques of physicochemical analytical methods are restricted to its detection limits, so that some higher order structure of the molecule or slight difference of mAb SBPs and reference mAbs are not easily detected by the physicochemical analysis. To complement the detection limits of physicochemical analysis, the biological analysis is performed to determine whether the heterogeneous variants have impact on the product safety.

2.2.1.2. Biological activity properties

Biological activity, also called potency, is defined as the product's specific ability to achieve the intended biological effects. It is an important parameter for characterizing the product quality and batch analysis. Biological assay is the quantitative measure of the biological activity and reflects the mechanism of action of the functional protein. The data obtained from the biological assays could connect to the clinical activity. Additionally, the biological assay complements the physicochemical analysis to confirm the structural integrity of the molecules. The analytical method for biological activity should be specific and sensitive enough to detect slight differences in batch analysis or comparative study. The biological activity should be determined by calibrating against international or national standards, and the results could be expressed in international units (IU) or units (U) of activity [8, 9, 12].

The mechanism of the action of mAbs varies ranging from simple antigen binding, which alone affects the clinical response, to antigen binding with one or more immunological effects,

which combines to present an overall clinical response. For example, infliximab, which is a chimeric monoclonal antibody specific for tumor necrosis factor alpha (TNF-α), achieves clinical efficacy in rheumatoid arthritis through the mechanism of antigen binding [35]. However, rituximab, specific for binding to CD20, requires the Fc function for its clinical efficacy in all the clinical indications [36]. The mAb consists of two major functional domains, including Fab and Fc fragments. For characterizing biological activity properties, the assay should be designed for analyzing binding affinity and functional activities of these two regions. If it can be shown that the clinical effects are only affected through antigen binding, the ligand binding assays could estimate biological activity. Given that the Fc part of mAb might mediate the immunobiological effects, the relevant, validated potency assay for the determination of other immunobiological effects other than just potency should be developed. In this regard, the choice of appropriate cell-based assays to determine the potency should be considered.

2.2.1.3. Immunological properties (immunogenicity)

Immunogenicity is the ability/capability of molecules to elicit the immune response against external substances. The immune response against the mAb biotherapeutic products is affected by many factors, including the drug substances, excipients, process derived impurities, route of administration, dosing regimen, or other related factors [12]. For the analysis of immunological properties, the binding specificity, binding affinity, and binding kinetics all need to be analyzed by scientifically analytical methods, such as surface plasmon response, microcalorimetry, or classical Scatchard analysis. Moreover, the Fab-associated functions (neutralization of soluble antigens or receptor activation/blockade) and the Fc-associated functions (antibody-dependent cell cytotoxicity, complement-dependent cell cytotoxicity, apoptosis, or complement activation) should also be analyzed using appropriate analytical methods [8, 9]. These analytical methods should be sensitive enough to detect the difference between biosimilar products and reference products.

2.2.2. Nonclinical study

Nonclinical study encompasses the pharmacological/toxicological assessments of biosimilar products. By referring to the results from the physicochemical and biological characterization studies, the nonclinical study program is designed to detect potential impacts on safety and efficacy of biosimilar products. Nonclinical studies can be divided into *in vitro* studies and *in vivo* studies. *In vitro* studies should be conducted first, since the results from *in vitro* studies could make a decision to the extent of what *in vivo* studies are required. The considerations for *in vitro* studies and *in vivo* studies are discussed as follows [9, 37, 38].

2.2.2.1. In vitro study

To assess the difference of biological activity between a biosimilar product and a reference product, *in vitro* studies should be performed. Compared to animal studies, an *in vitro* assay is more specific and sensitive to detect differences between the biosimilar products and

reference products [39]. For establishments of *in vitro* studies of biosimilar mAbs, the following points should be taken into account.

- The assay needs to be scientifically valid and has the ability to detect biological differences between biosimilar mAbs and reference mAbs, not just the response of biosimilar mAbs.
- An appropriate number of batches of reference mAbs and biosimilar mAbs are required, given that the results will be affected by variabilities with different batches.
- The number of tests should be adjusted sufficiently to make the meaningful conclusions that biosimilar mAbs demonstrate similarity in biological activity to reference mAbs.
- The data from *in vitro* studies should cover the pharmacological/toxicological assessments, which could be a reference supportive for the clinical design.

For nonclinical *in vitro* program of biosimilar mAbs, the biological analysis of Fab and Fc fragments should be included. Following table summarizes the analytical items and analytical methods in the nonclinical *in vitro* program of biosimilar mAbs [9] (**Table 2**).

2.2.2.2. In vivo study

In vivo study is designed to provide more information on "unexpected" pharmacological/toxicological activities relevant to the clinical application. Such studies could be comparative in nature and can detect the differences between biosimilar products and reference products. However, when the necessary information has already obtained from *in vitro* studies, *in vivo* studies are not required. Following points are provided for the determination of the need for *in vivo* studies [40].

	Item		**Method**
	Fab-associated	**Fc-associated**	
Binding studies	• Target antigen binding	• Binding to Fc receptors (FcγRI, FcγRII, FcγRIII, and FcRn) • Binding to complement (C1q)	• ELISA • Surface plasmon resonance (SPR) • Flow cytometry
Biological activities/ functional assay	• Neutralization of soluble ligand • Receptor activation • Receptor blockade	• Antibody-dependent cell cytotoxicity (ADCC) • Complement-dependent cytotoxicity (CDC) • Complement activation • Apoptosis	• Cell-based assay

Table 2. Analytical items and analytical methods of ***in vitro*** nonclinical study of biosimilar mAbs.

- The data of biological activity or pharmacodynamics could be available from the biological assays in the part of the quality assessment. If these data are sufficiently reliable to reflect the relevant clinical situation, *in vivo* studies would not be necessary. Accordingly, if the data are not fully elucidated by *in vitro* assay, *in vivo* assay is required.
- The monoclonal antibodies might mediate the unprecedented effects that cannot be fully characterized by an *in vitro* assay. In this situation, *in vivo* studies are required to provide complementary information.

If *in vivo* studies are required, the following points are needed for consideration.

- Choice of animal species and the relevant models (in-breed animals, transgenic animals, or transplant models) for the assay.
- If there are no appropriate animal models for *in vivo* assay, the manufacture needs to evaluate any potential risks by the data from *in vitro* assay, when proceeding to the clinical trials.
- Some factors need to be considered, when considering whether the additional *in vivo* assays should be performed

1. Presence of potential quality attributes in biosimilar mAb products, which have not been detected in the reference mAbs.
2. The relevant quantitative differences in the comparative measurements between biosimilar mAbs and reference mAbs.
3. The difference formulation is used. For example, the excipient is not commonly used in the mAbs.

2.2.3. Clinical study

Clinical study for biosimilar mAb aims to confirm the safety and efficacy issues from the clinical view. For the design in the biosimilar mAb clinical trial program, the natural characteristics, intended indication, and duration should be taken into consideration. In fact, the design of most comparative clinical study is based on the clinical experiences, which had already been acquired from the reference mAb. It is advisable to use the finished products for clinical studies, so as to obtain pivotal data for marketing authorization from the regulatory authorities. The clinical comparability exercise is performed in a step-wise procedure, and usually begins with the clinical pharmacodynamics (PD) and pharmacokinetic (PK) studies, followed by the comparative clinical safety and efficacy study in a selected indication. Due to the clinical experiences of reference products, some steps of the biosimilar mAb clinical trial are not necessary, such that the phase 2 clinical trial (dose finding study) is not required, when the dosage used in the biosimilar mAb administration regimen is the same as that used in the reference mAb [11, 41]. Therefore, compared to the development of reference mAbs, the development of biosimilar mAbs needs less time.

The extent and number of clinical trials of biosimilar mAbs compared to reference mAbs could be affected by the following factors [42]:

- The intrinsic complexity (structural and biological properties) of biosimilar mAbs.
- The limitations of studies in the nonclinical comparative structural and biological study.

- The complexity of mechanisms of action of biosimilar mAbs.
- The degree of uncertainty of biosimilar mAbs in efficacy and safety issues.
- The clinical experiences obtained from the reference mAbs.

Although the clinical trial design of biosimilar mAbs followed the same guideline as other similar biotherapeutic products, additional considerations are required. The indication extrapolation is one of the important considerations for biosimilar mAb clinical studies. To provide justification for indication extrapolation, the equivalence clinical trial is preferred over the noninferiority trial. An equivalence trial is demonstrated to confirm that the biosimilar mAb is clinically similar to the reference mAb. This demonstration could provide the efficacy and safety data of biosimilar mAbs that could be a strong rationale for extrapolation to other indications of reference mAbs. In an equivalence trail, it is advisable to choose the sensitive and well-established study models regarding to the study population and study endpoints, given that assay with sensitivity should have the ability to detect differences between the biosimilar mAbs and reference mAbs, even if only tiny difference exists. In order to minimize the impacts on inter-patients variability, the selected study population for the clinical trial should be homogeneous and increase the likelihood that the observed clinical effects are caused by the difference between biosimilar mAbs and reference mAbs. In general, patients without previous treatments are good study models, because the observed clinical effects could exclude the interference effects of other medications [42–45].

2.3. Post-market surveillance

Post-market surveillance is an important process in achieving a maximum safety and effectiveness of mAb biosimilars. It is a long-term monitoring to detect or assess any product-derived adverse effects. Some of these effects may not easily be detected during the preapproval clinical testing, because the narrow population is tested in the trials. In addition, due to the changes of material sources, facility or regulatory requirements, the manufacturing process of biosimilar mAb products might change. In some situations, the profiles of post-translational modification alter during the product life cycle, which might directly or indirectly affect the product safety or effectiveness. For example, Remicade (infliximab) has gone through over 35 changes since product approval in 1999, but no any adverse effects were reported in the clinical usage [46]. However, the change of glycosylation profiles of Rituxan (anti-CD20 antibody) has been reported from batches to batches, which directly or indirectly affects the product immunogenicity [47]. Therefore, continuous post-marketing surveillance of products is required so as to make prompt prevention for adverse effects.

The following considerations are indicated when designing the program of post-marketing safety monitoring.

- Whether to identify low-frequency adverse reactions associated with biosimilar mAb products (not easy to identify the pre-marketing stages).
- Whether to identify some high-risk groups.
- Whether to discern that the adverse effects are caused by the biosimilar mAb product, not by the reference mAb.

- Whether safety monitoring is continuous.
- Whether the risk or hazard prevention measures could be initiated promptly.

3. Indication extrapolation

The comparative study data of biosimilar products and reference products in one indication could extrapolate to other indications, in which reference products originally have been approved. Extrapolation is an important process for biosimilar developments, because it could reduce/eliminate the need for duplicative clinical studies [48]. The recommended principles of indication extrapolation of biosimilar mAbs could refer to the WHO guidance document about the evaluation of SBP. In general, to make indication extrapolation possible, the following points are needed.

- The mechanism of action of a biosimilar product and a reference product is the same.
- The clinical test is sensitive enough to detect the potential differences between biosimilar products and reference products.
- The safety and immunogenicity data of biosimilar products in one indication are well characterized and there are no additional safety concerns when extrapolating these data to other indications.
- Additional convincing data must be provided to support extrapolation to other conditions of use.

For biosimilar mAbs, some points should be considered. Unlike other biologics, monoclonal antibodies have two functional domain—Fab and Fc domains. Each domain might exert their clinical effects through different mechanisms, including the receptor blockage, signaling induction or down-regulation, receptor down-regulation, and cell cytotoxicity (ADCC, CDC, or apoptosis). One monoclonal antibody might exert the clinical effects through one or a combination of these mechanisms in different indications. For example, infliximab does not require Fc function in rheumatologic and psoriatic indications; however, it exerts the clinical effects through the Fc domain in inflammatory bowel disease (IBD) [49]. When the mechanism of action (MoA) of biosimilar products is different to that of reference products, the indication extrapolation could be challenging. In some cases, the drug dosage of one product might not be the same between different indications; therefore, different dosages are needed to be tested. Moreover, a reference mAb might hold different types of indications. For example, rituximab (anti-CD20 mAb) is authorized for the treatment of both inflammatory diseases and cancer [50]. Since the pharmacokinetic data are different between these two diseases, it is inappropriate for biosimilar products to extrapolate.

4. Conclusions

With the trend of global pharmaceutical developments, the era of biosimilar mAbs has begun. It is clear that the entry of biosimilar products to the markets would bring benefits

for science and healthcare. With regard to biosimilar mAb manufactures, the reduction of production costs, choice of suitable cells, and control parameters setting to avoid product heterogeneity are important in the manufacturing process. From the regulatory perspective, the abbreviated development program is adopted in the biosimilar mAb products. Besides the data, which support the quality, safety, and efficacy of products, the comparative data to demonstrate the similarity between the biosimilar mAb product and the reference product needed to be submitted. Considering the impacts of batch variability on comparative results, different lots of products should be included in the in-depth comparative analysis. The integrated set of data from the comparative results would be the foundation for biosimilar development and the determination of the need for the extents that animal studies and clinical trials should be performed. For the clinical studies, it is advisable to choose one condition of use that would be sensitive to detect the clinical meaningful differences between the proposed biosimilar mAb and the reference mAb. However, some product-derived adverse effects might not be easily detected during the preapproval clinical testing. Based on the regulatory guideline requirements, pharmacovigilance and risk management plan for biosimilar mAbs should be submitted to regulatory authorities for dossier review. The risk management plans, which are proposed by the manufactures, should include the detailed information on the safety and risk concerns. However, challenges remain with an abbreviated pathway for biosimilar mAbs, including the lack of detailed information and acceptance criteria for biosimilarity demonstration. In order to promote the global development and achieve the maximal safety of biosimilar mAbs, it is expected that manufacturers should cooperate with regulatory authorities to fight against current challenges with more detailed scientific considerations from a regulatory perspective.

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