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Quality, safety and efficacy of follow-on biologics in Japan

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A B S T R A C T

Recently, WHO, EU, Japan and Canada have published guidelines on biosimilar/follow-on biologics. While there seems to be no significant difference in the general concept in these guidelines, the data to be submitted for product approval are partially different. Differences have been noted in the requirements for comparability studies on stability, prerequisites for reference product, or for the need of comparability exercise for determination of process-related impurities. In Japan, there have been many discussions about the amount and extent of data for approval of follow-on biologics. We try to clarify the scientific background and rational for regulatory pathway of biosimilar/follow-on biologics in Japan in comparison with the guidelines available from WHO, EU and Canada. In this article, we address and discuss the scientific background underlying these differences to facilitate the harmonization of follow-on biologic principles in the guidelines in future.

1. Introduction

Over the last three decades, many biotechnology products have been developed and marketed as new therapeutics for difficult-to-treat diseases. Consequently, these products have become essentials for the treatment of many serious diseases. However, the cost of these products has often been high, which in conjunction with an expansion of biotechnological products has contributed to an increase in health-care costs.

Recently, the expiration of patents and/or data protection for the first major group of innovator's biotechnology products has ushered in an era of products that are designed to be 'similar' to a licensed innovator product [1–4]. These products rely, in part, for their licensing on prior information and experiences regarding safety and efficacy obtained with the innovator products. Therefore, the clinical experience and established safety profile of the innovator products contributes to the development of similar biotechnology products (namely follow-on biologics in Japan and biosimilar in EU) [5–7]. The amount and extent of data required for the licensing of biosimilar/follow-on biologic products is likely to be less than is normally required for the innovator products.

Japanese regulatory authority has been confronted with the new challenge of regulating biosimilar/follow-on biologic products. To ensure the quality, safety and efficacy of biosimilar/follow-on biologic products, Japan has published a guideline [8] for quality, safety and efficacy of biosimilar/follow-on biologics based on the similarity concept outlined by the EMA. Following the adoption of the guideline, two follow-on biologic products have been approved or marketed, and more than ten products are in development in Japan. WHO and Canada have also published guidelines for similar biotherapeutic products (SBPs) and subsequent entry biologics (SEB) for products termed biosimilar/follow-on biologics [9,10]. These guidelines have generally similar fundamental concepts and similar regulatory framework for the licensure of biosimilar/follow-on biologics. However, several regulatory requirements for these products seem to be different from each other. Therefore, it is very interesting to compare the requirements of each guideline, and help in the harmonization of regulatory pathway for biosimilar/follow-on biologic products.

2. Japanese guideline for follow-on biologics

The Japanese regulatory authority published the guideline on follow-on biologics and the related notifications in March of 2009. The guideline indicates that biotechnology-derived products generally have unique characteristics such as structural complexity, being comprised of several functional domain sites, with specific bioactivity or stability and immunogenicity attributes. Furthermore, quality attributes of biotechnology-derived products determine the highly complex characteristics of the desired product, the

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Table 1
Scope of the Japanese guideline.

Decision	Products	Reasons	Notes
Yes	Recombinant plasma proteins	There is no reason to exclude recombinant plasma proteins from the scope, even though some proteins have a highly complicated structure	Some patients might prefer non- recombinant products. Blood product supply might be affected, even though an overlapped product development ensures the consistent supply
	Recombinant vaccines	Well characterized recombinant vaccine can be possibly developed as follow-on biologics	Vaccine is administrated to healthy humans Lot-to-lot variation of adjuvant activity is relatively large
	PEGylated recombinant proteins	Conjugates are in the scope as is in ICH Q6B	Development of PEGylated protein as follow-on biologics might be difficult due to the structural complexity
No	Synthetic peptides	Impurity profile is different from that of recombinant proteins	Synthetic peptides can be generic drugs, because the desired product can be easily defined by structural analyses
No	Polyglycans	Characterization is difficult	Several polyglycan products have been approved as generic drugs in Japan[a]
Case by case	Non-recombinant proteins[a]	Proteins that are highly purified and characterized could be developed as follow-on biologics	Several urine-derived protein products have been approved as generic drugs in Japan

[a] e.g. proteins such as isolated from tissues or body fluids.

product-related substances, product-related impurities, and process-related impurities which constitute the product. As a result, it is much more difficult to prove that the quality attributes of a follow-on biologic are identical to that of the approved innovator product as compared with small chemically synthesized drugs. Therefore, the generic approach used for small chemically synthesized drugs cannot be applied to these products. The guideline defines a follow-on biologic as a biotechnological drug product, which is comparable to an approved biotechnology-derived product of an innovator company. Therefore, a sponsor should submit the data to prove that their product is highly similar and that existing knowledge is sufficiently predictive to ensure that any differences in quality attributes between their product and the reference product have no adverse impact on the drug product or on its safety or efficacy.

2.1. Scope and paradigm of Japanese guideline

The scope of Japanese guideline is summarized in Table 1; the focus is predominantly on recombinant protein products as follow-on biologics. The complexity of some biotechnology-derived products will make it difficult to develop them as follow-on biologics [8]. However, since the current technology to analyze biotechnology products is very rapidly progressing, it maybe possible to analyze the comparability of these complex products in near future. Therefore, no recombinant protein products are excluded as scope of guideline and until recently, polyglycans such as low-molecular weight heparin have unlike EU, been excluded from this guideline.

Paradigm of data to be required for development of follow-on biologics is illustrated in Fig. 1. Since dossiers containing all data of the innovators products may not be disclosed, the sponsor developing a follow-on biologic should independently establish the robust manufacturing process to ensure the consistency of the product is the same as in the case for approval of new biologics. In addition, the follow-on biologic product should be fully characterized independently as same as for new biologics.

The sponsor should compare the quality attributes of the product with the reference innovator product as far as possible and provide the data demonstrating the high similarity in quality attributes with the reference innovator product. On the basis of these data, the sponsor should evaluate the comparability of the follow-on biologic with its reference product through non-clinical and clinical studies.

Even though the biosimilar/follow-on biologics may be developed with abbreviated non-clinical and clinical data, the sponsor should submit all data according to the ICH CTD guideline (ICH M4) [11] for new drugs. The data concerning the comparability of quality attributes with the reference innovator products are recommended to be included in the 2.3.R of module 2 in CTD (Fig. 2).

Concerning the comparability exercise, the application of ICH Q5E guideline to comparability studies on follow-on biologics has been discussed. The objective of ICH Q5E guideline is to provide the principles for assessing the comparability of biotechnological/biological products where changes are made on manufacturing processes. Innovator manufacturers can compare both products head-to-head in such a case. Since the information of innovator's

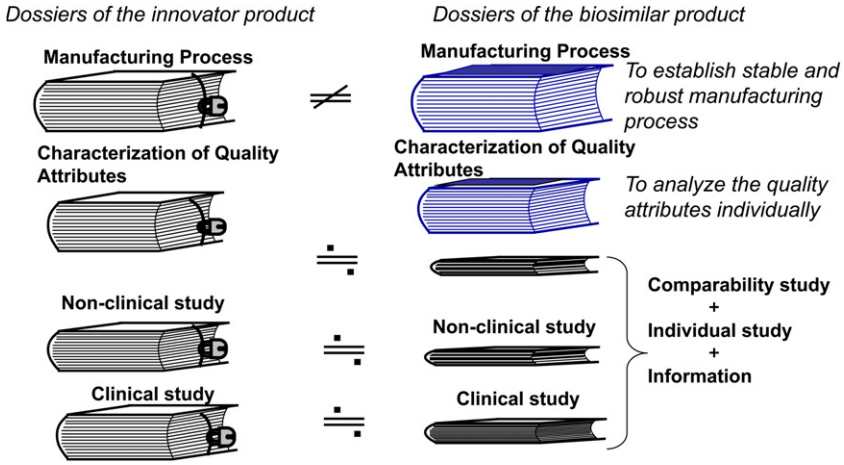

Fig. 1. Dossiers of follow-on biologics to be submitted.

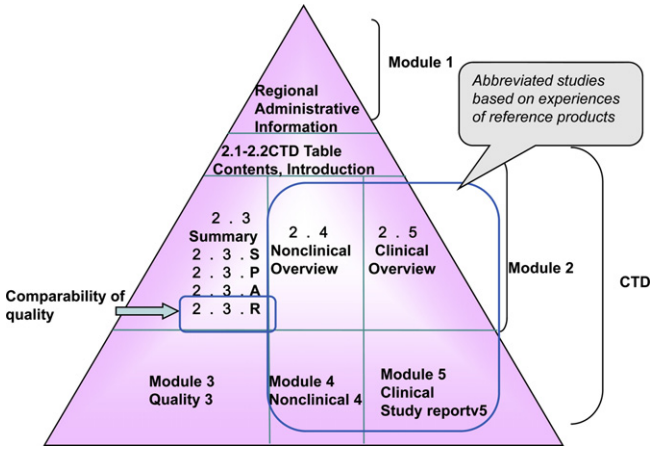

Fig. 2. Diagrammatic representation of the organization of follow-on biologics according to the ICH CTD common technical document.

products is generally not disclosed, same approaches by ICH Q5E can not always be applied to the evaluation of follow-on biologics.

Therefore, based on the concept of Q5E, sponsors developing follow-on biologics should consider the comprehensive approach including comparability studies and other approaches that utilize public information or existing experiences.

2.2. Development and optimization of manufacturing process

As for a new biotechnological product, a well-defined manufacturing process should be established, and extensive characterization studies should be conducted to reveal the molecular and quality attributes of the follow-on biologic.

If the host cell line used for the production of reference innovator product is disclosed, it is highly recommended to use the same cell line. For the establishment and characterization of the cell banks, ICH Q5A, Q5B, Q5D guidelines should be referred. It is recommended to adopt the manufacturing processes that potentially improve the safety of the product but these should not affect efficacy.

During the development of manufacturing process, alteration and optimization of the purification process may be necessary to produce a product that is similar in quality attributes to the reference product (Fig. 3). Much effort may be needed for the optimization of manufacturing processes during the development of follow-on biologics.

2.3. Characterization and evaluation of quality attributes of follow-on biologics

The quality attributes of follow-on biologics which are manufactured with stable and robustly-established manufacturing processes should be as thoroughly characterized as new recombinant protein products.

The comparability of quality attributes with those of reference innovator biologics should be evaluated as far as possible and applicable. The comparability exercise should include structural characterization and physicochemical properties, biological activities and other immunological properties to examine the similarity of quality attributes.

The acceptable criteria for differences in quality attributes will vary depending on the characteristics of the product and the clinical purpose and dosage form in clinical use. Assessment of the variation of quality attributes observed in different batches of the innovator product will provide the basis of acceptable criteria for the biosimilar products (Fig. 4). However, it is not always feasible to analyze the variation of quality attributes of innovator products, because of the limitation of accessibility to various lots of innovator products.

On the basis of data obtained from the comparability exercise of quality attributes, demonstration of the high similarity in quality attributes with the reference medicinal product is required.

3. Non-clinical studies and clinical study

Demonstration of high similarity of the candidate follow-on biologic with the reference innovator products enables the utilization of experiencing reference products, because follow-on biologics are generally developed long after the approval of innovator products. Therefore, not only the data submitted for the approval of the innovator products but also the safety and efficacy data accumulated from the treatment of many patients provides important and useful information about the product. Based on the innovator's experiences, the sponsor may develop the follow-on biologics with abbreviated data from non-clinical and clinical studies.

As a minimum requirement, the sponsor should evaluate the safety of a follow-on biologic for human use prior to entering into

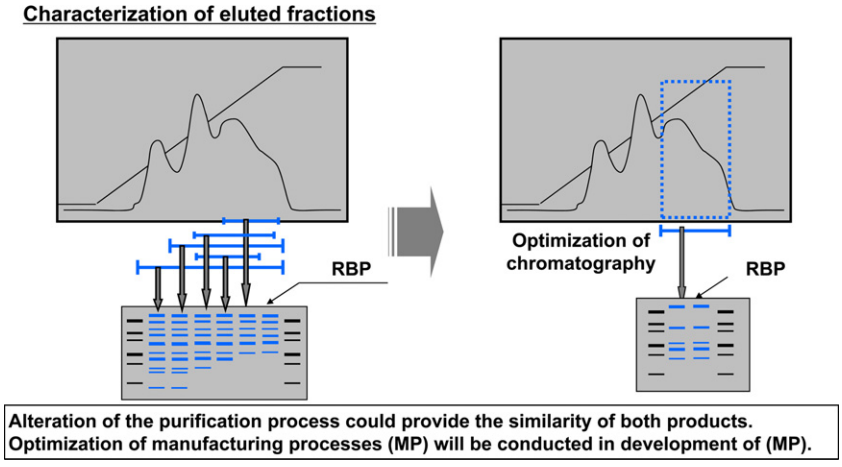

Fig. 3. Model of optimization of manufacturing process according to the comparability studies.

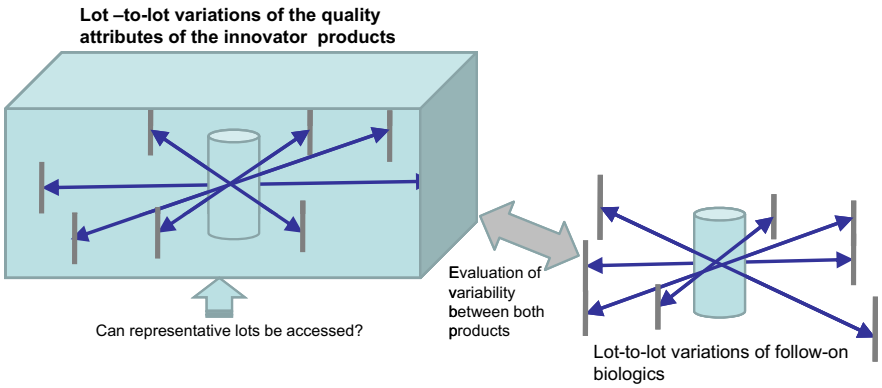

Fig. 4. Acceptance criteria for the variation of the quality attributes of follow-on biologics. It is not always feasible to analyze the variation of quality attributes of innovator products, because of the limitation of accessibility to various lot of inovator products.

clinical trials. Generally, genotoxicity, carcinogenicity and reproductive toxicity studies are not required for toxicology studies on follow-on biologics, if applicable. Single dose toxicology study could be conducted as a part of repeated dose toxicology study as well as evaluation of local tolerance.

On the other hand, comparability studies may be useful and appropriate to verify the similarity of pharmacological effects between the follow-on biologic and reference product.

In general, it is difficult to verify the comparability of a follow-on biologic with the originator biologic based on data from the quality attributes and non-clinical studies alone. Therefore, the sponsor should evaluate the comparability of a follow-on biologic with the innovator product in clinical studies.

While there is sufficient data to assure the comparability in clinical endpoint has been obtained by clinical pharmacokinetic (PK), pharmacodynamic (PD) and/or PK/PD studies, further clinical studies may be reduced in some cases. Arato et al have reported case studies about clinical studies conducted in Japan and discussed the comparability criteria for clinical studies [12].

In certain cases, it may be possible to extrapolate from one indication to the other indications of the originator biologic used as the reference product. The extrapolation of indications is limited to the indications of the reference product and does not include the indications of other approved recombinant protein products with similar indicators.

4. Comparison of the guideline EU, WHO and Japanese for the follow-on biologics

A comparison of the guidelines EU, WHO and Japanese for the follow-on biologics is summarized in Table 2. The scope of each guideline is virtually identical as they all focus on recombinant protein products, except for low-molecular heparin in EU. In terms of Chemistry, Manufacturing and Control (CMC), all guidelines require the establishment of a robust manufacturing process to ensure the product consistency (as expected for new drugs), and the necessity for full data to characterize the quality attributes of a follow-on biologic.

4.1. Reference products for follow-on biologics

The Japanese guideline clearly describes the definition of reference products (innovator products) as well as EMA guideline; the sponsor should demonstrate comparability with the original innovator biologic through both non-clinical and clinical studies. Furthermore, the original biologic should be already approved in Japan, the same product should be used throughout the development period of the follow-on biologics (i.e., during the characterization of quality attributes, non-clinical and clinical studies).

On the other hand, in WHO and Health Canada guidelines, innovator products which are approved by the regional regulatory

Table 2
Comparison of requirement for evaluation of SBPs between WHO and Japan.

	Japan	WHO	EU
Scope	Recombinant protein products	Recombinant protein products	Mainly recombinant protein products
Category of application for approval	Follow-on biologics different from new drugs or generic drugs	Regulation in each nation	Biosimilar products
Manufacturing process and CMC	Manufacturing process as well as new drugs, full data of CMC	Manufacturing process as well as new drugs, full data of CMC	Manufacturing process as well as new drugs, full data of CMC
Reference products	Same reference product approved in Japan through development	May not be country specific	Same reference product approved in EU through development
Comparative studies	Q, NC, C Not always required to evaluate safety about process-related impurities	Q, NC, C	Q, NC, C
Stability tests	Expire period: Real time/real temperature Optional: Compare accelerated stability of SBP and RBP	Expire period: Real time/real temperature Should compare accelerated stability of SBP and RBP	performing stress and accelerated stability studies
Interchangeability/ substitutability	Interchangeability is accepted, Substitutability is not suitable	Not described	Interchangeability is accepted, but not substitutability
Ab production	Enough period	Enough period	Recommendation (1yr)
Others		International harmonization	

Q: quality attributes; NC: non-clinical study; C: clinical study.

Table 3
Nonproprietary & Brand Names of follow-on biologics.

Nonproprietary Name:
○○○○○ (genetical recombination) [× × × × × Biosimilar 1]
Brand Name: × × × × × BS Inj Content Company-Name
× × × × × excludes "genetical recombination" from the Nonproprietary Name of original biologic
[Example]
Nonproprietary Name: Epoetin Kappa (Genetical Recombination) [Epoetin Alfa Biosimilar 1].
Brand Name: Epoetin Alfa BS Inj 750 "JCR" ("JCR" is an example of the company name).

authority are not always necessary as the reference products. The reason for this is that all countries can not always access the relevant innovators product.

4.2. Stability test for follow-on biologics

To evaluate the stability of follow-on biologics, long-term, real-time, and real-condition stability studies are required according to the ICH Q5C guideline on "Stability Testing of Biotechnological/Biological Products". Since either excipients and/or buffer composition of drug substance or pharmaceutical formulation of follow-on biologics are not necessarily identical to those of innovator products, identical storage condition and storage period of follow-on biologics is not always required to follow the reference medicinal products in Japan. Furthermore, a comparison of stability with the reference medicinal product will not be essential, but in some cases, a comparison of stability with reference medicinal product, such an accelerated stability test, provides some useful information about the difference of quality attributes, such as degradation products. Therefore, a comparison of the stability of a follow-on biologic with the reference innovator product as a strategy for development of follow-on biologic is not always necessary.

4.3. Evaluation of safety of process-related impurity

There are some differences in the requirement of toxicology study for impurity in follow-on biologics between EU, WHO and Japan. The Japanese guideline describes that since the impurity profile of a follow-on biologic may be assumed to be different from that of the original biologic in many cases, it is not required to evaluate the safety of impurities in the follow-on biologic through non-clinical studies without comparison to the original biologic. Culture method, including medium composition such serum, growth factor or additives, and purification method will remarkably affect the profile of the process-related impurity in biotechnology products. It is recognized that it is very difficult to evaluate the comparability of the impurity profile between a follow-on biologic and reference product from the viewpoint of quality and quantity.

4.4. Interchangeability and substitutability

After the marketing of follow-on biologics, the change of prescription from the innovator products to follow-on biologics (interchangeability) is generally permitted. On the other hand, it is very important to assure the traceability of any adverse events arising during the respective surveillance period. Therefore, it is strongly recommended to avoid automatically substituting (substitutability) the originator biologics with the follow-on biologics throughout a certain period of patient treatment.

4.5. Naming of follow-on biologics in Japan

Japanese notification for naming of follow-on biologics has been published at the same time of guideline for follow-on biologics. The notification describes the Nonproprietary & Brand Names of follow-on biologics (Table 3).

For Nonproprietary Names, Biosimilar should be suffixed to the Nonproprietary name of the original biologic at the time of the approval. The individual products are determined to be the follow-on biologics through a reviewing process for the approval.

On the other hand, for brand name, the dosage form, dosage, and company name should be attached to the nonproprietary name.

5. Conclusion

The approval of follow-on biological/biosimilar will be the matter of regional regulatory authorities as several follow-on biologics/biosimilar have been marked globally. Since the follow-on biologics/biosimilar are generally approved with the abbreviated clinical data, the accumulation of safety data during the post marketing surveillance and sharing the safety data with each regulatory authority are very important. Therefore, it is desirable to globally harmonize how to collect the safety data.

Conflict of interest

The authors have disclosed no potential conflicts of interests.

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