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Considerations of critical quality attributes in the analytical comparability assessment of biosimilar products

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ABSTRACT

Based on experience in clinical trial approvals and marketing authorizations for biosimilar products in Korea, we suggest principles for the analytical comparability assessment of biosimilar products with respect to regulatory considerations. The composition and manufacturing processes of biosimilar products can differ from those of the reference product depending on the information available for the reference product and the time of product development; however, the analytical characteristics of biosimilar products should be highly similar to those of the reference product. Although manufacturing an identical product in terms of the quality profile is nearly impossible due to the high molecular weight and complex structure of biological products, the developer of the biosimilar product should attempt to establish a quality level as similar to that of the reference product as possible. When comparing the similarity of quality attributes, the criticality of the quality attributes and the characteristics of orthogonal quality attributes need to be considered carefully. Based on the results from the analytical comparability assessment, the comparability results of non-clinical and clinical studies should be evaluated before claiming biosimilarity to the reference product. In this review, we focus on quality attribute evaluation based on our regulatory experience.

1. Introduction

Biotherapeutics, including monoclonal antibodies (mAbs), successfully treat many serious diseases with high efficacy and relatively low adverse events but are very costly, with yearly treatments requiring up to tens of thousands of dollars. Highly expensive biologicals have become burden on both patients and the health care system, and this fact drives a need to develop biosimilar products. However, the high molecular weight and complex structure of protein products means that identical products cannot be manufactured with the currently available technology. In addition, the structure of biological products is highly sensitive to subtle changes in the manufacturing process and is the reason why different manufacturers produce similar protein products rather than identical products.

Experience in the development of recombinant protein products has accumulated in recent decades, and the consistency of manufacturing processes has improved due to advances in manufacturing technology. Thus, it is now possible to manufacture a protein product with a quality profile that is similar to that of the original product, but the two products are not identical.

Based on technical and economic backgrounds, a regulatory pathway for the approval of biosimilar products has emerged internationally, and this pathway differs from that of chemically synthesized generic products in that it simply evaluates the bioequivalence of the product with the original product. Unlike chemically synthesized generic products, biosimilar products should be evaluated based on the totality of evidence from quality, non-clinical and clinical comparability studies with the reference product. Since the European Medicines Agency (EMA) introduced the biosimilar approval pathway in 2005, biosimilar guidelines

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Table 1
List of clinical trial approvals for candidate biosimilar products in Korea.

Reference product	Company	Therapeutic area	Phase
Humira	Samsung Bioepis	Rheumatoid arthritis	3
	LG Life Science	Rheumatoid arthritis	3
	BIO CND	–	1
	Boehringer Ingelheim Korea	Rheumatoid arthritis	3
	Pfizer Korea	Rheumatoid arthritis	3
	Sandoz	Rheumatoid arthritis	3
Remicade	Schnell Biopharmaceuticals	Rheumatoid arthritis	1
	Pfizer Korea	Rheumatoid arthritis	3
Enbrel	LG Life Science	Rheumatoid arthritis	3
	Daewoong Pharmaceutical	–	1
MabThera	Samsung Electronics	Non-Hodgkin's lymphoma Rheumatoid arthritis	1
	Celltrion	Follicular lymphoma Rheumatoid arthritis	3
	Pfizer Korea	Follicular lymphoma	3
	Amgen	Non-Hodgkin's lymphoma	3
Herceptin	Pfizer Korea	Breast cancer	3
	Samsung Bioepis	Breast cancer	3
Nesp	Chong Kun Dang Pharmaceutical	Anemia associated with chronic renal failure	3
	CJ CheilJedang	–	1
Iprex	PanGen Biotech	Anemia associated with chronic renal failure	3
Lantus	Mylan	Diabetes mellitus, type 2	3
Humalog	Sanofi-Aventis Korea	Diabetes mellitus, type 2	3
Avastin	Pfizer Korea	Non-small cell lung cancer	3
	Boehringer Ingelheim Korea	Non-small cell lung cancer	3
	Samsung Bioepis	Non-small cell lung cancer	3
	Centus Biotherapeutics	Non-small cell lung cancer	3

have been prepared by the World Health Organization (WHO) and other national regulatory authorities (NRAs), such as agencies in Japan, Canada, the United States, Switzerland and Korea [1–7].

The evaluation of the comparability of biosimilar products involves a step-wise approach; thus, the comparability of the quality profiles of biosimilar and reference products should be considered the first priority for reducing non-clinical and clinical studies. Although the amino acid sequence of biosimilar products should be the same as that of the reference product, the expressed proteins, which have undergone post-translational modifications, might present different profiles in quality attributes (QAs), such as terminal amino acid variants, charge variants, and oligosaccharide profiles. Based on the characteristics of the product, its QAs should be classified according to their criticality. Therefore, determination of the critical quality attributes (CQAs) that might impact the safety and efficacy of a product is important for the evaluation of biosimilarity.

In Korea, since the regulatory pathway and guidelines for biosimilars were introduced in 2009 [8], 25 products corresponding to 10 reference products are being investigated in clinical trials (Table 1), and seven products with biosimilarity to infliximab, trastuzumab, somatropin, etanercept, insulin glargine, and rituximab have been authorized as of November 2016 (Table 2). In this review, we provide a regulatory perspective on the CQAs that should be used in the comparability evaluation of biosimilars, particularly when the active substances are peptides or proteins produced by recombinant DNA technology. This position is based on previous experience in the approval of biosimilar products within the Korean Ministry of Food and Drug Safety (MFDS) and can be adjusted as further regulatory experience is attained.

2. Strategy for developing a biosimilar product

The development of a biosimilar product requires extensive considerations regarding the whole aspect of the medicinal product of interest. In general, biosimilar manufacturers investigate the reference product of interest in considerable detail. The first step is identifying the quality target product profile (QTPP) of the reference product by testing many batches of the reference product and extensively characterizing the product using a range of methods (Table 3) [9]. To obtain as much comprehensive information as possible, the biosimilar manufacturer should collect sufficient batches of the reference product over several years and regions and characterize the product thoroughly to gain information regarding its various attributes and quality ranges. Based on the QTPP, the manufacturer then develops and optimizes the manufacturing process of the biosimilar product to achieve quality characteristics that are highly similar to that of the reference product. Batches of the targeted product are then compared with those of the reference product to demonstrate that the final product is biosimilar to the reference product.

A biosimilar manufacturer should consider the structure of the drug substance as well as the formulation and presentation of the final product. Information regarding the formulation of the reference product is not publically available from most NRA's except the US FDA. Furthermore, excipients in a reference product are sometimes protected by intellectual property rights; therefore, the biosimilar manufacturer is unable to use the excipients of the reference products. Thus, it is understood that biosimilar companies will employ current state-of-the-art technology to develop a new formulation that can maintain the stability of the biosimilar product. Many biosimilar guidelines indicate that the composition of the biosimilar product can differ from that of the reference

Table 2
List of authorized biosimilar products in Korea.

Product name	Company	Reference product	Date of authorization
Remsima	Celltrion	Remicade	2012 Jul 20
Herzuma	Celltrion	Herceptin	2014 Jan 15
Scitropin A	SciGen Korea	Genotropin	2014 Jan 28
Truxima	Celltrion	MabThera	2015 Jul 16
Brenzys	Samsung Bioepis	Enbrel	2015 Sep 07
Basaglar	Lilly Korea	Lantus	2015 Nov 25
Renflexis	Samsung Bioepis	Remicade	2015 Dec 04