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Biosimilar Drugs

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ABSTRACT

Biological medicines are medicines that are made or derived from a biological source and as such are complex molecules, with inherent variability in their structure. A biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety, and efficacy based on a comprehensive comparability exercise. Biologic products are widely used in treatment for neutropenia, cancer, inflammatory and autoimmune diseases, and enzyme or hormone deficiencies.

Keywords: Biological medicine, biosimilar, drugs

ABSTRAK

Obat-obatan biologis adalah obat-obatan yang dibuat atau berasal dari sumber biologis dan merupakan molekul kompleks, dengan variabilitas yang melekat pada strukturnya. Obat biosimilar adalah obat biologi yang sangat mirip dengan obat biologis lain yang sudah berlisensi untuk digunakan. Hal ini menunjukkan bahwa obat biologis terbukti tidak memiliki perbedaan bermakna secara klinis dari obat biologis pencetusnya dalam hal kualitas, keamanan, dan efikasi berdasarkan uji perbandingan secara komprehensif. Produk biologis banyak digunakan dalam pengobatan untuk neutropenia, kanker, penyakit inflamasi dan autoimun, dan enzim atau kekurangan hormon.

Kata kunci: *Biosimilar*, obat, obat-obatan biologis

Biological medicines are medicines that are made or derived from a biological source and as such are complex molecules, with inherent variability in their structure. Wide ranges of substances are included in this category, such as recombinant therapeutics, monoclonal antibodies, growth factors, and fusion proteins.[1,2] Biologic products are widely used in treatment for neutropenia, cancer, inflammatory and autoimmune diseases, and enzyme or hormone deficiencies.[3,4] Global biologics sales have grown to more than $100 billion.[5] Biologics and vaccines sales were estimated $289 billion (24% from total worldwide prescription share) in 2014 and are projected to grow to $445 billion by 2019.[6]

Despite of having proven benefit in treating many life-threatening and chronic diseases, cost of treatment with biologics are very expensive, thereby limiting their access to patients. World Health Organization in their 67th World Health Assembly in May 2014 adopted two major resolutions to overcome the issue of affordability and accessibility issue of biologics products. First is promoting access to biotherapeutic products and ensuring their quality, safety and efficacy, while the second strategy is on regulatory systems strengthening in which WHO was requested to provide guidance, especially on dealing with increasingly complex biotherapeutic products, including similar biotherapeutic products (SBPs) or biosimilar.[3]

The expiry of patents for several originator biologics had led to introduction of "similar" products to provide additional options for patients as well as the prescribers.[4,7] First time entered to pharmaceutical market in 2006 (Omnitrope®, a somatropin biosimilar to Genotropin®), increasing range of biosimilar medicines are under development by pharmaceutical companies in Europe. By mid-2015, twelve biosimilar molecules have been marketed as 19 brands and have been widely used for patients' treatment across Europe.[4] As an increasing number of biologics face patent expiration, biosimilars offer a major opportunity for drug developers. By 2020, patents will expire on twelve biologics with global sales of more than $67 billion.[5]

What is Biosimilar?

A biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy based on a comprehensive comparability exercise.[4,8] Biosimilar contains a (copy) version of the

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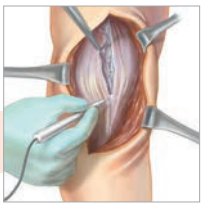


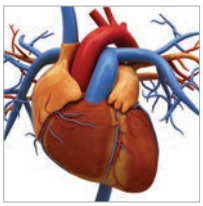


Table 1. Biosimilar definition in some countries

Previous Terminology	Regulatory Body/Country	Current Terminology	Definition
Similar Biologic Product (SBP)	WHO	Similar Biologic Product (SBP)	A biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product that was developed and approved on the basis of the principles outlined in WHO guidelines on evaluation of SBPs.[3]
Follow on Protein or Follow on Biologic (FOB)	US FDA	Biosimilar (FOB is use in regulatory context on the drug approval process of FDA).[12]	A product highly similar to the reference product without clinically meaningful differences in safety, purity, and potency.[10]
Subsequent-entry Biologic (SEB)	Health Canada	Change term in to Biosimilar Biologic Drug in November 2016	A biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug.[11]
Biosimilar	Europe EMA Korea India China Australia	Biosimilar	Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy.[10]

active substance of an already authorised original biological medicinal product (reference medicinal product).[9] Biosimilar medicines are not considered generic equivalents to their originator biological medicine because the two products are similar but not identical. However, they will have met regulatory requirements in terms of comparative quality, safety, and efficacy.[4]

There was disparity of definitions on biosimilar in some countries (**Table 1**). Nowadays, most countries are using the term Biosimilar, and the uniform terminology will increase possibility in harmony of regulations and escalating entree to safe medicines globally.[10] The main determinant from those definitions is the requirement of the proposed drug to demonstrate "similarity" with previously licensed biological products.

As patents for the biologics began to expire, questions arose regarding the ability to produce "generic" substitutes for original biologics. Producing a generic substitute's equivalent to an innovator product is relatively a straightforward process compared to process of developing a biosimilar. Biologics are produced by cells in culture or whole organisms, which are inherently more variable than chemical synthesis methods. Therefore, unlike generic pharmaceuticals, it is impossible to generate the same or identical copy of an innovator product.[1] **Table 2** shows the different complexities of small molecule drugs with the biological products.

The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product and to convincingly demonstrate the similar nature of the concerned products.[8] Reference product is a single biological product, already licensed for use, against which a proposed biosimilar product is compared.[13] Comparability is a well-established concept. A proposed biosimilar must pass a comprehensive scientific comparability exercise prior their approval to enter the market. The active substance of a biosimilar must be similar to the active substance of the reference medicinal product, both in in molecular and biological terms, including sequence of amino acids (if it's a protein), posology, and route of administration. Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification as well as additional data when required.[8]

Nearly all biosimilars will require at least one

Table 2. Relative size of chemical and biological drugs

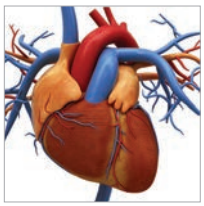
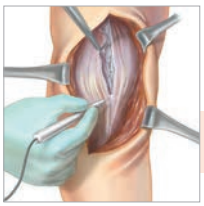
Drug (Nonproprietary Name)	Molecular Formula
Chemical Drugs	
Aspirin	C_9HO_4
Acetaminophen	$C_8H_9NO_2$
Sofosbuvir	$C_{22}H_{29}FN_3O_9P$
Small Biological Products	
Insulin glargine	$C_{267}H_{404}N_{72}O_{78}S_6$
Epoetin alfa	$C_{809}H_{1301}N_{229}O_{240}S_5$
Filgrastim	$C_{845}H_{1339}N_{223}O_{243}S_9$
Somatropin	$C_{990}H_{1528}N_{262}O_{300}S_7$
Large Biological Drugs	
Etanercept	$C_{2224}H_{3472}N_{618}O_{701}S_{36}$
Infliximab	$C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$

(Source: Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/, and Drugs.com.[12])

Table 3. Approved biosimilar products globally

Country	Agency	First Biosimilar Approved in the Region	Year of Approval	Manufacturer	Current number of biosimilar approved
Europe	European Medicines Agency (EMA)	Omnitrope (Somatropin)	2006	Sandoz	19
United States	US FDA	Zarxio (Filgastrim)	2015	Sandoz	10
Canada	Health Canada	Omnitrope (Somatropin)	2009	Sandoz	7
Japan	The Pharmaceuticals and Medical Devices Agency (PMDA) Japan	Somatropin BS.	2009	Sandoz	10
South Korea	Korean FDA	Remsima (infliximab)	2012	Celtrion Inc	9
India	Indian Ministry of Health and Family Welfare and Science and Technology.	epoetin alfa	2001	Wockhardt	68

(Source: Generics and biosimilars initiative, http://www.gabionline.net)

head-to-head clinical trial to confirm similarity with the originator biologic as the basis for approval to be deemed as "interchangeable" with their originator counterparts. Biosimilar product that performs interchangeability with the reference product is expected to produce the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.[14]

The biosimilar pathway does not seek to demonstrate safety and efficacy for each indication of the biosimilar medicine.[4,9] When total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer. This concept is called "extrapolation", whereby the regulatory and scientific process of granting a clinical indication to a medicine without own/new clinical efficacy and safety data to support that indication.[8]

Current Status of Biosimilar

Pharmaceutical companies in many countries have been developing biosimilar products and use it as treatment in clinical setting (**Table 3**).

Since its introduction into market, the following issues of biosimilars have been put into concern:

- Safety concerns
  As its originator, biosimilar is intended for long-term use to treat chronic diseases. Safety concerns are likely to arise referring to the risk of immunogenicity as well as the concept of extrapolation applied as part of approval process of proposed biosimilar. One case related to the immunogenicity of biosimilar was reported in India, where a patient in later stages of adrenal disease developed pure red cell aplasia (PRCA) associated with stimulation of antibodies to administered erythropoietin (EPO) after administration with the EPO product Wepox that is referred to as a 'follow on' product.[10]
  The assessment of toxicity and safety of biosimilar from the oncology practice point of view is even more complex since molecular antibodies (mAbs) have complexity and molecular size, giving rise to higher variability.[15]

- Classification of biosimilar.
  Dissimilar classifications of biosimilars are applied in some countries, leading to difference in approval process of proposed biosimilar product. As an example, low molecular weight heparins (LMWHs) are classified as generic drugs in the US and therefore become approved on the approval process of generic drugs, which are less extensive compared to approval process of biosimilar. In contrast, LMWHs are classified as biosimilars in the EU since heparins are derived from biological source material.[15]

- Naming system for biosimilars
  There has been growing debate on what INN (International Nonproprietary Name) should be given to biosimilars. The World Health Organization (WHO) has issued a draft proposal covering the issue of how to name biosimilars, which are random alphabetic codes, to help standardize the naming of biologicals, including biosimilars.[16] Not all regulatory authorities agree with the WHO's approach to naming,[16,17] leading to divergent naming system across countries.
  Similar to its reference biological product, data from pre-authorization clinical studies are usually too limited to identify all potential adverse reactions of a biosimilar. Pharmacovigilance during the post-marketing phase should be implemented in place to identify the rare adverse events. For pharmacovigilance in a global setting, harmonization in naming is crucial as different naming systems may cause confusion and hinder clear data analysis for a specific biosimilar product.[15]
  Biosimilar has been always expected to be solution for the high-cost of treatment with biological products. In EU, biosimilars in some therapeutic areas are priced below reference biologics, often with discounts of 25 percent or more.[14,18] Market study performed by the RAND Corporation

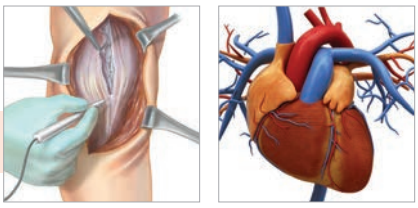
Table 4. Strategic plan of biosimilar development in Indonesia (Direktorat Jenderal Bina Kefarmasian dan Alat Kesehatan, 2015)

API	PERIOD		
	2015-2018	2019-2022	2023-2025
BIO PHARMACEUTICAL	EPO (Erythropoetin) GCSF (Granulocyte Colony Stimulating Factor) Probiotic Insulin Stem cell protein (Wound care and cosmetics) Somatropin EGF Enoxaparin	Blood Fractionation (Albumin, imunoglobulin, Faktor VIII, Faktor IX) Growth Hormone Interferon Trastuzumab Insulin MAB (oncology)	MAB (Monoclocal Anti Body) Insulin analogue

Table 5. Patents expiry for best selling biologicals

Brand Name	Biologics	EU	US
Avastin	Bevacizumab	2022	2019
Herceptin	Trastuzumab	2014	2019
Humira	Adalimumab	2018	2016
Synagis	Palivizumab	2015	2015
Erbitux	Cetuximab	2014	2016
Remicade	Infliximab	2015	2018
Rituxan/MabThera	Rituximab	2013	2016
Aranesp	Darbepoetin alfa	2016	2024
Avonex/Rebif	Interferon beta-1a	2015	2015
Enbrel	Etanercept	2015	2028
Epogen/Eprex	Epoetin alfa	2013	2013
Neulasta	Pegfilgratim	2017	2015
Neupogen	Filgrastim	2013	2013
Lantus	Insulin Glargine	2014	2014
Lovenox	Enoxaparin sodium	2012	2012

(Source: Generics and Biosimilars Initiative, http://www.gabionline.net[33]



estimated that the implementation of biosimilars would save the U.S. healthcare system $54 billion over the next decade, with a potential minimum of $25 billion and maximum savings of $150 billion.[19] The use of biosimilar in clinical practice can affect health care cost by several mechanisms discussed below:

- Decreased unit cost

The abbreviated pathway and implementation of extrapolation concept will potentially lower the cost because less overhead is needed for research and development and less time to obtain approval compared with originator manufacturers. Even though the price reductions as traditional generic medicines won't be as drastic as traditional generic medicines, there are significant savings associated with increased competition.

- Price competition

Introduction of biosimilar to pharmaceutical market and clinical practice increases choice for patients and clinicians, increases commercial competition and enhances value propositions for individual medicines. From the economic point of view, increased number of competitors will drive biologics prices downward. In other word, lower price offered by biosimilar treatment will drive the costs of the reference products down as their manufacturers attempt to stay competitive in the market.[4]

- Increased volume

The entry of lower-cost competitors will cause patients and payers to choose biologic treatment options to a greater degree. Lower treatment cost may increase patients' adherence to medication regimens, whereby in the end will improve their health.

Are We There yet?

Indonesia is a developing country which has more than 250 million people. The World Bank classifies Indonesia as lower–middle income country; where 10.12% of the total populations are classified as poor.[20] Patients are often asked to bear the cost of expensive treatment, where in many cases cause them to face financial hardship. In 2010, 30% of total health expenditure was in the form of out-of-pocket payments.[21] World Health Organization has called on countries in South-East Asia region to implement universal health coverage with goal to ensure that all people obtain the health services they need without risking financial hardship from unaffordable out-of-pocket payments.[22] Indonesia has started its universal healthcare system since 2014.

Treatment with biological products shows significant clinical benefit, yet it relatively less accessible by patients in developing countries. Annual cost of treatment with a biological drug can be as much as US$40,000, while earnings per capita in many emerging markets are only US$4,000–12,000. This figure puts most biological therapies out of the reach of the majority of the potential patient population.[23] The option to have lower cost treatment of chronic disease will offer access as well as adherence to treatment. Biosimilar comes to light as a solution for issues related to treatment with biologic. Equitable access to safe, quality, affordable, and effective medical products is one of the cornerstones of universal health care.

In the late of 2015, Indonesia launched its biosimilar guideline. Guideline issued by National Agency for Drug and Food of Indonesia (locally known as Badan Pengawas Obat dan Makanan [BPOM] Republik Indonesia) provide legal framework comprise of definition of biosimilar, registration procedures, evaluation of biosimilar products (comparability studies, selection of reference product, production process, physicochemical characterization, analytical techniques, non-clinical and clinical safety-efficacy evaluation) as well as pharmacovigilance plans.[24] Biosimilar development has been included in strategic plan of Indonesian pharmaceutical industry. **Table 4** shows the plan for developing biosimilar in 10 year period.

Numbers of biological originators are scheduled to come off patent in the upcoming years and will be exposed to biosimilar competition by 2020 (**Table 5**). This could be a big opportunity for pharmaceutical companies to start biosimilar development. Biosimilar product of trastuzumab and rituximab were approved by FDA in late 2017 and early 2018, indicating a potentially better access to cancer treatment in the future.

Pharmaceutical companies in Indonesia have started to take part in the development of biosimilar. PT Biofarma signed an agreement with ProBioGen AG (a German company) in 2015 for the development of a biosimilar trastuzumab.[30] PT Kalbe Farma Tbk. has launched a biosimilar version of insulin on March 2017[31] and intend to develop biosimilar of erythropoietin and granulocyte colony-stimulating factor analogue, followed by the production of monoclonal antibodies.[32]

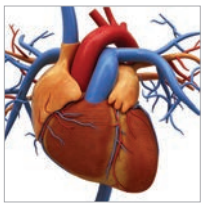
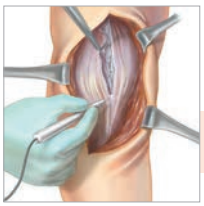
Challenges in Biosimilar Development – Learn the Right Lessons

Being positioned as part of emerging market for biosimilar development, Indonesia can learn the lesson from countries that have started their journey in developing biosimilar. Government has prepared the legal framework to encourage local pharmaceutical companies to develop biosimilars.

Taking part as a player in biosimilar industry is not merely about having local guideline; instead it's the first step to start the quest. Let us consider the challenges associated with a successful launch of biosimilars in other countries.

- Originators

The companies of originator biologic will response with strategy to keep ahead of the competition and have responded in different ways to the potential entry of biosimilars. Some company counteracted biosimilar product development and responded with patent defenses and extension. As an example, in 2016, company which produced originator bevacizumab filed multiple litigious complaints and patent infringement suits to the company who intend to produce a biosimilar to bevacizumab. Even though the biosimilar product gained FDA approval, the response from the originator company had slowed both the approval and market availability of the biosimilar.[19] However, some company responded "positively" by improving its first-generation products (by reducing the frequency of dosing schedules and providing more convenient administration technologies) and decreasing price (through discount). For example, the company of originator filgastrim (Neupogen) introduced Neulasta, a second-generation of Neupogen.

Neulasta has 40% lower treatment cycle cost compared to Neupogen, which can compete to the cost reduction offered by the use of biosimilar product.

- Health Care Practitioners

  Biosimilars can improve access to therapeutically effective but costly treatment of chronic diseases. Similar like the generic product to its originator, when a biosimilar product gains 'interchangeable' status, it can be automatically substituted for the prescribed biological product once by the pharmacist without the consent of the prescribing physician.[28] However, due to safety concern, health care practitioners and patients continue to emphasize concerns about switching from biologics to biosimilars. The complexity of manufacturing process of biosimilar may exhibit batch to batch variability, which could possibly lead to new adverse drug reactions. Health care practitioners (physician, pharmacist, nurse) as well as patient and their caregiver must be fully aware upon starting treatment with biosimilar product and perform cautious monitoring on patient's condition. Automatic substitution is not applicable in most of the countries at this time. Automatic substitution will make post-marketing surveillance more difficult due to potential issues with traceability and identification of the products, especially with the concern of the uniformity of the biosimilar naming system.

  Acceptance of biosimilars will not build up immediately. According to a survey conducted by the National Comprehensive Cancer Network in 2011, only about 20% of providers would be early adopters of biosimilar products.[19] Biosimilar companies must have robust evidence regarding biosimilars to reassure the medical and patient community about the safety and efficacy of switching. One strategy to overcome the acceptance issue is to get the 'interchangeable' status, which requires at least one head-to-head clinical trial to confirm similarity with the originator biologic. This requirement may limit the potential of cost saving on production process.

- Biosimilar manufacturer

  Pharmaceutical companies intending to develop a biosimilar product must plan a clear business strategy way ahead the development process. Strategy should comprise target market segment as well as value proposition offered by the biosimilar product. Upgrade on facilities of biologics-development and product-launch capabilities will absolutely take time, which may delay the development and introduction of biosimilar product to the market. Biosimilar company will need 7 to 8 years to develop a biosimilar, at a cost of between $100 million and $250 million. It may cause challenge to provide lower net-cost pricing relative to its biologic originator.

  As mentioned earlier, the lack of awareness and education could hinder potential cost-saving as well as accessibility to the treatment. Biosimilar manufacturer will be required to actively promote the benefit of biosimilar use coinciding the launch of the biosimilar product.

  Accessibility and affordability of treatment is the spotlight in the era of universal health care. In countries such as EU and US, biosimilars are positioned at 40-60% discount compared to the price of its originator product.[29] Stringent approval process for biosimilar products in both countries has prompted biosimilar companies to target emerging market such as Eastern Europe, Latin America, and Asia. To achieve the aim of the introduction of biosimilar into market, all stakeholders must provide full support in biosimilar development. Regulatory bodies have to be equipped with their local regulatory framework; drafted with concerns on safety profile of biosimilars. Regulatory bodies can direct the companies to conduct clinical trials in a small population to establish the safety and efficacy profile of biosimilars, as solution to concern on interchangeability. By doing so, the acceptance rate of biosimilar among healthcare practitioners and patients would increase, and patients' accessibility to biosimilar can be improved. On the other hand, affordability of biosimilar product remains a concern. Biosimilar manufacturer needs to effectively balance the pricing that will enable profits and be competitive enough to gain payer reimbursement.

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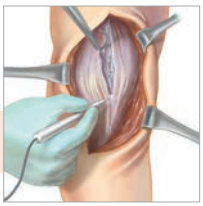

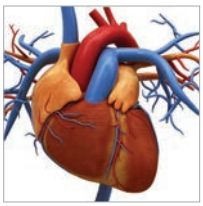

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