The emergence of Biosimilars in Indonesia: guidelines, challenges and prospects

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Abstract

According to the Food and Drug Administration (FDA), biosimilar is defined as a product which is highly similar to the reference product without clinically meaningful differences in safety, purity and potency. Indonesia is a developing country which has more than 250 million people. In 2008, the world market of biosmilar was USD 100 billions with 10-20% of domestic need from total market. Even though the need is very high, Indonesia still has not been able to produce Biosimilar independently. To stimulate the domestic production on biosimilar, National Agency for Drug and Food Control (NADFC) Republic of Indonesia has assigned Regulation of Biosimilar as Peraturan Kepala Badan Pengawas Obat Dan Makanan Republik Indonesia Nomor 17 Tahun 2015 Tentang Pedoman Penilaian Produk Biosimilar. The guidance covers the quality requirement and evaluation of Biosimilar products. Indonesian Ministry of Health has a strategic plan in biopharmaceutical covering biosimilar, which is going to be developed from 2015 to 2025. The strategy is expected to initiate biosimilar production in Indonesia. This review focuses on the guidelines of biosimilars in Indonesia compared to other international regulatory bodies, as well as the challenges and prospects of biosimilars development.

Keywords: Biosimilar, Indonesia, Guidelines, Challenges and Prospects

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1. Introduction

Biologics are a class of pharmaceutical products containing protein substances and/or its derivatives produced in living system by advanced biotechnology and molecular biology. These drugs are designed to substitute the real substances in human body, which can modulate the immune response and down regulate the inflammation response for treating many illnesses including cancer, anaemia, diabetes, multiple sclerosis and other immune mediated inflammatory diseases. Wide ranges of substances are included in this class of pharmaceuticals, such as recombinant therapeutics, monoclonal antibodies, growth factors and fusion proteins (Bhupinder Singh Sekhon, 2011; Boehncke & Radeke, 2007). In the last few years, the expiration of patents and other intellectual property rights for innovator biologic products lead to open market for "generic" version of biologics, known as biosimilars in Europe and Korea, follow-on biologics (FOBs) in the USA, subsequent-entry biologics (SEBs) in Canada, and termed similar biologic products (SBPs) by WHO. There are different definitions of biosimilars in different regions (Table 1). However, all of the terms refer to the necessity of demonstrating "similarity" with a certain licensed biological products.

The term of "generic" version of biologics is called biosimilars and cannot be called "biogenerics". Biosimilars have several fundamental differences with small molecule drug counterparts. Firstly, biologic products are macro molecular compounds. Secondly, the complexity of their structure makes them difficult to be characterized and manufactured. Furthermore, the safety and efficacy controls of biosimilars are not the same as generic drugs, because this product is not identical to its innovator. The final products of biologics will depend on production and purification process, and different host cells creates different characteristic of molecules. The safety of biologics drugs relies on several factors such as drug mechanism in human body, production process, and protein composition related to side products and impurities. As a consequence, these factors can cause immunogenicity, which is the big issue on biologic product production. Therefore, bioequivalence assessment is not enough to prove this product as therapeutic drugs. It needs other clinical procedures and some comparability studies between biologics candidate and reference drugs prior to launch into the market (Chow & Liu, 2009).

Even though European Medicines Agency (EMA) had established a legal approval of biosimilars in 2003, the first biosimilar was approved in 2006, namely Omnitrope containing the active ingredient somatropin. Currently, there are 19 biosimilar products approved by EMA to be used in the European Union (Table 2). The first biosimilar approved in Canada was Sandoz's Omnitrope in April 2009 (Health Canada, 2009). Human growth hormone, somatropin, was also the first biosimilar approved in Japan in 2009, which is marketed as Somatropin BS. To date, The Pharmaceuticals and Medical Devices Agency (PMDA) Japan has approved other eight biosimilars within the product classes of human growth hormone, granulocyte colony-stimulating factor, erythtropoesis stimulating agent, insulin and tumour necrosis factor (TNF)-inhibitor. Those products are marketed in Japan (Gabi Online, 2016). In 2012, Korean FDA approved Remsima (infliximab) as the first biosimilar in South Korea, manufactured by Celtrion Inc., which is used for Rheumatoid arthritis therapy (Jung *et al*., 2014). Several biosimilar products are being developed even already marketed in some Asian countries (e.g China, India, Israel) and South America (e.g Brazil and Columbia). On the other hand, the regulatory and legal issues of biosimilars in the US is just settled a few years ago causing US company having "late" arrival in biosimilars market (Kay, 2011). Zarxio, a biosimilar of filgastrim is the first biosimilar approved by FDA in 2015 which is manufactured by Sandoz (FDA, 2015; Sörgel *et al*., 2015). The second biosimilar approved by FDA is planned to be launched in the end of 2016 called Basaglar, a biosimilar of insulin glargine, which is manufactured by Eli Lilly/BoehringerIngelhem (Diatribe, 2016)

Table 1. Definitions of Biosimilar products

Term	Regulatory Body/Country	Definition
Similar Biologic Product (SBP)	WHO	A biotherapeutic product similar to an already licensed reference biotherapeutic product in terms of quality, safety and efficacy
Follow on Biologic (FOB)	US FDA	A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency
Subsequent-entry Biologic (SEB)	Canada	A biologic drug that enter the market subsequent to a version previously authorized in Canada with demonstrated similarity to a reference biologic drug
Biosimilar	Korea	Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy

(Adapted from Wang and Chow 2012)

Table 2. Biosimilars approved by EMA 2015. (Siegel, 2015)

Product Name	Active Substance	Reference Drug	Year of Approval	Manufacturer/ Company Name
Epoetins				
Abseamed	Epoietin alfa	Eprex/EPO	2007	Medice
Binocrit	Epoietin alfa	Eprex/EPO	2007	Sandoz
Epoetin alfa hexal	Epoietin alfa	Eprex/EPO	2007	Hexal
Retacrit	Epoietin zeta	Eprex/EPO	2007	Hospira
Silapo	Epoietin zeta	Eprex/EPO	2007	Stada
Filgastrims				
Accofil	Filgastrim	Neupogen	2014	Accord
Biograstim	Filgastrim	Neupogen	2008	AbZ-Pharma
Filgastrim Hexal	Filgastrim	Neupogen	2009	Hexal
Grastofil	Filgastrim	Neupogen	2013	Apotex

Nivestim	Filgastrim	Neupogen	2010	Hospira
Ratiogastrim	filgastrim	Neupogen	2008	Ratiopharm
Tevagrastim	Filgastrim	Neupogen	2008	Teva
Zarzio	Filgastrim	Neupogen	2009	Sandoz
Follitropins				
Bemfola	Follitropin alfa	GONAL-f	2014	Finox
Ovaleap	Follitropin alfa	GONAL-f	2013	Teva
Growth Hormones				
Omnitrope	Somatropin	Genotropin	2006	Sandoz
Insulins				
Abasaglar	Insulin glargine	Lantus	2014	Eli Lilly
Monoclonal Antibodies				
Inflectra	Infliximab	Remicade	2013	Hospira
Remsima	Infliximab	Remicade	2013	Celltrion

2. Biosimilar in Indonesia

2.1 The guidelines

The first biosimilar concept has been approved in European Union in 2003. However, as international organization, WHO drafted the biosimilar guidelines in 2009. In the USA, FDA issued the regulation of biosimilars in 2012. To date, the general guidelines for biosimilars have been developed or even approved in many countries, both in developed countries such as Canada, Japan, Australia and in developing countries such as South Africa, Egypt, some countries in South America, India and other countries in Asia. Within ASEAN countries, Singapore and Malaysia are the pioneer in drafting this guideline. In a recent year, the Philippines has launched biosimilar guidelines in 2014 followed by Indonesia in the late of 2015. Badan Pengawas Obat dan Makanan (BPOM) or National Agency for Drug and Food Control (NADFC) Republic of Indonesia, which has functions and tasks like FDA in the United States, has launched the biosimilar guideline documented in "*Peraturan Kepala Badan Pengawas Obat Dan Makanan Republik Indonesia Nomor 17 Tahun 2015 Tentang Pedoman Penilain Produk Biosimilar* ". In general, the guideline gives details about biosimilar meaning, registration procedures and evaluation of biosimilar products including comparability studies, selection of reference product, production process, physicochemical characterisation, analytical techniques, non-clinical and clinical safety and efficacy evaluation as well as pharmacovigilance plans. In Indonesia, beside the biosimilar guideline (Perka BPOM RI No 17/2015), the company proposing a new development of biosimilar product has also to comply the guideline for evaluation of new drug development as stated in "*Peraturan Kepala Badan Pengawas Obat dan Makanan Nomor 16 Tahun 2015 tentang Tata Laksana dan Penilaian Proses Obat Pengembangan Baru*".

2.2 The quality, safety and efficacy assessments of biosimilar

The quality, safety and efficacy of biosimilar products are highlighted in all biosimilars guidelines. In general, regulation drafted by BPOM has the same degree of guidance with other guidelines in term of the assessment of quality, safety and efficacy. The product quality is assessed by head to head comparison of physicochemical analyses to show the high degree of similarities between biosimilar and its originator. These analyses play a key role to minimize the requirements in non-clinical and clinical data analyses. To conduct the quality assessment, the knowledge in the interaction of biochemistry, physical chemistry and biology of biologics are required. For example, the post translational modification (PTM) in eukaryotic system might obtain the heterogeneity of final product. Therefore, the chosen of expression system as a bioreactor to produce biosimilar haproducts should be carefully considered to gain high quality product. Another case is about the oxidation of methionine residues of proteins that might affect the biological functions. However, in some proteins, this methionine has no significant effect in clinical outcomes. Therefore, the comparability studies should be conducted independently for each biosimilar product.

The company that will develop biosimilar products has to gather as much information as possible about the innovator product that will be used as a reference in comparability assessment regarding to production system, fermentation techniques, harvesting product, purification, modification as well as storage. This information is important to gain a high degree of

similarity. The physicochemical characterization plays a pivotal role in assessing biosimilarity. The test methods involve in determination of primary structure, higher order structures (secondary and tertiary structures), post-translational modification, glycoform analyses, biological activity, purity/impurity, contaminants and immunochemistry. Like the EMA or FDA biosimilar guidelines, the BPOM guideline in biosimilar characterization seems to be referring to The International Conference on Harmonisation (ICH) including ICH Q5E (Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process) and ICH Q6B (Specification: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products). If there is discrepancy in characterization between biosimilar and reference, the scrutinized evaluation of product efficacy and safety should be done. Furthermore, the justification of differences showing insignificance effect in biological functions should be well explained. In BPOM biosimilar guideline, there is no detailed explanation in analytical methods for characterization. However, there are some analytical methods commonly used to assess the quality, efficacy, and safety of biologics or biosimilars (Table 3).

Table 3. Analytical techniques for quality, efficacy and safety assessment of biosimilars (Adapted from Visser *et al*., 2013)

Quality attribute	**Methods**
Primary structure (Amino Acid Analysis)	Reduced RP-HPLC-ESI-MS peptide mapping,
Higher Order Structure (conformation)	
• Disulfide Bridging	• Non-reduced/Reduced RP-HPLC-ESI-MS peptide mapping
• Free Thiol Analysis	• Ellman's assay
• Secondary and tertiary structure	• CD, FTIR,HDX-MS, X-ray-crystallography
• Thermodynamic stability	• DSC
Glycosilation	Monosaccharide composition analysis, oligosaccharide profiles, CE, LC-MS, MS-MS/ESI-Maldi TOF
Oxidation	Peptide mapping with MS
Deamidation	Capill ary IEF, peptide mapping with MS, CEX HPLC, C-terminal lysine (Capilary IEF, peptide mapping with MS, CEX HPLC), miss-folds RP-HPLC
Size Heterogeneity (Monomer, aggregates)	SEC, AF4, gel electrophoresis, SE-HPLC, light scattering, AUC
Host Cell protein	ELISA, DNA, endotoxin
Target and Receptor Binding	Cell assays, spectroscopy, ELISA, SPR
Biological Activity	Cell-based binding assay and animal models
Biological Potency	Cell-based bioassay, gene expression bioassay, ADCC, CDC

2.2.1 Analytical techniques for quality, efficacy and safety assessments of biosimilars

2.2.1.1 PAGE, Western Blot

Polyacrylamide gel electrophoresis (PAGE) is an analytical method that has been utilised extensively in recombinant protein characterization (Lee-Huang, 1984; Miozzari *et al*., 1979). PAGE is a simple, qualitative analysis giving the information of molecular weight of protein by comparison with known molecular markers. In addition, it can be used to detect the purity of protein. Therefore, PAGE is still performed as a routine analysis in the process of regulatory approval for recombinant protein-based biologics. Proteins are separated according to size and shape (hydrodynamic radius), and can be visualized by either a colorimetric stain (e.g Coomassie blue, silver stain) or immunoblotting (Western blot). The stained bands can be removed from the gel as a sample material for further analyses including amino acid sequencing and peptide mass printing (Wilm *et al*., 1996). However, the variation on staining-destaining protocol may obtain a misleading data interpretation due to the differences in the intensity of the faint bands; thus, the qualitative assessment of purity might be ambiguous. The combination between PAGE and Western blotting is often used to visualize the specific protein of interest; a technique whereby the separated protein from PAGE is electro-transferred into a membrane and specifically detected using antibody preparation (either monoclonal or polyclonal). PAGE/Western blotting analysis can identify a multimerization of protein whereby the aggregation of protein from the small dimer, trimer to larger aggregates can be spotted which was demonstrated by Park *et al*., to

detect multimerization of EPO in various preparations (Park *et al*., 2009).

2.2.1.2 IEF, CZE and microfluidic IEF

Isoelectric focusing (IEF), like PAGE, is an electrophoretic method for separating protein based on their isoelectric point (pI). The technique identifies qualitatively or quantitatively and can be used in conjunction with protein blotting. IEF-protein blotting has been utilized to characterize a range of biosimilar EPO preparations, which clearly exhibit heterogeneity with respect to charge isoform distribution (Park *et al*., 2009). This technique is also useful for detection of charged isoforms due to the variability of C-terminal lysine residues on monoclonal antibodies (Jung *et al.*, 2014).

Capillary zone electrophoresis (CZE) is widely practiced as an alternative method to PAGE which separates protein by a combination of hydrodynamic radius, friction and charge protein. This technique has an advantage due to being automated and better suited to compliance with method qualification and validation for protein analysis. CZE has been utilized in separating charged isoforms of EPO, which demonstrate a better outcome compared with PAGE/IEF blotting (Park *et al*., 2009). The combination of CZE and microfluidic IEF are willing to follow a procedure similar to HPLC validation in analytical testing, thus the technique validation tends to play a significant role in procedure analysis in the industry.

2.2.1.3 Spectroscopic methodologies

The utility of spectroscopic methods using UV absorbance can be applied to detect contaminant on biopharmaceutical product such as DNA content. In addition, UV fluorescence spectroscopy is able to determine the intrinsic fluorescence of protein. The aromatic amino acids including tryptophan, tyrosine and phenylalanine exhibit the intrinsic fluorescence, which is having different absorbance fluorescence spectra. Detection of tryptophan residues which have the strongest fluorescence (absorbance maxima at 280 nm and fluorescence maxima around 350 nm) is widely employed as sensitive method to report protein conformational changes, unfolding, aggregation, and complex formation of proteins (Chen & Barkley, 1998; Duy & Fitter, 2006; Hanslip *et al*., 2008). Research shows that by studying the intrinsic fluorescence, differentiation of the structural conformation of two different epoetin alfa products is capable to be determined (Epogen and Eprex) (Deechongkit *et al*., 2006).

2.2.1.4 Mass Spectrometry-based techniques

In biologics production, the bioprocess defines the product. Subtle differences in the manufacturing process between a biosimilar and innovator product contribute to variability in product heterogeneity. Determination of heterogeneity is still a challenge in comparability studies of a biosimilar with an innovator product. A standard testing method has been utilized to characterize product variants using a combination of protein enzymatic cleavage (e.g trypsin), followed by HPLC and tandem mass spectrometry (LC-MS) technologies which provide detailed data in comparability studies. This characterization facilitates identification of post-translational modifications (PTMs) (e.g. glycosylation), disulfide linkages and free cysteine residues, chemical modifications (e.g deamidation and oxidation), and sequence variance due to mistranslation.

Peptide mapping analysis using LC-MS is widely used as a standard testing protocol for comparison study of a biosimilar and innovator product. In a simple non-glycosylated protein, such as human growth hormone, LC-MS analysis can identify different levels of oxidation of methionine residues, deamidation of asparagines and cleavage at two sites (Jiang *et al.*, 2010). In complex, glycosylated proteins such as EPO, TNK-tissue plasminogen activator and monoclonal antibodies, which exhibit a high degree of heterogeneity, the utility of peptide mapping analyses using LC-MS is essential to determine the composition of carbohydrate moieties, location of glycosylation sites, chemical modification of amino acid residues, and the location of disulfide linkage (Jiang *et al*., 2010; Xie *et al.*, 2010).

Detection of small but significant changes in protein structure is still a challenge in comparability studies of recombinant biologics. Classical biophysical techniques such as CD spectra, UV Spectroscopy, DSC, ITC and FTIR generally provide only an average readout of the protein elements. Sophisticated tools including NMR and X-ray crystallography are able to detect the small changes in protein structure. However, these techniques are time consuming and complex to use and inapplicable for routine analysis in biopharmaceutical company due to the large size of protein (for NMR) or the time consuming process of protein crystallization and structure determination by X-ray crystallography. Hydrogen/deuterium exchange-mass spectrometry (HDX-MS) has been utilized in biopharmaceutical comparability studies and provides good precision, consumes a small amount of protein (picomoles), interrogates of nearly molecules with peptide level resolution, and allows the result to be obtained within a few days. Since HDX-MS method can reveal the detail of

protein structure, it has potential to become important tool in comparability assessment between a biosimilar and the innovator product. Furthermore, research shows that HDX-MS can be used to monitor the effect of interaction between a protein biologic and its receptor, which is important for determining biological activity (Berkowitz, *et al.*, 2012; Houde *et al.*, 2011). Consequently, this technique may also have potential in the discovery and development of biopharmaceuticals.

2.2.1.5 In vitro assays

Potency determination using in vitro assays is a powerful method for regulatory submission in therapeutic proteins. The quality of protein is assessed by comparing biological response related to its binding to a specific receptor or ligand. The binding functionality may correspond to biological activity of the protein. Even though physicochemical analyses of protein are essential to confirm the actual structural of molecules, determination of in vitro bioassays are important to confirm the functional conformation of protein and provide information how the molecule interact with intended target. Different assay formats can be used to assess biosimilar such as ligand or receptor binding assays, enzymatic assays, cell-based assays, and functional assays. The most common binding assay is enzyme linked immunosorbent assay (ELISA), which generally obtains robust performance and can be developed relatively quickly (Wang, 2014). The integration of analytical methods and ELISA has been established in many testing protocols. Although ELISA is still an outstanding analytical tool in protein assay, more sophisticated tools in protein binding assay such as SPR and ITC are becoming utilized offering advantages in assay format versatility, speed, as well as sensitivity. Even though ligand binding assays are often used for comparability study of biosimillars, for ligand-type therapeutic molecules (e.g erythropoietin), cell-based assays are preferred for potency determination due to biomimicry to the ligand mechanism of action and more sensitive to small structural changes (Gianoncelli *et al.*, 2015).

There are a range of different types of cell-based bioassays that is widely used for characterization of biopharmaceuticals including proliferation and cytotoxicity assays, apoptosis assays, and assays based on the measurement of either induction or inhibition of functionally essential signal molecules (e.g cAMP, phosphorylated protein, enzymes, and cytokines). In a class of cancer therapeutics such as recombinant growth hormone and Antibody-drug conjugate, the cell viability assays are common examined using cell proliferation and cytotoxicity assays. Apoptosis assay is used for product that induces cell death through apoptosis pathways (Wang, 2014). Assays that measure induction/ inhibition of signal molecules tend to be more complex using either growth factor-dependent cell lines or natural cell lines that respond to therapeutic proteins. In the case of EPO, in vitro bioactivity was performed by measuring radio-labelled thymidine uptake utilizing 32D cell line which was introduced by human EPO receptor to obtain dependent on EPO for growth (Elliott *et al.*, 2004). Furthermore, the utility of erythropoietin-dependent human leukemic megakaryocyte cell line was developed by Amgen for cell based-bioassay (Park *et al*., 2009). On the other hand, natural cell line can also be used in bioassay which was demonstrated by Elliot *et al*. that utilized murine bone marrow cells to test erythropoietin activity as well as assessment of stimulation cell growth using counting cell colonies by microscope (Elliott *et al*., 2004). The NFS-60, murine myelogenous leukaemia cell line was utilized in functional comparability study of biosimilar filgastrim (FDA, 2015).

3. Challenges of comparibility and other regulatory issues of Biosimilar

Berkowitz *et al*. (2012) claimed that there are at least two general challenges in assessing comparability of biosimilar products. First, defining the definition of "similar" proposed by EMA and "highly similar" proposed by FDA. It is known that biopharmaceutical industry has multistep processes leading to several changes of structures. Second, defining the acceptable level to demonstrate whether the biosimilar product is similar or highly similar with its innovator. The different of living system as a bioreactor for biologic production will have different structures or even isoforms of glycosylation in post-translational modification. Thus, FDA and other regulatory authorities agree that the main point of comparability is to assess the biosimilar product pre- and post- manufacturing changes; therefore it can be interchangeable or highly similar with a licensed innovator product (Berkowitz *et al.,* 2012). The EMA has their own comparability guidelines that detailed for biosimilars market approval (Mc Camish & Woollett, 2011).

The FDA initiates the international guideline for quality design and process analytical technology for manufacturing biosimilars. There are several scientific issues as criteria for bioequivalence analyses of biossimilar products, such as similarity of size and structure, biosimilarity of biological activity, the problem of immunogenicity, manufacturing process and statistical consideration (Chow & Liu, 2009). Sophisticated biochemical characterization is required to underpin analyses of those criteria. Due to the complexity of protein molecules, all those methods cannot completely reveal the characters of biological products (Schellekens, 2009). In addition, the traditional bioequivalence studies cannot be applied for comparability study of biosimilars. As an example in Retrocite® case, one of biosimilar epoetin revealed the challenges in bioequivalence studies when it was compared to Eprex® as a reference biologic. The potential variation in batch-to batch production in both biosimilar product and its innovator product may result the imprecise data. Though every single biologic product is different; however, there are no meaningful differences in clinical efficacy (Jha *et al*., 2012; Schellekens, 2009).

It is clear that the complex methods are required to produce biosimilar products leading to high cost production. Behrman *et al*. (2008) estimate the development of one biosimilar product will take at least 5-8 years. This is more time consuming compare to small drugs development, which only need 1-2 years. Therefore, the big portion of national pharmacy budget is consumed by biosimillars. However, some countries in Latin America abbreviated the long pathway regulation of biosimilars for economic reasons. They refer to WHO guidelines for biosimilars that launched in 2009. Brazil led to establish a "local" model for biosimilars regulation to produce two kinds of biosimilar products, complex molecules such as monoclonal antibodies and simple molecules such as pegylated interferon (Behrman *et al.*, 2012). The scheme of regulatory for biosimilars has more complexity compare to innovator products because it is not easy to demonstrate highly similar. The modification of structures, even slightly different, may lead very different effects to the patients. Therefore, the quality, safety, and efficacy of biosimilar products must be approved before marketing approval (Bhupinder Singh Sekhon, 2011).

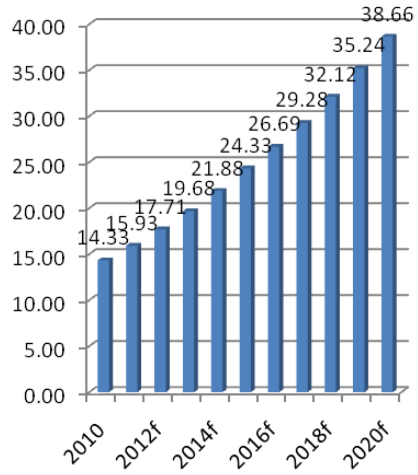

Figure 1. The prediction of generic market in Indonesia (Peraturan Menteri Kesehatan Republik Indonesia: peta jalan pengembangan bahan baku obat, 2013)

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 PHARMA-CEUTICALS	• 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 (Monoclonal Anti Body) • Insulin analogue

4. Impact of biosimilars on global industry and future prospects in Indonesia

Not all biosimilar products have been approved by authorities. A biosimilar of IFN-α 2A was rejected by EMEA; and another biosimilar application for insulin was withdrawn by Marvel Lifesciences in Mumbai India (Schellekens & Moors, 2010). In 2014, the biosimilar market was about 16% from total global pharmaceutical market and raised until 30% in 2015. The biosimilars market is predicted to reach almost three times by 2020 compared to 2015 from $2.29 billion to $6.22 billion (Markets and Markets, 2016). The market of biologic and biosimilar products is not only in developed countries but also in developing countries, such as China, India, Brazil and Rusia (Mahler & Gray, 2011). Azevedo *et al*. (2012) point out the potential commercial environment of biosimilars in several Latin America countries outside Brazil, such as Argentina, Chile, Mexico and Venezuela (Azevedo *et al.,* 2012). The main reason is the fast growth of biopharmaceutical companies in the few last decades with total sales of biologic products up to US $40 billion in 2006 (Behrman *et al.,* 2012) biotech market is expected to be promising since several blockbuster biologic products will lose their patent protection in the next couple years. The main advantage of biosimilar development can reduce the cost of treatments for patients and will be more accessible since the patent is no longer in use. For producers of biosimilars, they can expand the market since the lower prices of biosimilar production (Rovira *et al.,* 2011).

Indonesia has the biggest pharmaceutical market in ASEAN countries. The Indonesian Pharmaceutical Market achieved US$ 6 billion last year with the 3-4% of growth (Prahadi, 2015). The prediction of generic market, including biosmilar in Indonesia is shown in Figure 1. In 2015, ProBioGen AG and Bio Farma Indonesia signed an agreement for development of biosimilar Trastuzumab for breast cancer treatment. Under the terms of the agreement ProBioGen will develop a highly efficient manufacturing process based on a specifically designed recombinant CHO-cell line, conducting engineering runs and the industrial scale-up (Biofarma, 2015). In the same year, Biofarma also collaborated with Indonesian Institute of Sciences to produce biosimilar human erythropoietin (Fahrul, 2015). Currently, at least four other big companies (PT. Kalbe Genexine Biologics and PT Etana Biotechnologies Indonesia, PT. Combiphar, PT. Phapros) are starting to develop biosimilar products, and it is projected to reach the market the next few years in Indonesia and in Southeast Asian countries later (Lona, 2014; Combiphar, 2016)

The development of biosimilar is an important issue in strategic plan of Indonesian pharmaceutical industry. In the strategic plan of 2015-2018, there are several biosimilars that will be developed, such as erythropoietin, GCSF, Insulin and somatropin. In the next three year periods will be continued for Blood fractionation, growth hormone, interferon, trastuzumab, insulin and monoclonal antibody. The last two also will be developed on 2023-2025 (Table 4). The strategic plan is also integrated with the regulation of BPOM which assign lighter requirement for registration of Indonesian biosimilar. This policy is expected to encourage the Indonesian biosimilar production.

There are three important stakeholders with central role in biosimilar development, pharmaceutical industry, researcher and government. The government should have a political will to support the autonomy production of biosimilar. The conducive policy form the government will intensify the activities of industry and researcher as well. As a "pharmerging" country, Indonesia has about 100 pharmaceutical companies, potential human resources and various research activities

to support biosimilar development. Therefore, the autonomy production on biosmilars will be achieved.

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