Manufacturing of Biosimilars and Their Uses

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Abstract: One of the pharmaceutical industry's fastest-growing segments, "biologics," has developed several innovative medicines for serious and uncommon diseases. In the 1980s, the first generation of recombinantly produced biopharmaceutical products was introduced, and its patent protection is about to expire. As a result, both research-based and generic pharmaceutical firms are vying for the chance to create biosimilars, or "generic" replacements for original biologics. In contrast to the relatively simple procedure of releasing a generic alternative to an innovator product based on a novel chemical entity, the introduction of a biosimilar to an innovator product is far more difficult. Since complete organisms or cultured cells manufacture biologics, these processes are intrinsically more unpredictable than chemical synthesis techniques. Because of this, it is hard to produce a similar or exact clone of an innovative product, unlike generic drugs. By being similar yet distinct, or " not the clone, but the twin," of the original biologic innovator product, biosimilars are described in this way. Therefore, the field of biosimilars presents a number of significant challenges, including i) the verification of similarity, ii) the interchangeability of biosimilars and innovator products, iii) the potential need for unique product names to distinguish the various biopharmaceutical products, iv) the regulatory framework, v) commercial opportunities as well as guidelines to assist manufacturers in product development, vi) intellectual property rights, and vii) public safety.

Key Words: —*Biosimilars, Generics, Biologics, Drugs.*

I. INTRODUCTION

A biologic is defined as "any virus, therapeutic serum, toxin, antitoxin, or comparable product relevant to the pre-vention, treatment, or cure of illness or injury of man" in the U.S. Federal Code of Regulations (CFR)[5].Recombinant methods were originally used to create biologics in the 1980s in order to duplicate or enhance complicated peptides, proteins, and glycoproteins found in nature [1,3,4]. Since then, even more complicated products, such monoclonal antibodies, have been created by altering the DNA of bacteria, yeast, or mammalian cells to create therapeutic or diagnostic products. [1,6–8] Enzymes, vaccines, human insulin, interferons, interleukins, erythropoietins, gonadotropins, granulocyte-colony-stimulating factors (G-CSFs), human growth hormones, monoclonal antibodies, blood coagulation modifiers, and tissue plasminogen activators are examples of biologic therapies that are currently accessible. [7]

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The links between a biologic's structure and function are extremely delicate since changes to primary or higher-order (secondary, tertiary, or quaternary) configurations may have an impact on a biologic's safety, purity, or potency.[6] Primary amino acid sequences can change due to glycosylation throughout the manufacturing process for biologics or biosimilars, modifying the shape of a protein due to changes in how it folds.[5] These post-translational alterations are influenced by the cell line and the environment in which the cell line is cultured rather than the recombinant DNA that was put into the host cell.[3]

It is difficult to develop biosimilars that are identical to the original medicine since every producer of biologics or biosimilars utilises a distinctive cell line and a patented technique to produce a specific bio- logic agent. [1,5,8] Contrarily, typical chemical drug molecules are considerably smaller, have a more straightforward structure, and are readily produced by a predictable and regulated chemical process that yields identical copies. On the other hand, with biologics, even tiny changes in the production process can lead to a different final product. [3,5] Because the final product is heavily dependent on a proprietary manufacturing method that is unique to each manufacturer, the therapeutic effectiveness, safety, and quality of a bio-similar biologic may differ from the originator, or "reference," biologic. [5] The word "biosimilar" as opposed to "biogeneric" or "bioidentical" is

used since it is impossible to replicate an original biologic exactly. [3]

II. Literature Review

2.1 Drugs against biologics versus tiny molecules

Biologics and ordinary small-molecule medications differ significantly from one another primarily due to their different origins (Tables 1). Small-molecule medications are often produced using chemical techniques, whereas biological products are typically created by cells or other living things.[9] Due to the origin differences, there are also variations in the structure, content, manufacturing processes and tools, intellectual property, formulation, handling, dosage, regulation, and marketing. Biologics are 100 to 1000 times bigger in size than manufactured tiny molecules, with several hundred amino acids (average molecular weight of 150 per amino acid) that are biochemically linked together by peptide bonds to create a polypeptide. Contrarily, traditional medications are typically chemically manufactured, molecular weight 1000, self-contained organic compounds. [10] Additionally, the intricacy and number of atoms that go into a molecule's structure increase with size.

Table.1. Comparison of innovator, generic, and biosimilar supplies

Process	Biologic	Biosimilar	Generic
Manufacturing	produced in host cell lines by biological processes. sophisticated and specialised manufacturing facilities that are sensitive to changes in the production process. Establishing reproducibility is challenging.	produced in host cell lines by biological processes. sophisticated and specialised manufacturing facilities that are sensitive to changes in the production process. Establishing reproducibility is challenging.	used chemical synthesis to create. less responsive to changes in the production process. It is simple to establish reproducibility.
Clinical development	extensive clinical research, spanning Phase I through III. Periodic safety updates and pharmacovigilance are required.	extensive clinical research, spanning Phase I through III. Periodic safety updates and pharmacovigilance are required.	frequently only Phase I trials. Short approval timeframe.
Regulation	Demonstrates "comparability" is required. European Union-defined regulatory process (EMEA). No automatic replacement is envisaged at this time.	Demonstrates "comparability" is required. European Union-defined regulatory process (EMEA). There can be no automatic substitute.	must demonstrate bioequivalence. shortened registration processes in the US and Europe Allowable automatic substitution

As a result, biologics are substantially more complex than low molecular weight medications since they are made up of primary (amino acid sequence) and secondary (□-helix and □-pleated sheet) structures that are folded into intricate 3D tertiary structures.[11] Stable interactions between the tertiary structures of several proteins produce quaternary structures in some biopharmaceuticals. These structures are frequently further altered after synthesis by post-translational processes such glycosylation or sialylation, which may be essential for biological function.[12] Furthermore, a biopharmaceutical's characterisation is extremely difficult because to its increased size and structural complexity.

2.2 Manufacturing of Biosimilars

Biosimilars are viewed as affordable alternatives to expensive, large-molecule biologics. Biosimilars must, however, fulfil the same standards of quality, safety, and effectiveness as their reference biologic. A more involved process is needed for producing biosimilars than when producing generic small molecule drugs. Companies that produce biosimilars are focused on developing a chemical structure that is as comparable to the reference product's as is humanly achievable. Companies producing biosimilars have different challenges than those producing small molecule generics, including higher failure rates and higher operating expenses.[13]

Small molecule generics are produced using the same active pharmaceutical ingredient (API) as the brand-name drug and are thus chemically equivalent to it. Compared to biologic medications, the manufacturing process for small molecules only includes one-fifth of all in-process testing necessary to comply with Good Manufacturing Practice (50 vs. 250 in-process tests). In reality, because the cells used to make biologic medications are exclusive to the firm that makes each biologic, the manufacturing process for a big molecule is so complicated that it cannot be recreated by two distinct producers.[13]

A cell that will serve as the foundation for a cell line utilised to produce the essential protein for the biologic therapy is genetically altered as part of the biologic manufacturing process. After that, the protein is extracted from the cells and refined. Small modifications to the manufacturing process result in a molecule that is not exact but closely resembles the reference product, which is how biosimilars are made. The effectiveness and safety of a biosimilar relative to the reference biologic can be impacted by changes in the manufacturing process, even if the variations in the biosimilar molecule may be minor. The cost of producing biosimilars has decreased as a result of the standardizedization of the protein manufacturing process and the rising accessibility of the necessary technologies over the past ten years. A higher

number of businesses have started producing biosimilars as a result, while producers of reference brand pharmaceuticals are focusing on building pipelines and producing biobetters to preserve market share for their soon-to-be off-patent reference drugs.[13]

2.3 Aspects of biosimilars regulation

A dosage form is a significantly more affordable version of an innovator drug. Generics can be manufactured when a drug's patent has run out, for medications that have never had a patent, in nations where a patent is (are) not active, and when the generic businesses certify that the patents owned by the branded companies are invalid, unenforceable, or won't be violated. Under the FDA-established Abbreviated New Medicine Application (ANDA) procedure, generic drug manufacturers can submit applications for marketing clearance of their products. Additionally, because preclinical and clinical evidence to show safety and efficacy are typically not necessary, generic medication applications are known as "abbreviated" applications. Only pharmaceutical and bioequivalence between the generic and innovator products must be demonstrated by the generic product maker in order for their product to be approved.

Desired gene isolation → Insertion into vector →Host cell expression →Cell culture → Cell bank establishment & characterization → Protein production → Protein purification → Analysis → Formulation → Storage & handling

However, because the active ingredient in a biopharmaceutical is a collection of big protein isoforms rather than a single molecular entity, as is typically the case for traditional small-molecule medications, this technique cannot be used to biosimilars. As a result, it is extremely improbable that the active ingredients in two products would be the same, making biosimilars, unlike generics, only somewhat comparable to the originator medications. These distinctions suggest that biosimilars shouldn't be authorised and controlled similarly to traditional generic medications.

Because it is difficult to construct scientifically sound research to show the resemblance of a highly process-dependent product, the regulatory procedure for approval of biosimilars is more complicated than for the generic innovator product. Additionally, the currently available analytical assays are not sophisticated enough to identify the little but significant structural variations between originator and biosimilar medicines. Small variations may have clinical repercussions and represent a serious threat to patient safety. As a result, it is believed that before receiving marketing authorisation, biosimilars must undergo credible preclinical and clinical studies to evaluate their clinical effectiveness and safety. [14,15–17].

2.4 Biosimilars' EMEA status: approved or rejected

Since the road for regulatory approval of biosimilars was created, a total of 14 brand-name biosimilars (based on 4 reference medicines) from nine businesses have been authorized in the EU [18]. A biosimilar interferon product's application for approval was turned down by the EMEA in 2006 because of issues with the product's characterization, production, and quality control [19]. Additionally, Marvel Life Sciences formally informed the CHMP in December 2007 that it intended to withdraw its requests for marketing authorizations for a number of biosimilar insulins due to the CHMP's refusal to extend the deadline for their submission of a list of questions [20] The CHMP's concerns about bio similarity, drug product and content, as well as clinical and non-clinical characteristics, underscore how difficult it is to quickly approve biosimilars because each product must be evaluated individually [21]. The European Public Assessment Report (EPAR), which is provided by EMEA, contains information on the approval procedure for human pharmaceuticals as well as a scientific analysis of the clinical data requested for approval. According to the EPARs for biosimilars, the biosimilar was approved because it had a quality, safety, and effectiveness profile that was equivalent to the innovator product's [22–29].

Adverse medication responses are of significant relevance to pharmacovigilance. Pharmacovigilance worries have recently been expanded to cover originator products and biosimilars. Clinical studies and pharmacovigilance after product approval are thought to be necessary to ensure the product's safety and effectiveness throughout time. A thorough risk management approach must involve regular testing for the consistency of the drug's manufacture as part of pharmacovigilance [30]. Immunogenicity is the most important safety issue in regard to biopharmaceuticals (including biosimilars) [31,32]. Reduce or eliminate antigenic epitopes and incorporate beneficial physical and chemical features when designing molecules to minimise immunogenicity [33]. Due to the limited capacity to forecast the clinical effects of seemingly harmless alterations in the manufacturing process and the knowledge gap in the scientific community, pharmacovigilance is crucial in the biosimilars industry [34]. Other crucial factors are also shown by the Eprex example. First, it is crucial to carefully monitor a biologic's safety once it has been put on the market, regardless of whether it is novel or biosimilar. The pure red cell aplasia problem with Eprex (epoetin alfa) brought

attention to the need for increased pharmacovigilance with biopharmaceuticals. The CHMP guidelines stress the need of paying close attention to pharmacovigilance, particularly to spot uncommon but dangerous adverse events[34].

Novartis welcomes the recent EU proposal to examine and expand the pharmacovigilance system of pharmaceuticals in Europe in order to increase patient safety through improved pharmacovigilance. Furthermore, whether the relevant brand is an innovator product or a biosimilar product should not matter; appropriate pharmacovigilance processes should be required for all goods of a given category (such as biopharmaceuticals) [35].

Special dangers apply to biologicals. Spontaneous reports of possible adverse medication responses have helped to identify safety issues, such as those related to infliximab and the risk of TB (ADRs). Data from the WHO Collaborating Centre for International Drug Monitoring's ADR database (VigiBase) showed that biologicals have a distinct safety profile than all other medications in the database, and that there are variances across mechanistic classes within the category of biologicals. Additionally, spontaneous reporting continues to be a crucial strategy for the early discovery of signals because not all bad responses can be anticipated or recognized during development [36].

Table.2. Biosimilars approved or rejected timeline

Biosimilar	Approval or Rejection year	References
Omnitrope	2006*	Somatropin
Valtropin	2006*	Somatropin
Binocrit	2007*	Epoetin alpha
Epoetin alpha	2007*	Epoetin alpha
Hexal		
Abseamed	2007*	Epoetin alpha
Silapo	2007*	Epoetin zeta
Retacrit	2007*	Epoetin zeta
Filgrastim	2008*	Filgrastim
Ratiopharm		
Ratiograstim	2008*	Filgrastim
Biograstim	2008*	Filgrastim
Tevagrastim	2008*	Filgrastim
Filgrastim hexal	2009*	Filgrastim
Zarzio	2009*	Filgrastim
Nivestim	2010*	Filgrastim
Alpheon	2006**	Roferon-A
Human insulin	2007**	Humulin

Notes: *Approved, **Declined

Additionally, manufacturers frequently include pharmacovigilance plans in their post-approval pledges to regulatory authorities to conduct follow-up safety evaluations. Years of pharmacovigilance allowed doctors to conclude that the issue with Eprex may have arisen as a result of the medicine reacting with the rubber stopper used in vials after the transition to polysorbate 80. There have been reports of biosimilar pharmacovigilance from a regulatory standpoint [37].

2.5 Biosimilars in clinical uses

Despite the fact that biosimilars and the innovator product are comparable, doctors and other healthcare professionals should be aware of a few problems that sprang up throughout the development and approval of these medicines and emphasise the difficulties with biosimilars [38] Utilizing biosimilars fundamentally involves a shift in clinical management [39]. The Pan American and Health Education Foundation actively contributes to patient safety by playing a major role in informing patients and medical professionals about the advantages and hazards of biosimilars [40].

Because patients must be closely watched if their therapy is switched between products, it is crucial that the hospital pharmacist is aware that originator drugs and biosimilars are not interchangeable. Additionally, pharmacists must prioritise the needs of their patients, so understanding that biosimilars are not generic medications and the potential effects of switching products on clinical results will allow them to do so.[41]

In contrast to interchangeable goods, biosimilars are also thought to include a novel active component. The Eprex example offers another justification for not thinking of a biosimilar as being interchangeable with a cutting-edge medicine. According to the FDA, it has not yet figured out how interchangeability for complicated proteins can be shown. [42,43]

For the evaluation of newly released biopharmaceuticals, systematic checklists have been suggested, which has given the pharmacist further peace of mind. For instance, information on manufacturing, protein and product formulation, batch consistency, supply dependability, good handling practise, clinical efficacy, and clinical safety and tolerability is provided by the Pharmacy Checklist for Retacrit (epoetin zeta).[44] Hospital pharmacists now have the chance to save costs and enhance the care of anaemic patients thanks to the successful launch of EU biosimilar erythropoietins like Retacrit.

2.6 Biosimilar versions of medications used to treat cancer

There are a number of biopharmaceutical treatments for cancer patients for which biosimilar drugs are anticipated to be created.

Table.3. summarizes the features of biopharmaceutical drugs in Europe that have either lost or will shortly lose their patent protection. [45-50]

Products	**Description**	**Source**	**Indication**
Colony-promoting elements Filgrastim	175-amino-acid recombinant protein that is nonglycosylated and has an additional methionine at the N-terminus.	*Escherichia coli*	AML chemotherapy, BMT, mobilization of PBPC, severe congenital, cyclic, idiopathic neutropenia, HIV-related neutropenia, and chemotherapy-induced neutropenia (apart from CML and MDS).
Lenograstim	174 amino acid recombinant protein with 4% carbohydrate.	CHO	Neutropenia brought on by chemotherapy, receiving BMT, and PBPC mobilisation
Interferons IFN a2a	165 amino acid recombinant protein that is nonglycosylated and has lysine at position 23.	*Escherichia coli*	Chronic-phase Philadelphia chromosome-positive chronic myelogenous leukaemia, cutaneous T-cell lymphoma, AIDS-related Kaposi's sarcoma, follicular lymphoma, advanced renal cell carcinoma, chronic HCV (adults), chronic HBV (adults).
IFN a2b	165 amino acid recombinant protein that is nonglycosylated and has arginine at position 23.	*Escherichia coli*	AIDS-related Kaposi's sarcoma, hairy cell leukaemia, malignant melanoma, follicular lymphoma, condyloma acuminata, chronic HCV in adults, and chronic HBV in children under one year
Epoetins Epoetin alfa	165 amino acid recombinant protein that is glycosylated.	CHO	CRF anaemia, chemotherapy-induced anaemia, higher autologous blood donation yield, and lower allogeneic blood donation following surgery.
Epoetin beta	165 amino acid recombinant protein that is glycosylated.	CHO	Enhancing the yield for autologous blood donation; anaemia of CRF; symptomatic renal anaemia; chemotherapy-induced anaemia; anaemia in patients with multiple myeloma, low-grade NHL, or CLL;

[AML stands for acute myelogenous leukaemia; BMT stands for bone marrow transplant; CHO stands for Chinese hamster ovary; CLL stands for chronic lymphocytic leukaemia; CML stands for chronic myelogenous leukaemia; CRF stands for chronic renal failure; HBV stands for hepatitis B

virus; HCV stands for hepatitis C virus; MDS stands for myelodysplastic syndrome; NHL stands for non- Hodgkin's lymphoma; PBPC stands for peripheral blood progenitor cell.]

Table 3 provides an overview of some of the innovative cancer management medications that have lost their patent protection in Europe or will do so soon.

III. Conclusion

Biosimilars are anticipated to play a crucial role in lowering healthcare expenses and improving patients' access to critical, frequently life-saving pharmaceuticals.[52] It is hoped that the FDA will soon complete these regulatory guidelines, address any outstanding issues, and create a pathway for biosimilars that is based on reliable scientific knowledge.[51,52] The government will have to strike the right mix between strict data and testing standards and offering a quick, inexpensive approach to approve biosimilars.[53] However, in order to promote the availability of biosimilars, it must be too burdensome to deter firm sponsors from developing and delivering biosimilars to the market. Robust evidence is essential to guarantee medication effectiveness and safety. [54,55].

References

[1]. Calo-Fernández B, Martínez-Hurtado J. Biosimilars: Company strategies to capture value from the biologics market. Pharmaceuticals 2012:5(12);1393–1408.
[2]. Hirsch BR, Lyman GH. Biosimilars: Are they ready for primetime in the United States? J Natl Compr Cancer Network 2011; 9:934–943.
[3]. McCamish M, Woollett G. The state of the art in the development of biosimilars. Clin Pharmacol Ther 2012;91(3):405–417.
[4]. Blackstone E, Fuhr J. Innovation and competition: Will biosimilars succeed? Biotechnol Healthcare 2012;9(1):24–27.
[5]. Hoffman JM, Li E, Stevenson JG. Preparing for biosimilars: Scientific, regulatory, and practice management issues for phar- macists. Live webcast, 47th ASHP Midyear Clinical Meeting and Exhibition, Las Vegas, December 3, 2012.
[6]. Lee JF, Litten JB, Grampp G. Comparability and biosimilarity: Considerations for the healthcare provider. Curr Med Res Opin 2012;28(6):1053–1058.
[7]. Simoens S, Verbeken G, Huys I. Biosimilars and market access: A question of comparability and costs? Target Oncol 2012;7(4):227– 231.
[8]. Simoens S. Biosimilar medicines and cost-effectiveness. Clinico- economic Outcomes Res 2011:3;29–36.
[9]. Marshall SA, Lazar GA, Chirino AJ, Desjarlais JR. Rational design and engineering of therapeutic proteins. Drug Discov Today. 2003;8: 212–221.
[10]. Revers L, Furczon E. An introduction to biologics and biosimilars. Part II: subsequent entry biologics: biosame or biodifferent? Can Pharmacists J (CPJ/RPC). 2010; 143:184–191.
[11]. Crommelin DJA, Storm G, Verrijk R, Leede L, Jiskoot W, Hennink WE. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Intern J Pharmaceut. 2003;266:
[12]. Revers L, Furczon E. An introduction to biologics and biosimilars. Part I: biologics: what are they and where do they come from? Can Pharmacists J CPJ/RPC. 2010; 143:134–139.
[13]. Crommelin DJ, Bermejo T, Bissig M, et al. pharmaceutical evaluation of biosimilars: important differences from generic low-molecular-weight pharmaceuticals. Eur J Hosp Pharm Sci. 2005; 11:11–17.
[14]. Roger SD. Biosimilars: how similar or dissimilar are they? Nephrology (Carlton). 2006; 11:341–346.
[15]. Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern?
[16]. J Pharm Pharmaceut Sci. 2007; 10:405–410.
[17]. Schellekens H. Follow-on biologics: challenges of the 'next generation'.
[18]. Nephrol Dial Transplant. 2005; 20:31–36.
[19]. Questions and answers on recommendation for refusal of marketing application for Alpheon. London, UK: European Medicines Agency, 2006.
[20]. Questions and answers on the withdrawal of the marketing authorisa¬tion application for Insulin Human Rapid Marvel Insulin Human Long Marvel Insulin Human 30/70 Mix Marvel. London, UK, European Medicines Agency, 2008.
[21]. Misra A. Are biosimilars really generics? Expert Opin Biol Ther. 2010; 10:489–494.
[22]. European Medicines Agency. Omnitrope: EPAR summary for the public 2007.
[23]. European Medicines Agency. Valtropin: EPAR summary for the public 2006.
[24]. European Medicines Agency. Retacrit: EPAR summary for the public 2008.
[25]. European Medicines Agency. Silapo: EPAR summary for the public 2007.
[26]. European Medicines Agency. Epoetin alfa HEXAL: EPAR summary for the public 2007.
[27]. European Medicines Agency. Binocrit: EPAR summary for the public 2007.
[28]. European Medicines Agency. Abseamed: EPAR summary for the public 2007.
[29]. Schellekens H Biosimilar therapeutics – what do we need to consider?
[30]. NDT Plus. 2009;2(Suppl 1): i27–i36.

[31]. Locatelli F, Roger S. Comparative testing and pharmacovigilance of biosimilars. Nephrol Dial Transplant. 2006;21(Suppl 5): v13–v16.
[32]. Nowicki M. Basic facts about biosimilars. Kidney Blood Press Res. 2007; 30:267–272.
[33]. Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern?
[34]. J Pharm Sci. 2007; 10:405–410.
[35]. Singh SK. Impact of product-related factors on immunogenicity of biotherapeutics. J Pharm Sci. 2011; 100:354–387
[36]. Zuniga L, Calvo B. Biosimilars: pharmacovigilance and risk management. Pharmacoepidemiology Drug Saf. 2010; 19:661–669.
[37]. Giezen TJ, Mantel-Teeuwisse AK, Meyboom RHB, Straus SMJM, Leufkens HGM, Egberts TCG. Mapping the safety profile of biologicals: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase. Drug Saf. 2010; 33:865–878.
[38]. Schellekens H, Lisman J, Bols T. Biosimilars in clinical practice –the challenges for hospital pharmacists. EJHPP Practice. 2008;14: 32–33.
[39]. Questions and answers on recommendation for refusal of marketing application for Alpheon. London, UK: European Medicines Agency, 2006.
[40]. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars.
[41]. Ann Omol. 2008; 19:411–419.
[42]. Background on Biosimilars.
[43]. Schellekens H, Lisman J, Bols T. Biosimilars in clinical practice –the challenges for hospital pharmacists. EJHPP Practice. 2008;14: 32–33.
[44]. Declerck PJ, Darendeliler F, Góth M, et al. Biosimilars: controversies as illustrated by rhGH. Curr Med Res Opin. 2010; 26:1219–1229.
[45]. Hospira symp on assessing biosimilars.
[46]. Carter CR, Whitmore KM, Thorpe R. The significance of carbohydrates on G-CSF: differential sensitivity of G-CSFs to human neutrophil elastase degradation.
[47]. J Leukoc Biol 2004; 75: 515–522.
[48]. European Medicines Agency. Guidance on similar biological medicinal products containing recombinant granulocyte-colony stimulating factor. 2006.
[49]. Kim IH, Park SK, Suh OK et al. Comparison of lenograstim and filgrastim on haematological effects after autologous peripheral blood stem cell transplantation with high-dose chemotherapy. Curr Med Res Opin 2003; 19: 753–759.
[50]. Granocyte (lenograstim). Summary of product characteristics. Chugai, London, UK, 2005.
[51]. Neupogen (filgrastim). Summary of Product Characteristics. Amgen, Cambridge, UK, 2006.
[52]. Rana JB, Chang DY. Pharmacist perception of biosimilar agents in the U.S. Pharmacy Purchasing Products 2012;9(7):8.
[53]. Revers L, Furczon E. An introduction to biologics and biosimilars. Part II: subsequent entry biologics: biosame or biodifferent? Can Pharmacists J (CPJ/RPC). 2010; 143:184–191.
[54]. Crommelin DJA, Storm G, Verrijk R, Leede L, Jiskoot W, Hennink WE. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Intern J Pharmaceut. 2003; 266:3–16.
[55]. Genentech Inc. Corporate Chronology. 1982.
[56]. Blackstone E, Fuhr J. Innovation and competition: Will biosimilars succeed? Biotechnol Healthcare 2012;9(1):24–27.