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Research Article

Comparing Drug Handling Efficiencies and Expenses for Short-Acting Granulocyte-Colony Stimulating Factor Injection Originators and Biosimilars from the Perspective of Hospital Resource Management in Formulary Decision-Making

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Abstract

Background/Aim: With the availability of biosimilars, hospital formulary drug selection among biologics extends beyond clinical and safety considerations when comes to hospital resource management, to factors like human resource allocation and financial sustainability. However, research assessing the time and cost of labor, supplies, and waste disposal of biologics from the standpoint of hospitals remains limited. This study focuses on short-acting granulocyte-colony stimulating factor originators (Granocyte® and Neupogen®) and biosimilar (Nivestim®), comparing them based on mean total handling times per dose and total annual expenses.

Materials and Methods: Ten nurses from a Taiwanese cancer center were recruited; they each prepared three doses of each drug.

Results: Findings showed that the mean total handling times per dose of Granocyte® and Neupogen® were significantly higher than that of Nivestim®. Handling Nivestim® required the lowest total annual expense.

Conclusion: Nivestim® is an advantageous alternative to Granocyte® and Neupogen®, benefiting hospital resource management.

Kew Words: filgrastim; filgrastim biosimilar; granulocyte-colony stimulating factor; hospital resource management; lenograstim

Introduction

When comes to drug selection in the context of resource management within healthcare organizations, factors beyond clinical efficacy and safety should be taken into consideration, as decision-making for formularies impacts the allocation of human resources, use of pharmaceuticals, and overall financial sustainability of the healthcare facility [1]. When chemical or biologic originators were initially the exclusively available products on the market, health providers were constrained to procure them owing to their patented market [2, 3]. However, the market competition has since evolved with the introduction of generics and biosimilars [4]. Notably, biologics are delivered as injections or infusions [5], thus requiring special handling, specific storage conditions, ancillary supplies, and careful waste management strategies. In response to these needs, manufacturers of biosimilar drugs add other values to their products, like offering greater consumer convenience by packaging with prefilled syringes and providing formulations with extended beyond-use dates [6, 7]. In light of this, healthcare providers are now faced with a choice not previously available – selecting among originators and biosimilars – in their pursuit for sustainable resource management.

One such example is granulocyte-colony stimulating factors (G-CSFs), a biologic that stimulates neutrophil production in the bone marrow to intervene chemotherapy-induced myelosuppression [8-10]. In Taiwan, several originator and biosimilar G-CSFs have been developed and approved for clinical application (Table 1) [11-17]. They can be categorized into short- and long-acting types; the former includes Granocyte® (lenograstim), Neupogen®, also known as 惠爾血添® in Taiwan (filgrastim), and Nivestim® (filgrastim biosimilar), while the latter includes Neulasta® (pegfilgrastim), Ziextenzo® (pegfilgrastim biosimilar), Fulphila® (pegfilgrastim biosimilar), and Lonquex® (lipegfilgrastim) [18]. Short- and

long-acting G-CSFs serve different therapeutic roles [19]. Short-acting G-CSF is administered for the treatment and prophylaxis of neutropenia or febrile neutropenia. By contrast, long-acting G-CSF is administered once per chemotherapy cycle for prophylaxis [20].

Table 1: Taiwan Food and Drug Administration- (TFDA-) approved G-CSF (updated as of December 29th, 2023)

Short-acting G-CSFs						
Generic name	**Brand name**	**Originator/ Biosimilar**	**Manufacturer**	**Dosage form**	**Strength**	**Storage conditions**
Leno-grastim	Granocyte®	Originator	Chugai Pharma Taiwan Ltd.	Lyophilized powder in vial and accompanying solvent in ampoule	100 μg/vial 250 μg/vial	Do not store above 30°C. Do not freeze. Reconstituted solution is recommended to be used immediately, or stored up to 24 hours at 2°C - 8°C.
Filgrastim	Neupogen®	Originator	Kyowa Kirin Taiwan Co., Ltd.	Solution for injection	75 μg/0.3 mL/ampoule 150 μg/0.6 mL/ampoule	Store in the refrigerator between 2°C to 8°C
	Nivestim®	Biosimilar	Pfizer Inc.	Solution for injection/infusion (pre-filled syringe)	120 μg/0.2 mL/syringe 300 μg/0.5 mL/syringe 480μg/0.5 mL/syringe	Store in the refrigerator between 2°C to 8°C
Long-acting G-CSFs						
Pegfil-grastim	Neulasta®	Originator	Kyowa Kirin Taiwan Co., Ltd.	Solution for injection (prefilled syringe)	6 mg/ 0.6 mL/ syringe	Store at 2° to 8°C. Do not freeze or shake. Protect from light.
	Ziextenzo®	Biosimilar	Novartis Taiwan Co., Ltd.	Solution for injection (prefilled syringe)	6 mg/ 0.6 mL/ syringe	Store at 2° to 8°C. Do not freeze or shake. Protect from light.
	Fulphila®	Biosimilar	Mylan Taiwan Ltd.	Solution for injection (prefilled syringe)	6 mg/ 0.6 mL/ syringe	Store at 2° to 8°C. Do not freeze or shake. Protect from light.
Lipegfil-grastim	Lonquex®	Originator	Teva Pharmaceutical Industries Ltd.	Solution for injection (prefilled syringe)	6 mg/ 0.6 mL/ syringe	Store at 2° to 8°C. Do not freeze or shake. Protect from light.

Focusing on short-acting G-CSFs, Nivestim® is a biosimilar of Neupogen® that comes in convenient, prefilled syringes [13]. This contrasts with the originators, Granocyte® and Neupogen®, which are packaged into vials of dry powder and solution, respectively, making Nivestim® a potentially more attractive option in terms of expediting the administration process [21]. With ever increasing demands on medical resources, assessing the time and cost of labor, supplies, and waste disposal associated with biologics is critical in deciding between originators and more affordable biosimilars. This study aims to compare these three drugs, namely the two originators (Granocyte® and Neupogen®) and one biosimilar (Nivestim®), based on their mean total handling times per dose and total annual expenses at a local, independent cancer center in Taiwan.

Materials and Methods

Study design and participants

This study was conducted at the Koo Foundation Sun Yat-Sen Cancer Center in Taipei, Taiwan. Ten nurses from the Department of Nursing were recruited into the study. Each nurse was responsible for handling three doses of each short-acting G-CSF product: Granocyte® (250 μg/vial), Neupogen® (150 μg/0.6 mL/ampoule), and Nivestim® (120 μg/0.2 mL/syringe). The nurses adhered to the standardized drug handling protocol (Appendix A). All the necessary ancillary supplies, namely alcohol swabs, syringes, needles, and artificial skin, were provided (Appendix B).

Drug handling time

The nurses prepared each of the three short-acting G-CSFs three times. They were video-recorded while following the drug handling protocols (Appendix A). Subsequently, one researcher documented the time (in seconds) spent by the nurses on each step of the protocols. The "mean handling time per step" for each nurse was derived from the three separate attempts. Those means were then summed to yield the "mean total handling time per dose" by each nurse, which was tested for statistically significant differences among Granocyte®, Neupogen®, and Nivestim®. Additionally, the "median handling times per step" across the 10 nurses were computed and summed to obtain the "median total handling time per dose"; this value was then utilized in the calculation of the labor cost for each product, as detailed in the next section. The time needed for the refrigerated drug ampoule or syringe to reach room temperature was not considered in our study.

Cost of handling G-CSF in a healthcare setting

The total annual expense for handling a G-CSF product in a healthcare setting was broken down into three components: cost of labor, medical supplies, and waste disposal in New Taiwan Dollars (NT$). Firstly, labor cost was determined based on each medication's median total handling time per dose, as described in the previous section, and the nurses' average hourly

wage in 2022 (NT$ 271/hour) [22]. Secondly, the cost of medical supplies encompassed alcohol swabs, syringes, and needles, and it was computed using unit prices provided by medical suppliers. Third, waste disposal fees were calculated based on the total weight of the products themselves, vials, alcohol swabs, syringes, and needles, which followed the established pricing method. The sum of labor cost, medical supplies, and waste disposal yielded the total expense per dose. And to compare the expenses on a yearly basis, the total annual expense for each G-CSF product was calculated based on the quantity of 10,000 doses.

Statistical analysis

The Friedman test was used to determine if there were overall significant differences in the average drug handling times among the three drugs: two originators (Granocyte® and Neupogen®) and one biosimilar (Nivestim®). Subsequently, post hoc analysis via Wilcoxon signed-rank tests was performed with a Bonferroni correction applied to identify the pairs of drugs with statistically significant differences in drug handling times. A Bonferroni-adjusted significance level of $p < 0.017$ was interpreted as statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

Results

Ten nurses were recruited into this study and were each tasked with handling three doses of three G-CSF products: Granocyte® (lenograstim), Neupogen® (filgrastim), and Nivestim® (filgrastim biosimilar). The "mean handling time per step" by each nurse (denoted by A to J) was measured (Appendix C). Across the three protocols, steps such as hand washing, drug inspection, reconstitution, and injection were the most time-consuming. Figure 1 illustrates the mean and median total handling times per dose for Granocyte®, Neupogen®, and Nivestim®. The median total handling time per dose for a single Nivestim® administration was 85 seconds, which was notably shorter than the times required for Granocyte® and Neupogen® administrations, measured at 242.5 and 120.5 seconds, respectively. The Friedman test demonstrated statistically highly significant differences in mean total handling time per dose among the three drugs (Friedman's $\chi 2 = 20.000$, $df = 2$, $p < 0.001$). Post hoc comparisons using Wilcoxon signed-rank tests with a Bonferroni correction revealed statistically significant differences between all three groups: Neupogen® and Nivestim® ($Z = -2.805$, $p = 0.005$), Granocyte® and Nivestim® ($Z = -2.803$, $p = 0.005$), as well as Granocyte® and Neupogen® ($Z = -2.803$, $p = 0.005$).

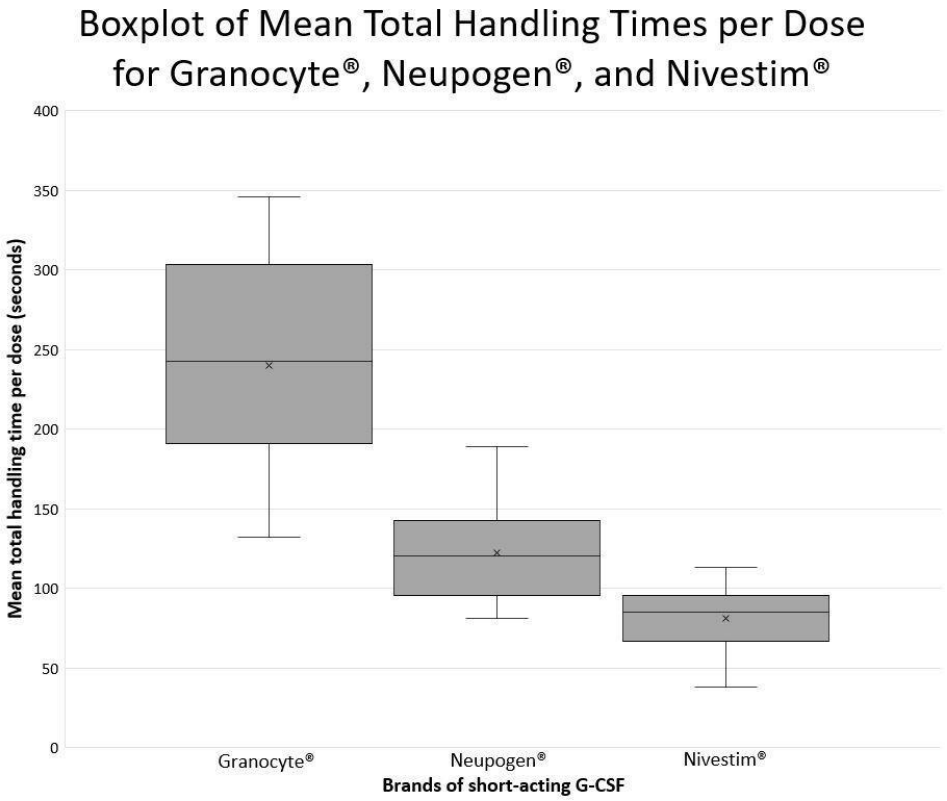

Figure 1: Boxplot of mean total handling times per dose in seconds for Granocyte®, Neupogen®, and Nivestim®. The three boxplots illustrate the distribution of mean total handling times per dose for Granocyte® (n=10), Neupogen® (n=10), and Nivestim® (n=10). The shaded box represents the interquartile range with the mean indicated by the "x" and the median indicated by the horizontal line within the box. The vertical lines extending from the box show the range from the minimum to the maximum values, excluding outliers.

The total expenses per dose of Granocyte®, Neupogen®, and Nivestim® were NT$ 23.66, NT$ 12.35, and NT$ 7.31, respectively (Table 2). Labor costs made up the largest portion of total expenses per dose for all three drugs, constituting 77%, 73%, and 88% of the cost for Granocyte®, Neupogen®, and Nivestim®, respectively (Figure 2). Nivestim®, the filgrastim biosimilar, incurred the lowest labor and medical supply costs among the three drugs. Meanwhile, the cost for waste disposal was highest for Granocyte®, followed by Nivestim® and Neupogen®. When considering total annual expenses, Granocyte® was the highest (NT$ 236,563), followed by Neupogen® (NT$ 123,502) and Nivestim® (NT$ 73,128).

Table 2. Cost breakdown for handling short-acting G-CSFs in a healthcare setting

	Granocyte®	Neupogen®	Nivestim®
Labor cost (NT$)	18.25	9.07	6.40
Medical supplies (NT$)	4.6	2.8	0.4
Waste disposal (NT$)	0.8063	0.4802	0.5128
Total expenses per dose (NT$)	23.66	12.35	7.31
Total annual expenses (NT$)	236,563	123,502	73,128

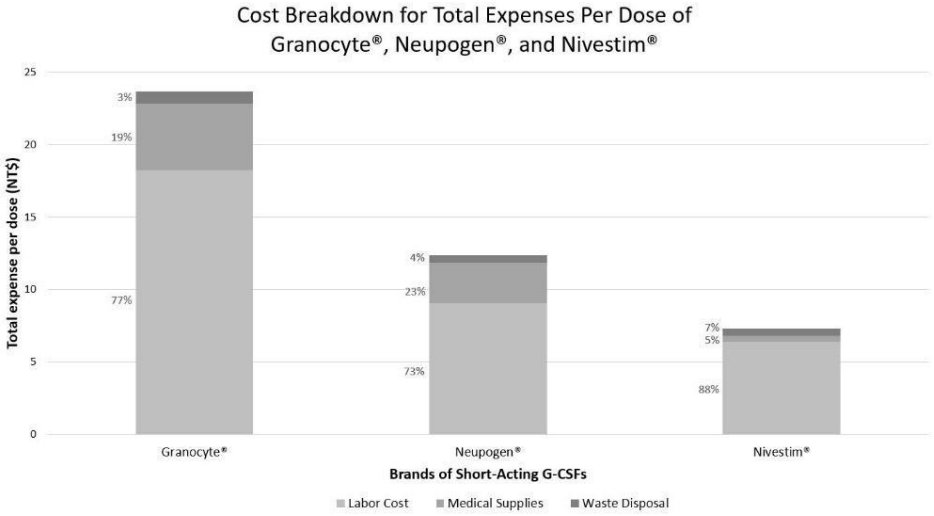

Figure 2: Cost breakdown for total expenses per dose. Stacked bar chart visualizing the total expenses per dose of Granocyte®, Neupogen®, and Nivestim® in a healthcare setting, broken down into three components: labor cost, medical supplies, and waste disposal. Labor cost was determined based on nurses' average hourly wage of NT$ 271/hour and the median total handling time for each product. The proportions of each component for the three brands of drugs are expressed as percentages.

Discussion

This is the first study to compare three short-acting G-CSF products in terms of their handling times and expenses. Nivestim® required a statistically significantly shorter mean total handling time per dose and the lowest total annual expense compared with Granocyte® and Neupogen®. The cost effectiveness of Nivestim® may be attributed to its ready-to-use packaging, eliminating the need for ancillary supplies and lowering the spending on waste disposal. In addition, the pre-filled syringes of Nivestim® streamline its drug handling protocol, thereby reducing labor cost. Notably, air bubbles may become trapped in syringes when products are drawn from vials or ampoules, as is the case with Granocyte® and Neupogen®, and those bubbles need to be expelled to ensure accurate dosing and patient safety [23]. However, small quantity of bubbles can often be disregarded in manufacturer-prefilled syringes, as is the case with Nivestim®, thereby expediting the preparation process [24].

Aside from differences in labor requirements, the three short-acting G-CSFs vary in storage requirements. As with most protein-based therapeutics, optimal storage conditions are vital for maintaining the stability and shelf-life of G-CSFs, as they are susceptible to denaturation and degradation when exposed to environmental stressors like temperature extremes, light, or pH changes [25]. Whereas Granocyte® can be stored at room temperature for 30 months [11], Neupogen® and Nivestim® require refrigeration and can be stored for 36 and 30 months, respectively [12, 13]. Based on manufacturers' instructions, however, Neupogen® and Nivestim® can remain stable at room temperature for up to 24 hours post-refrigeration [12, 13], a step that would not have impacted the nurses' drug handling efficiency. Therefore, the present study did not factor the time needed to bring Neupogen® and Nivestim® to room temperature into the analysis of total drug handling time.

Beyond lowering expenses and workforce demands within individual medical facilities, the adoption of biosimilars also has significant implications for public health. Recent expert reports from high-income countries highlight that nearly all stakeholders in healthcare can benefit from biosimilars [26], as they provide more treatment options for the growing aging population and foster market competition to make products more affordable [27-29]. According to the United States Food and Drug Administration, developing biosimilars can take from 8 to 10 years, incurring between USD $100 and 200 million, whereas an estimated USD $2.6 billion would be required for the development of a novel drug [30, 31]. Having a broader array of treatment options for a particular disease or condition also incentivizes manufacturers to adjust pricing to sustain or expand their market share [32]. Moreover, biosimilars may even introduce competition that pressures reference products to drop in prices, leading to greater reductions in healthcare spendings [33].

This study is subject to certain limitations. One potential concern is the relatively small sample size, which consists ten nurses from a single healthcare center in Taipei, Taiwan who are tasked with handling each product three separate times. The single-center design may also affect the external validity of the findings. Nonetheless, given that the nurses have all undergone proper training and followed the standard operation procedure provided by the Principal Investigator, increasing the number of participants would likely have limited impact on our results. The second limitation is that our study focuses on three short-acting G-CSF products currently approved for clinical use in Taiwan. As a result, the findings may not be generalizable across other countries, where variations in dosage forms and healthcare practices can influence drug handling times and expenses. With that considered, caution should be exercised when extrapolating the findings to

diverse healthcare settings and healthcare systems outside of Taiwan. Nevertheless, our study contributes novel perspectives on formulary decision-making in the context of hospital resource management.

Conclusion

The present study demonstrates that the short-acting G-CSF biosimilar, Nivestim®, is an advantageous alternative to the short-acting G-CSF originators, Granocyte® and Neupogen®, significantly reducing both time and expenses spent on the drug handling process. Given the growing cancer patient population and finite medical resources, the practical and financial benefits of biosimilars signal an opportunity for local healthcare facilities to re-strategize their formulary decision-making to optimize resource management.

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Author Contributions

Yi-Ying Chen: formal analysis; writing – original draft; writing – review and editing; visualization.

Winnie Khor: formal analysis; writing – original draft.

Pei-Ling Cheng: conceptualization; data curation.

Shao-Chin Chiang: conceptualization; methodology; writing – review and editing; supervision.

Conflicts of Interest

All authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available within the article's supplementary materials.

References

1. Olsen JC. (1995). What is resource management? *J Healthc Resour Manag*;13(1):11-13.
2. FDA. Biosimilar Basics for Patients: United States Food and Drug Administration; 2023 [cited 2023 Oct 17].
3. Declerck P, Danesi R, Petersel D, Jacobs I. (2017). The Language of Biosimilars: Clarification, Definitions, and Regulatory Aspects. *Drugs*;77(6):671-677.
4. Sarzi-Puttini P, Marotto D, Caporali R, Galeazzi M, Atzeni F, et al. (2019). Biosimilars vs originators: Are they the same? *Autoimmunity Reviews;*18(12):102404.
5. Nongkhlaw R, Patra P, Chavrasiya A, Jayabalan N, Dubey S. (2020). Chapter 6 - Biologics: Delivery options and formulation strategies. In: Shegokar R, editor. *Drug Delivery Aspects: Elsevier;* p. 115-155.
6. Allocati E, Godman B, Gobbi M, Garattini S, Banzi R. (2022). Switching among biosimilars: a review of clinical evidence. *Frontiers in Pharmacology;* 13:917814.
7. Makwana S, Basu B, Makasana Y, Dharamsi A. (2011). Prefilled syringes: An innovation in parenteral packaging. *Int J Pharm Investig*;1(4):200-206.
8. Karagiannidis I, Salataj E, Said Abu Egal E, Beswick EJ. (2021). G-CSF in tumors: Aggressiveness, tumor microenvironment and immune cell regulation. *Cytokine;* 142:155479.
9. Link H. (2022). Current state and future opportunities in granulocyte colony-stimulating factor (G-CSF). *Supportive Care in Cancer;*30(9):7067-6777.
10. Hart L, Ogbonnaya A, Boykin K, Deyoung K, Bailey R, et al. (2023). Burden of chemotherapy-induced myelosuppression among patients with extensive-stage small cell lung cancer: A retrospective study from community oncology practices. *Cancer Medicine;*12(8):10020-10030.
11. EMC. GRANOCYTE 13 million IU/mL, powder and solvent for solution for injection/infusion: emc; 2022 [cited 2023 Aug 10]. Available
12. EMC. Neupogen 30 MU (0.3 mg/ml) solution for injection: emc; 2022 [cited 2023 Aug 10].
13. Pfizer. Nivestim™. 2023.
14. Amgen. Neulasta® Safety Data Sheet 2023.
15. Ziextenzo. Convenient dosing and administration: ZIEXTENZO® (pegfilgrastim-bmez); 2023 [cited 2023 Sep 10].
16. Drugs.com. Fulphila Injection Dosage: Drugs.com; 2023 [cited 2023 Sep 10].
17. Teva Pharma Australia. AUSTRALIAN PI – LONQUEX® (LIPEGFILGRASTIM) SOLUTION FOR INJECTION. 2023.
18. Ba Y, Shi Y, Jiang W, Feng J, Cheng Y, et al. (2020). Current management of chemotherapy-induced neutropenia in adults: key points and new challenges: Committee of Neoplastic Supportive- Care (CONS), China Anti-Cancer Association Committee of Clinical Chemotherapy, China Anti-Cancer Association. *Cancer Biol Med*;17(4):896-909.
19. Calum Polwar GJ, Will Horsley, (2018). Guideline for the use of granulocyte-colony stimulating factor (G-CSF) in adult *oncology and haematology patients.*
20. Hsu SW, Chiang SC, Hsu JC, Ko Y. (2023). Prescription patterns of granulocyte colony-stimulating factors in patients with breast cancer: A real-world study. *PLoS One;*18(7): e0288642.
21. Smale EM, Egberts TCG, Heerdink ER, van den Bemt BJF, et all., (2021). Waste-minimising measures to achieve sustainable supply and use of medication. Sustainable *Chemistry and Pharmacy*; 20:100400.
22. MOHW. Some primary care nurses have stated that their monthly salary is only 36,000 NTD. What is the overall wage situation of nurses? : Department of Nursing and Health Care, *Ministry of Health and Welfare;* 2023 [cited 2023 Nov 23].
23. DoHAC. Administration of vaccines: Australian Government Department of Health and Aged Care; 2023 [cited 2023 Aug 31].
24. Immunize.org. Ask the Experts/ Administering Vaccines/ General Issues: Immunize.org; 2023 [cited 2023 Aug 31].
25. Krause ME, Sahin E. (2019). Chemical and physical instabilities in manufacturing and storage of therapeutic proteins. *Current Opinion in Biotechnology;* 60:159-167.
26. Smith S. Manufacturing, Approval and Advantages of Biosimilars. Edu Journal of International Affairs and Research, ISSN: 2583-9993. 2022;1(1):30-8.
27. NHIA. Frequently Asked Questions about Health Insurance Coverage for Biosimilars. 2023.
28. EMC. Biosimilar medicines can be interchanged: European Medicines Agency; 2022 [cited 2023 Dec 1].
29. DoHAC. Biosimilar medicines: the basics for health care professionals 2017.
30. FTC. Emerging health care issues: follow-on biologic drug competition. 2009.
31. Goozner M. A (2017). Much-Needed Corrective on Drug Development Costs. *JAMA Internal Medicine*;177(11):1575-6.
32. FDA. Overview of Biosimilar Products. 2023.
33. Boccia R, Jacobs I, Popovian R, de Lima Lopes G. (2017). Can biosimilars help achieve the goals of US health care reform? *Cancer Management and Research;* 9:197-205.

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