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## COMMENTARY:

### LOCAL POLICIES ON BIOSIMILARS - ARE THEY DESIGNED TO OPTIMIZE USE OF FREED RESOURCES; findings and implications?

Brian Godman<sup>1,2,3\*</sup>, BSc, PhD; Eleonora Allocati<sup>4</sup>, BSc, MSc; Evelien Moorkens<sup>5</sup>, MSc, PhD; Hye-Young Kwon, PhD<sup>1,6</sup>

<sup>1</sup>Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: [brian.godman@strath.ac.uk](mailto:brian.godman@strath.ac.uk)

<sup>2</sup>Division of Public Health Pharmacy and Management, School of Pharmacy, Faculty of Health Sciences, Sefako Makgatho Health Sciences University, Pretoria, South Africa

<sup>3</sup>Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden. Email: [Brian.Godman@ki.se](mailto:Brian.Godman@ki.se)

<sup>4</sup>Istituto di Ricerche Farmacologiche 'Mario Negri' IRCCS, Milan, Italy. Email: [eleonora.allocati@marionegri.it](mailto:eleonora.allocati@marionegri.it)

<sup>5</sup>KU Leuven Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium. Email: [evelien.moorkens@kuleuven.be](mailto:evelien.moorkens@kuleuven.be)

<sup>6</sup>College of Pharmacy, Seoul National University, Seoul, Korea. Email: [haeyoungkwon0111@gmail.com](mailto:haeyoungkwon0111@gmail.com)

\*Author for correspondence: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: [Brian.godman@strath.ac.uk](mailto:Brian.godman@strath.ac.uk). Telephone: 0141 548 3825. Fax: 0141 552 2562

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#### Abstract

There is an increasing need to prescribe biosimilars to fund new medicines and increasing medicine volumes. Bertolani and Jommi document successful measures introduced regionally in Italy.

#### Body of the Commentary

The recent GABI Journal article by Bertolani and Jommi comprehensively assessed the implications of a range of policies including education, benchmarking, and financial incentives, implemented by the different healthcare organisations (HCOs) among the Regions in Italy to increase the use of biosimilars as a way to conserve resources. This included both prospective and retrospective analyses of shifts in prescribing behaviour among the different regions and potential savings generated as well as how the savings generated were used (1).

We reviewed the paper by Bertolani and Jommi (1) and linked these findings with other recent studies in an attempt to stimulate ongoing debate regarding potential ways to enhance the future use of biosimilars as well as how best to utilize the considerable resource savings produced (2, 3) without compromising care.

The Bertolani and Jommi study is seen as particularly important as a source of information that can be used to provide future guidance as there have only been a limited number of studies to date that assessed differences in regional policies to enhance the prescribing of biosimilars in the ambulatory care setting where biologicals are increasingly being used (4). A response rate to the survey of 38% is seen as acceptable (5, 6), especially since the Regions surveyed covered 93% of the Italian population (1).

The need to leverage competition from biosimilars will only increase since without a major increase in the use of biosimilars global expenditure on medicines is projected to reach US\$1.5 trillion by 2023 (7-9). This growth will be primarily driven by increased expenditures on specialty biological medicines, including new medicines for chronic, complex, or rare diseases such as cancer and orphan diseases. Global expenditure for these medicines is likely to reach 50% of total medicine expenditures in the near future (7, 10). Such expenditures are difficult to sustain, especially in countries with universal healthcare systems that need to fund a growth in the use of medicines driven by increasing rates of non-communicable diseases, changes in clinical practice, and the launch of new, high-priced medicines that address areas of unmet need (11-14). There are additional concerns raised about

some new, high-priced medicines for cancer and orphan diseases, for which funding appears driven more by the emotive nature of these diseases than by their proven clinical benefits (15-18). Their value is being increasingly questioned as more medicines advocated in guidelines become available as low cost, multiple sourced medicines or biosimilars (19-21).

Biological medicines under increasing scrutiny include Humira® with global sales of US\$19.9 billion in 2018. Although Humira® sales are now being decreased, especially in Europe, through increasing use of lower priced biosimilars as well as by the fact that AbbVie lowered the price of Humira® to compete (22-26). For example, among Danish hospitals, expenditures for adalimumab decreased by 82.8% following the availability of biosimilars with almost total replacement by biosimilars (95.1% utilisation). In the UK, expenditure on adalimumab is envisaged to fall by 75% following the availability of biosimilars (23, 25). Such reductions are welcomed, especially among lower- and middle-income countries, including Central and Eastern European countries, where the use of biologicals has been limited by available governmental resources as well as by high patient co-payments (27-29). Biosimilar switching programmes have been shown to conserve resources by a number of studies that also were unable to demonstrate meaningful differences in effectiveness or safety between biosimilars and originators. Such studies have included infliximab and other biologicals across a range of indications (30-38). There have however been some concerns requiring patient monitoring (39, 40). Such concerns could be exacerbated by multiple modifications in the manufacturing of originator biologic drugs that can occur without companies being required to undertake clinical studies to assess the effect of such changes on clinical outcomes in actual practice, even with major manufacturing changes (41, 42).

Other biological medicines of special interest to health authorities across Europe and beyond include rituximab, infliximab, and etanercept with current global sales of US\$7.9billion, US\$ 5.9 billion and US\$ 5.8 billion in 2017 respectively (43-45). These concerns persist despite the fact that these sales are being reduced as the result of the increasing use of lower cost biosimilars (38, 39, 45-49). Global sales of Herceptin® (trastuzumab) were stable in 2019 at US\$7billion due to increasing use of biosimilar trastuzumab. The use of biosimilar trastuzumab is expected to continue to increase globally. Trastuzimab biosimilars have already captured 45% of the European market (50-52). However, these savings are being offset by growing expenditures on pertuzumab in combination with trastuzumab; with annual sales of US\$2.8billion in 2019 as well as by the use of Kadcyla® (trastuzumab emtansine), which is expected to reach annual sales of US\$4.94billion by 2023 (50, 53).

Another important biologic is long acting insulin glargine used principally for patients with Type 1 diabetes. The insulin glargine market was valued at approximately US\$3.88 billion in 2018, and is envisaged to reach US\$9.26 billion by 2025 (54). However, potential savings associated with the introduction of biosimilar insulin glargine have been hampered by limited price reductions seen in practice in a number of countries. There are also concerns with switching because differences in devices between manufacturers could increase the rate of hypoglycaemia (55-58). These concerns have resulted in some health authorities advising against switching, despite similar effectiveness and safety being demonstrated in studies comparing the originator and a biosimilar (55, 56, 59-62). The situation is however changing, at least in the US, where biosimilar insulin glargine reached over 40% of market share in the US Medicaid programme in 2018. There are also a number of initiatives and publications pushing for increased use of biosimilars among European countries including those encouraging new patients to be started on a biosimilar (49, 63-66).

A number of published studies have shown the potential for considerable savings from biosimilars. These results are pushing health authority to employ initiatives to enhance their use (3, 9, 38, 49, 51, 67-70). Winegarden (2019) in the US estimated annual savings of up to US\$7billion from the use of a range of biosimilars, and that these savings are likely to grow as more biosimilars become available (3). However for maximum savings, both supply- and demand-side measures are needed (21, 69). This has been shown in studies of oral generic medicines comparing potential policies and savings in Korea with those in the UK (71-74). Multiple demand- and supply-side measures in Scotland resulted in a considerable reduction in expenditure on lipid lowering medicines and proton pump inhibitors despite appreciably increased volumes (73, 74). Moorkens *et al.* (2017), Rémuzat *et al.* (2017) and Vogler *et al.* (2017) have all recently summarised ongoing demand-side measures in Europe to enhance the use of biosimilars. Simoens *et al.* (2018) also provided guidance on additional demand-side measures that could be introduced to further realise the benefits of biosimilars (75-78). There are European countries where some lower cost biosimilars now account for the total market, e.g. EPO

and G-CSF (79).and countries such as France and the UK are actively working to increase biosimilar penetration rates (80, 81).

Brill in the US has recently discussed the benefits of shared savings to enhance biosimilar use among State Medicaid programmes (10). Siu *et al.* (2019) documented ongoing activities to enhance the use of biosimilars in both the private and public sectors in Canada (70). These activities include preferential coverage by private insurers for increasing use of biosimilars, the pan-Canadian Oncology Biosimilars Initiative to enhance adoption of biosimilars in oncology (an attempt to address concerns with funding in oncology), as well as the British Columbia Biosimilars Initiative in May 2019 that promotes switching, with the savings used to lower premiums and co-pays where pertinent (70). In addition, Biosimilars Canada has recently developed a centralised patient support service platform to assist manufacturers and patients with increasing the use of biosimilars (70). Such activities are needed to promote the use of biosimilars because originator manufacturers have been appreciably lowering prices of their originators just before patent expiry to dissuade biosimilar companies from entering the market. (22, 44, 79) Suggestions have been made that originator companies should automatically lower their prices following patent expiry, thereby negating the need for biosimilars to interfere with the market in the first place. (82) Methods are needed to counter other behaviors of originator companies such as developing new formulations just before patent expiry to create a barrier to biosimilars mirroring other evergreening tactics (79, 83).

It was impressive to see that 89% of HCO surveyed by Bertolani and Jommi had implemented policies to enhance the use of biosimilars (1). Educational activities were particularly prominent, increasing in recent years, including information on market access pathways for biosimilars as well as the results of tenders. Educational activities are crucial to allay fears regarding the effectiveness and safety of biosimilars. These fears are illustrated in Italy by the seven scientific Italian societies that recently expressed concerns about the Regional Administrative Court of Piemonte promoting the automatic substitution of biologicals in terms of therapeutic continuity for patients and concerns with the freedom of clinicians (84). Despite this, benchmarking of biosimilar prescribing among physicians was already taking place among 75% of HCOs surveyed and this is likely to grow since such benchmarking of physician prescribing is working well in other countries (1, 85). The 62% of HCOs that also provided physicians with prescribing targets for biosimilars is similar to what has been seen in other countries and regions (86-88), with 68% and 24% respectively introducing incentives and sanctions to improve prescribing rates. Sanctions include monetary sanctions and potentially removal of the right to prescribe (1).

A concern though is that patients were involved in educational/ information programmes among only 22% of the HCOs surveyed (1). This is a potentially important weakness since all key stakeholders need to be convinced about the value of biosimilars in order to reduce any potential nocebo effects (89, 90).

The study of Bertolani and Jommi adds to a number of examples of successful multiple demand-side measures including preferentially encouraging the prescribing of multiple sourced medicines versus originators and patented medicines in a class without compromising care (91-93). Monies saved can subsequently be used to fund new more expensive medicines as well as other healthcare services such as diagnostics. 93% of HCOs also provided physicians with information retrospectively or prospectively on potential savings from increased use of biosimilars, with 25% of HCOs also participating in post-marketing studies to help further address potential fears with biosimilars (1). However only 21% of HCOs systematically estimated the proportion of potential patients not receiving biosimilars, with only rare perceptual surveys among patients and other healthcare professionals. This situation may need to change given the stated concerns of the seven scientific Italian societies (84).

In conclusion, Bertolani and Jommi, have provided a comprehensive review of ongoing policies among HCOs in the different regions of Italy and their potential to influence on future directions. This information is useful for other countries where demand-side measures can be localised to meet future goals, with the potential for localities to learn from each other. This is important to stimulate increasing use of biosimilars in a way that addresses the accelerating resource challenges brought about by the expanding use of medicines in ageing populations as well as the need to pay for new, high-priced medicines that address areas of previously poorly or untreatable diseases.

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## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

1. Bertolani A, Jommi C. LOCAL POLICIES ON BIOSIMILARS: ARE THEY DESIGNED TO OPTIMIZE USE OF FREED RESOURCES? *Generics and Biosimilars Journal (GaBI) 2020 (In Press)*.
2. Pettit C. Biosimilars Market Is Ripe for Cost Savings. 2019. Available at URL: <https://www.centerforbiosimilars.com/contributor/chad-pettit/2019/06/biosimilars-market-is-ripe-for-cost-savings>.
3. Winegarden W. The Biosimilar Opportunity: A State Breakdown. Pacific Research Institute Publication. 2019. Available at URL: [https://www.pacificresearch.org/wp-content/uploads/2019/10/BiosimilarSavings\\_web.pdf](https://www.pacificresearch.org/wp-content/uploads/2019/10/BiosimilarSavings_web.pdf).
4. Moorkens E, Simoens S, Troein P, Declerck P, Vulto AG, Huys I. Different Policy Measures and Practices between Swedish Counties Influence Market Dynamics: Part 2-Biosimilar and Originator Etanercept in the Outpatient Setting. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*. 2019;33(3):299-306.
5. Pandya C. What is an Acceptable Response Rate for Online Surveys? 2019. Available at URL: <https://www.appjetty.com/blog/acceptable-response-rate-for-online-surveys/>.
6. Lindemann N. What's the average survey response rate? [2019 benchmark]. 2019. Available at URL: <https://surveyanyplace.com/average-survey-response-rate/>.
7. IQVIA. The Global Use of Medicine in 2019 and Outlook to 2023 - Forecasts and Areas to Watch. 2019. Available at URL: <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf>.
8. Inotai A, Csanádi M, Vitezic D, Francetic I, Tesar T, et al. Policy Practices to Maximise Social Benefit from Biosimilars. *J Bioequiv Availab* 2017; 9: 467-72.
9. Povero M, Pradelli L. Funding Innovation Thanks to Anti-TNF- $\alpha$  Biosimilars Uptake: The Economic Impact in Italy. *Farmeconomia. Health economics and therapeutic pathways*. 2020;21(1): 37-47
10. Brill A. Shared Savings Demonstration for Biosimilars in Medicare: An Opportunity to Promote Biologic Drug Competition. 2020. Available at URL: [http://www.getmga.com/wp-content/uploads/2020/05/Biosimilar\\_Shared\\_Savings.pdf](http://www.getmga.com/wp-content/uploads/2020/05/Biosimilar_Shared_Savings.pdf)
11. Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. *BMJ*. 2020;368:l4627-l.
12. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA*. 2018;68(6):394-424.
13. Gyasi RM, Phillips DR. Aging and the Rising Burden of Noncommunicable Diseases in Sub-Saharan Africa and other Low- and Middle-Income Countries: A Call for Holistic Action. *The Gerontologist*. 2019.
14. Godman B, Bucsecs A, Vella Bonanno P, Oortwijn W, Rothe CC, Ferrario A, et al. Barriers for Access to New Medicines: Searching for the Balance Between Rising Costs and Limited Budgets. *Front Public Health*. 2018;6:328.
15. Cohen D. Cancer drugs: high price, uncertain value. *BMJ*. 2017;359:j4543.
16. Luzzatto L, Hyry HI, Schieppati A, Costa E, Simoens S, Schaefer F, et al. Outrageous prices of orphan drugs: a call for collaboration. *Lancet*. 2018;392(10149):791-4.
17. Godman B, Wild C, Haycox A. Patent expiry and costs for anti-cancer medicines for clinical use. *Generics and Biosimilars Initiative Journal* 2017;6(3):105-6.
18. Haycox A. Why Cancer? *PharmacoEconomics*. 2016;34(7):625-7.
19. Godman B, Hill A, Simoens S, Kurdi A, Gulbinovič J, Martin AP et al. Pricing of oral generic cancer medicines in 25 European countries; findings and implications. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2019;8(2):49-70.
20. Derbyshire M, Shina S. Patent expiry dates for biologicals: 2017 update. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2018;7(1):29-34.
21. Dutta B, Huys I, Vulto AG, Simoens S. Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price! *BioDrugs*. 2020;34(2):159-70.

22. Sagonowsky E. AbbVie's massive Humira discounts are stifling Netherlands biosimilars: report. 2019. Available at URL: <https://www.fiercepharma.com/pharma/abbvie-stifling-humira-biosim-competition-massive-discounting-dutch-report>.
23. Jensen TB, Kim SC, Jimenez-Solem E, Bartels D, Christensen HR, Andersen JT. Shift From Adalimumab Originator to Biosimilars in Denmark. *JAMA Internal Medicine*. 2020;180(6):902-3.
24. Stanton D. Global Humira sales near \$20bn, but expect decline in 2019. 2019. Available at URL: <https://bioprocessintl.com/bioprocess-insider/global-markets/global-humira-sales-near-20bn-but-expect-decline-in-2019/>.
25. Davio K. After Biosimilar Deals, UK Spending on Adalimumab Will Drop by 75%. 2018. Available at URL: <https://www.centerforbiosimilars.com/news/after-biosimilar-deals-uk-spending-on-adalimumab-will-drop-by-75>.
26. Davio K. Researchers Predict Substantial Savings for Europe on the Strength of Biosimilar Adalimumab. 2019. Available at URL: <https://www.centerforbiosimilars.com/view/researchers-predict-substantial-savings-for-europe-on-the-strength-of-biosimilar-adalimumab>.
27. Baumgart DC, Misery L, Naeyaert S, Taylor PC. Biological Therapies in Immune-Mediated Inflammatory Diseases: Can Biosimilars Reduce Access Inequities? *Frontiers in pharmacology*. 2019;10:279.
28. Kostic M, Djakovic L, Sujic R, Godman B, Jankovic SM. Inflammatory Bowel Diseases (Crohn's Disease and Ulcerative Colitis): Cost of Treatment in Serbia and the Implications. *Applied health economics and health policy*. 2017;15(1):85-93.
29. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Annals of the rheumatic diseases*. 2014;73(1):198-206.
30. Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304-16.
31. Høivik ML, Buer LCT, Cvanarova M, Warren DJ, Bolstad N, Moum BA, et al. Switching from originator to biosimilar infliximab - real world data of a prospective 18 months follow-up of a single-centre IBD population. *Scandinavian journal of gastroenterology*. 2018;53(6):692-9.
32. Milassin Á, Fábíán A, Molnár T. Switching from infliximab to biosimilar in inflammatory bowel disease: overview of the literature and perspective. *Therapeutic advances in gastroenterology*. 2019;12:1756284819842748.
33. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. *Drugs*. 2018;78(4):463-78.
34. Gisondi P, Bianchi L, Calzavara-Pinton P, Conti A, Chiricozzi A, Fimiani M, et al. Etanercept biosimilar SB4 in the treatment of chronic plaque psoriasis: data from the Psobiosimilars registry. *The British journal of dermatology*. 2019;180(2):409-10.
35. Stebbing J, Baranau YV, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, et al. Double-blind, randomized phase III study to compare the efficacy and safety of CT-P6, trastuzumab biosimilar candidate versus trastuzumab as neoadjuvant treatment in HER2 positive early breast cancer (EBC). *Journal of Clinical Oncology*. 2017;35(15\_suppl):510-.
36. Pegram MD, Bondarenko I, Zorzetto MMC, Hingmire S, Iwase H, Krivorotko PV, et al. PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study. *Br J Cancer*. 2019;120(2):172-82.
37. Tweehuysen L, Huiskes VJB, van den Bemt BJF, Vriezekolk JE, Teerenstra S, van den Hoogen FHJ, et al. Open-Label, Non-Mandatory Transitioning From Originator Etanercept to Biosimilar SB4: Six-Month Results From a Controlled Cohort Study. *Arthritis & rheumatology*. 2018;70(9):1408-18.
38. Chan A, Kitchen J, Scott A, Pollock D, Marshall R, Herdman L. Implementing and delivering a successful biosimilar switch programme - the Berkshire West experience. *Future healthcare journal*. 2019;6(2):143-5.
39. Nisar MK. 292 Switching to biosimilar rituximab: a real world study. *Rheumatology*. 2018;57(suppl\_3).
40. Ratnakumaran R, To N, Gracie DJ, Selinger CP, O'Connor A, Clark T, et al. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. *Scandinavian journal of gastroenterology*. 2018;53(6):700-7.

41. Jimenez-Pichardo L, Gazquez-Perez R, Sierra-Sanchez JF. Degree of prescriber's knowledge about variability in biological drugs "innovators" in manufacturing process. *European journal of clinical pharmacology*. 2018;74(4):505-11.
42. Vezer B, Buzas Z, Sebeszta M, Zrubka Z. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. *Current medical research and opinion*. 2016;32(5):829-34.
43. PRNewswire. Global Tumor Necrosis Factor Inhibitors Drug Market, Dosage, Price & Clinical Pipeline Outlook 2024. 2018. Available at URL: <https://www.prnewswire.com/news-releases/tumor-necrosis-factor-inhibitors-drug-market-2024---humira-and-remicade-have-made-it-to-the-list-of-blockbuster-drugs-of-2017-with-global-sales-of-us-176-billion-300615283.html>.
44. Hoen E't. Humiragate: AbbVie's desperate attempts to keep its monopoly. 2019. Available at URL: <https://medicineslawandpolicy.org/2019/03/humiragate-abbvies-desperate-attempts-to-keep-its-monopoly/>.
45. Davio K. Roche's European Rituximab Sales Drop 11% Due to Biosimilar Competition. 2018. Available at URL: <https://www.centerforbiosimilars.com/view/roches-european-rituximab-sales-drop-11-due-to-biosimilar-competition>.
46. Davio K. Biosimilar Competition Leads to 9.7% Drop in Remicade Sales for Johnson & Johnson. 2018. Available at URL: <https://www.centerforbiosimilars.com/view/biosimilar-competition-leads-to-97-drop-in-remicade-sales-for-johnson--johnson>.
47. Matuszewicz W, Godman B, Pedersen HB, Furst J, Gulbinovic J, Mack A, et al. Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe. *Expert review of pharmacoeconomics & outcomes research*. 2015;15(5):755-8.
48. Småstuen MC, Madla R, Solli O, Hjelvin E. OP0311 RETROSPECTIVE ANALYSIS OF PRESCRIPTION DYNAMICS OF ETANERCEPT AFTER INTRODUCTION OF BIOSIMILARS BASED ON NORWEGIAN PRESCRIPTION DATABASE. AN INTERIM ANALYSIS. *Annals of the Rheumatic Diseases*. 2019;78: 237-238.
49. Mansell K, Bhimji H, Eurich D, Mansell H. Potential cost-savings from the use of the biosimilars filgrastim, infliximab and insulin glargine in Canada: a retrospective analysis. *BMC health services research*. 2019;19(1):827.
50. Taylor P. Roche's Herceptin/Perjeta fixed-dose combo filed with FDA. 2020. Available at URL: [http://www.pmlive.com/pharma\\_news/roches\\_herceptinperjeta\\_fixed-dose\\_combo\\_filed\\_with\\_fda\\_1326904](http://www.pmlive.com/pharma_news/roches_herceptinperjeta_fixed-dose_combo_filed_with_fda_1326904).
51. Lee SM, Jung JH, Suh D, Jung YS, Yoo SL, Kim DW, et al. Budget Impact of Switching to Biosimilar Trastuzumab (CT-P6) for the Treatment of Breast Cancer and Gastric Cancer in 28 European Countries. *BioDrugs*. 2019;33(4):423-36.
52. Jeremias S. Biosimilars Gain Market Share and Advocates Get Aboard. 2020. Available at URL: <https://www.centerforbiosimilars.com/view/biosimilars-gain-market-share-and-advocates-get-aboard>.
53. GlobalData PharmaPoint. KADCYLA (HER2-POSITIVE BREAST CANCER) - FORECAST AND MARKET ANALYSIS TO 2023. 2014. Available at URL: <https://www.marketresearch.com/product/sample-8464560.pdf>.
54. Zion Market Research. Insulin Glargine Market: by Type (Pre-filled Syringe and Single Dose Vial), by Application (Type 1 Diabetes and Type 2 Diabetes), by Distribution Channel (Hospital Pharmacy, Online Sales, Retail Pharmacy and Other Distribution Channels): Global Industry Perspective, Comprehensive Analysis and Forecast, 2018 – 2025. 2019. Available at URL: <https://www.zionmarketresearch.com/report/insulin-glargin-market>.
55. Lothian Formulary. 6.1.1 Insulins. 2020. Available at URL: <https://www.ljf.scot.nhs.uk/LothianJointFormularies/Adult/6.0/6.1/6.1.1/Pages/default.aspx>.
56. Greater Glasgow and Clyde. Medicines Update - Prescribing Medicines by Brand. 2020. Available at URL: <http://www.ggcprescribing.org.uk/blog/prescribing-medicines-brand/>
57. Aladul MI, Fitzpatrick RW, Chapman SR. Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study. *BMJ open*. 2018;8(11):e023603.
58. Greener M. Why isn't the NHS making the most of biosimilar insulin? *Prescriber* August 2019: 21-24.
59. Heinemann L, Carter AW. Will Biosimilar Insulins Be Cheaper? *Diabetes technology & therapeutics*. 2017;19(9):513-5.
60. Yamada T, Kamata R, Ishinohachi K, Shojima N, Ananiadou S, Nom H, et al. Biosimilar vs originator insulins: Systematic review and meta-analysis. *Diabetes, obesity & metabolism*. 2018;20(7):1787-92.

61. Blevins TC, Barve A, Raiter Y, Aubonnet P, Athalye S, Sun B, et al. Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study. *Diabetes, obesity & metabolism*. 2020;22(3):365-72.
62. Lamb YN, Syed YY. LY2963016 Insulin Glargine: A Review in Type 1 and 2 Diabetes. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*. 2018;32(1):91-8.
63. Greater Glasgow and Clyde. Medicines Update - Semglee® – preferred brand of insulin glargine. 2020. Available at URL: <http://ggcprescribing.org.uk/blog/alternatives-insulin-glargine-post-tc/>.
64. Saborido-Cansino C, Santos-Ramos B, Carmona-Saucedo C, Rodríguez-Romero MV, González-Martín A, Palma-Amaro A, et al. [Effectiveness of an intervention strategy in the biosimilar glargine prescription pattern in primary care]. *Atencion primaria*. 2019;51(6):350-8.
65. Agirrezabal I, Sánchez-Iriso E, Mandar K, Cabasés JM. Real-World Budget Impact of the Adoption of Insulin Glargine Biosimilars in Primary Care in England (2015-2018). *Diabetes Care*. 2020;43(8):1767-73.
66. Hernandez I, Good CB, Shrank WH, Gellad WF. Trends in Medicaid Prices, Market Share, and Spending on Long-Acting Insulins, 2006-2018. *Jama*. 2019;321(16):1627-9.
67. González-Fernández M, Villamañán E, Jiménez-Nácher I, Moreno F, Plasencia C, Gaya F, et al. Cost evolution of biological agents for the treatment of spondyloarthritis in a tertiary hospital: influential factors in price. *International journal of clinical pharmacy*. 2018;40(6):1528-38.
68. Gulacsi L, Brodsky V, Baji P, Rencz F, Pentek M. The Rituximab Biosimilar CT-P10 in Rheumatology and Cancer: A Budget Impact Analysis in 28 European Countries. *Adv Ther*. 2017;34(5):1128-44.
69. Kim Y, Kwon H-Y, Godman B, Moorkens E, Simoens S, Bae S. Uptake of Biosimilar Infliximab in the UK, France, Japan, and Korea: Budget Savings or Market Expansion Across Countries? *Frontiers in pharmacology*. 2020;11(970).
70. Siu ECK, Tomalin A, West K, Anderson S, Wyatt G. An Ever-Evolving Landscape: an Update on the Rapidly Changing Regulation and Reimbursement of Biosimilars in Canada. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2019;8(3):107-18.
71. Kwon HY, Godman B. Drug Pricing in South Korea. *Applied health economics and health policy*. 2017;15(4):447-53.
72. Kwon HY, Kim H, Godman B, Reich MR. The impact of South Korea's new drug-pricing policy on market competition among off-patent drugs. *Expert review of pharmacoeconomics & outcomes research*. 2015;15(6):1007-14.
73. Leporowski A, Godman B, Kurdi A, MacBride-Stewart S, Ryan M, Hurding S, et al. Ongoing activities to optimize the quality and efficiency of lipid-lowering agents in the Scottish national health service: influence and implications. *Expert review of pharmacoeconomics & outcomes research*. 2018;18(6):655-66.
74. Godman B, Kurdi A, McCabe H, MacBride-Stewart S, Leporowski A, Hurding S et al. Ongoing activities to influence the prescribing of proton pump inhibitors within the Scottish National Health Service: their effect and implications. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2018;7(4):142-51.
75. Simoens S, Le Pen C, Boone N, Breedveld N, Llombart-Cussac A, Jorgensen F et al. How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2018;7(2):70-4.
76. Moorkens E, Vulto AG, Huys I, Dylst P, Godman B, Keuerleber S, et al. Policies for biosimilar uptake in Europe: An overview. *PloS one*. 2017;12(12):e0190147.
77. Vogler S, Schneider P. Do pricing and usage-enhancing policies differ between biosimilars and generics? Findings from an international survey. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2017;6(2):79-88.
78. Rémuzat C, Kapuśniak A, Caban A, Ionescu D, Radière G, Mendoza C, et al. Supply-side and demand-side policies for biosimilars: an overview in 10 European member states. *J Mark Access Health Policy*. 2017;5(1):1307315.
79. IQVIA Report 2018: The impact of biosimilar competition in Europe. Available at URL: <https://ec.europa.eu/docsroom/documents/31642>
80. GABI. Policies & Legislation - France aims to reach 80% biosimilar penetration by 2022. 2018. Available at URL: <http://gabionline.net/Policies-Legislation/France-aims-to-reach-80-biosimilar-penetration-by-2022>
81. NHS England. Commissioning framework for biological medicines (including biosimilar medicines). 2017. Available at URL: <https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf>.

82. Atteberry P, Bach PB, Ohn JA, Trusheim M. Biologics Are Natural Monopolies (Part 1): Why Biosimilars Do Not Create Effective Competition. *Health Affairs Blog*. 2019. Available at URL: <https://www.healthaffairs.org/doi/10.1377/hblog20190405.396631/full/>.
83. Vernaz N, Haller G, Girardin F, Huttner B, Combescure C, Dayer P, et al. Patented drug extension strategies on healthcare spending: a cost-evaluation analysis. *PLoS Med*. 2013;10(6):e1001460.
84. Oggetto: Sentenza 465/20 TAR Piemonte Sezione I sull'approvvigionamento di farmaci biologici. 14 September 2020. Available at URL: <http://www.quotidianosanita.it/allegati/allegato628568.pdf>.
85. Gustafsson LL, Wettermark B, Godman B, Andersen-Karlsson E, Bergman U, Hasselstrom J, et al. The 'wise list'- a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. *Basic & clinical pharmacology & toxicology*. 2011;108(4):224-33.
86. Godman B, Allocati E, Moorkens E. Ever-Evolving landscape of biosimilars in Canada; findings and implications from a global perspective. *Generics and Biosimilars Initiatives (GABI) Journal*. 2019; 8 (3).
87. NHS Scotland. Secondary Care National Therapeutic Indicators 2018/19. Available at URL: <https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/08/Secondary-Care-National-Therapeutic-Indicators-Version-1.0.pdf>.
88. All Wales Medicine Strategy Group. National Prescribing Indicators 2018–2019. 2018. Available at URL: <http://www.awmsg.org/docs/awmsg/medman/National%20Prescribing%20Indicators%202018-2019.pdf>.
89. Colloca L, Panaccione R, Murphy TK. The Clinical Implications of Nocebo Effects for Biosimilar Therapy. *Frontiers in pharmacology*. 2019;10(1372).
90. Kristensen LE, Alten R, Puig L, Philipp S, Kvien TK, Manges MA, et al. Non-pharmacological Effects in Switching Medication: The Nocebo Effect in Switching from Originator to Biosimilar Agent. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*. 2018;32(5):397-404.
91. Godman B, Wettermark B, Bishop I, Burkhardt T, Fürst J, Garuoliene K, et al. European payer initiatives to reduce prescribing costs through use of generics. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2012;1(1):22-7.
92. Godman B, Wettermark B, van Woerkom M, Fraeyman J, Alvarez-Madrado S, Berg C, et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. *Frontiers in pharmacology*. 2014;5:106.
93. Godman B, Shrank W, Andersen M, Berg C, Bishop I, Burkhardt T, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert review of pharmacoeconomics & outcomes research*. 2010;10(6):707-22.