



## Economic evaluation of biosimilars for reimbursement purposes – what, when, how?

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### ABSTRACT

**Background:** Limited previous research and guidelines on the design of economic evaluation for biosimilars have led to unresolved methodological questions on how to assess biosimilars.

**Objectives:** We want to raise awareness of and explore methodological issues for the economic evaluation of biosimilars.

**Methods:** We relied on a literature review, exploratory interviews, and our experiences.

**Results and Conclusions:** In the majority of cases in which reimbursement for a biosimilar is sought, it will not be necessary to conduct an economic evaluation, given that the reference product is already reimbursed and standard of care. If the latter is not the case, a full economic evaluation of the biosimilar versus standard of care is needed. This might also be needed in the case of differences in administration form or adherence (for example, due to a nocebo effect) and to take into account value-added services. The entry of biosimilars and of next-generation biological products should trigger a re-assessment of the entire product class. HTA bodies and reimbursement agencies should provide clear guidance on how to assess the value of a biosimilar in each of these circumstances.

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## Introduction

The use of biological medicines has been successful in the treatment of many life-threatening and chronic diseases, however, they often come at high prices [1]. To sustain increasing healthcare budgets, healthcare systems might opt to use biosimilars. Biosimilars contain an active substance that is proven to be similar to that of an already authorized original biological medicine (reference product) based on extensive comparability testing [2]. Biosimilars can be marketed after expiration of patent protection and other exclusivity rights on the reference product and may, by introducing competition, lower treatment costs in a therapeutic class while maintaining the same quality, safety, and efficacy as with the reference product, resulting in savings and/or increased patient access to treatment.

To support reimbursement decisions on new medicines and ensure the implementation of cost-effective medicines, countries increasingly request an economic evaluation of the new healthcare invention versus existing technologies. In this respect, we argue that there are a number of unresolved methodological questions on how the value of biosimilars can be assessed (see Table 1). However, few national guidelines on the design of economic evaluation in reimbursement procedures specifically mention and

address biosimilars. Specific guidance for biosimilars is provided in the UK by the Scottish Medicines Consortium (SMC), the National Institute for Health and Care Excellence (NICE), and the All Wales Medicines Strategy Group (AWMSG) [3–5]. Approaches of other countries (France, Belgium, the Netherlands, Poland, and Hungary) have not been explicitly spelled out in guidelines, but can be deduced from general procedures related to the added clinical benefit class in which biosimilars are classified, which is described in the literature [6–12]. Available guidance on economic evaluation concerning biosimilars is presented for a selection of countries in Table 2.

The aim of this *Perspective* is to raise awareness of and explore methodological issues for the economic evaluation of biosimilars. This *Perspective* was informed by a literature review; interviews with 17 representatives of HTA bodies, health insurance agencies, pharmaceutical companies, reimbursement agencies, physicians and academia in European countries; and the authors' experiences. This *Perspective* is timely since determining the value of biosimilars was one of the top 10 health economics and outcomes research trends identified by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in 2018 [13]. Furthermore, ISPOR established

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**Table 1.** Methodological questions on how the value of biosimilars can be assessed.

1	Is there a need to perform an economic evaluation when the biosimilar applies for reimbursement in the same indication and population as the reference product?
2	Is there a need to conduct an economic evaluation of a biosimilar when the reference product is not used in a country or is not reimbursed for that specific indication or population?
3	How do the potential nocebo effect, differences in administration routes and the provision of value-added services impact the value of a biosimilar?
4	How can the value of a second-generation biological product be determined?
5	Is there a need to re-assess the value of the entire product class when next-generation biological products (and their subsequent biosimilars) enter the market?

**Table 2.** Guidance on the economic evaluation of biosimilars in a selection of European countries, derived from guidelines of Health Technology Assessment (HTA) bodies or relevant literature.

Country	Guidance on economic evaluation for biosimilars
England/UK[3]	Biosimilars might be included in a NICE Multiple Technology Appraisal.
Scotland[4]	Since May 2015, SMC does not require a full submission for a biosimilar for indications of the reference product that have been accepted for reimbursement. A full submission is required for indications/populations for which the reference product is not recommended by SMC.
Wales[5]	The advice of AWMSG for the reference product will automatically apply for the biosimilar (same indications/populations). When the reference product is not reimbursed, it is advised to engage with AWMSG.
Sweden	A health economic evaluation is not required for a biosimilar. Reference is made to the data provided for the originator product. The price of the biosimilar cannot exceed the price of the originator product. (Personal communication with TLV)
France[6,7]	Biosimilars are included in ASMR class V: no added therapeutic value. A health economic assessment is not conducted for products in this class.
Belgium[8,9]	Class 2 reimbursement is applied for biosimilars, where no added value is claimed. Applications for reimbursement in class 2 are not required to include an economic evaluation of the medicine.
Germany	Biosimilars are not included in HTA assessment. (Personal communication with IQWiG)
Netherlands[10]	ZIN does not have specific guidelines for biosimilars. An economic evaluation is not required when no added therapeutic value is claimed (List 1A).
Poland[11]	Biosimilars are not included in an HTA assessment, except when the reference product is not reimbursed.
Hungary[12]	Biosimilars can be reimbursed through a simplified procedure when the reference product is already reimbursed. This simplified procedure does not require an economic evaluation, only a comparison of price.

SMC, Scottish Medicines Consortium; NICE, National Institute for Health and Care Excellence; AWMSG, All Wales Medicines Strategy Group; TLV, *Tandvårds- och läkemedelsförmånsverket* (Dental and Pharmaceutical Benefits Agency); ASMR, *Amélioration du Service Médical Rendu* (Improvement in Actual Benefit); IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care); ZIN, *Zorginstituut Nederland* (National Health Care Institute).

a Special Interest Group on Biosimilars in 2019, which looks into gaps and challenges in the value assessment of biosimilars [14].

### What do we need economic evaluation of biosimilars for?

If the reference product is already reimbursed and is the standard of care and the biosimilar applies for reimbursement in the same indications and population, it can be argued that it is not necessary to conduct an economic evaluation provided that there is enough evidence on the similarity between those products. Arguments on the regulatory evidence supporting biosimilarity were suggested in different papers [15,16]. Stewart et al. [17] proposed to accept equivalence proven by pharmacokinetic and pharmacodynamics studies as a proxy for therapeutic equivalence. If an economic evaluation would be conducted, a cost-minimization analysis suffices, implying that the assessment process is in practice limited to comparing prices of the reference product and the biosimilar [18]. This is currently the practice in a number of countries (see Table 2) and is likely to apply to the majority of cases

in which reimbursement for a biosimilar is sought. Ideally, net prices are used in this comparison in order to accurately assess value. Since net prices are dynamic and may differ between regions/hospitals within a country, a periodic and local (re-)assessment of the value of a biosimilar is recommended.

It may also be argued that the effort of conducting a full economic evaluation (e.g., cost-effectiveness, cost-utility or cost-benefit analysis) would only delay the market entry of the biosimilar and is not in balance with the information that would be gained by carrying out such an evaluation. In case the reference product has not been appraised or is not the standard of care, a full economic evaluation is needed [18].

### When to perform an economic evaluation for a biosimilar?

If the reference product is not used in a country or if it is not reimbursed for a specific indication or population, we recommend to perform a full economic evaluation versus the standard of care. This might also be necessary to account for a potential nocebo effect with the biosimilar

(i.e., a negative expectation of the patient resulting in less response to treatment) and decreased adherence to therapy. Furthermore, market developments may lead to biosimilars that are administered subcutaneously while the reference product is an intravenous treatment, e.g., Celltrion's subcutaneous version of Remsima® (infliximab) [19]. These developments might impact the value of the biosimilar as quality of life aspects may differ between treatments. Also, it may be necessary to take into account market changes since the entry of the reference product and re-evaluate a specific class of medicines. Finally, how can differences in the provision of value-added services between the reference biological product and the biosimilar be considered in economic evaluation? [20]

HTA bodies or reimbursement agencies do not provide guidance on which type of economic evaluation is expected in such cases. The SMC and AWMSG indicate that a full dossier might be needed and advise to engage with them before submitting. A paper by Spoons and Kusel [21] also acknowledged an increased need for economic evaluation when the reference product is not reimbursed. Drummond and Martin [22] argued that an economic evaluation would normally not be necessary, except to establish a value-based price when the reference product was not deemed cost-effective. Inotai et al. [23] mentioned the use of non-biological therapies as a comparator in the economic evaluation of biosimilars in countries with significant resource constraints. They advocate in favour of a full economic evaluation in this situation.

### How to account for market entry of next-generation biological products?

Over the life cycle of a specific product, next-generation products might be developed and enter the market. This was, for example, the case for filgrastim (Neupogen®) with the entry of second-generation product pegfilgrastim (Neulasta®), and third-generation product lipegfilgrastim (Lonquex®). Also, darbepoetin alfa (Aranesp®) was developed as a second-generation product to epoetin alfa (Epogen®). Such a market development raises a question for value assessment given that the comparability of the biosimilar of the first-generation biological product with the second-generation biological product has in general not been established [18].

The authors are of the opinion that the value of a second-generation product needs to be defined versus the previous most cost-effective alternative in a disease area (efficiency frontier approach [24]). The comparator in the economic evaluation could then be the biosimilar or its reference product. A second-generation biological product can as well serve as a comparator in an economic

evaluation of a biosimilar of a first-generation biological product, when the second-generation biological product was introduced first and became standard of care, e.g., pegfilgrastim. Depending on whether efficacy and safety are comparable, a cost-minimization analysis or a full economic evaluation can be performed.

When next-generation biological products (and their subsequent biosimilars) enter the market, there might be a need to re-assess the value of the entire product class. This may also include a revision of the baseline for reimbursement. For example, you might be willing to pay more at the moment of launch of the first medicine in the absence of alternative treatments than you would at the time of reimbursement decision for the second-generation biological product. Therefore, there may be a need to evaluate new products against a revised baseline.

### Conclusion

This *Perspective* has explored unresolved methodological issues surrounding the economic evaluation of biosimilars. We recommend to conduct a cost-minimization analysis if the reference biological product is already reimbursed and is the standard of care and the biosimilar applies for the same indications and population. In this respect, it is important that net prices (after discounts/rebates) of the reference product and the biosimilar are used with a view to generate an accurate assessment of value. HTA bodies and reimbursement agencies need to provide guidance on the design of economic evaluation in other circumstances (e.g., reference product not reimbursed, differences in administration form or adherence, consideration of value-added services). Economic evaluations of specific biosimilar medicines submitted to reimbursement agencies or published in the scientific literature may provide additional insight into what, when and how to carry out such exercises.

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### Authors' Contribution

SS, IH, EM and HB developed the idea for and were involved in the design of this study. EM and HB were involved in data collection and drafted the initial version of the manuscript. IH, AV and SS critically revised the manuscript. All authors read and approved the final manuscript.

## Disclosure Statement

SS, IH and AV have conducted biosimilar research sponsored by Hospira (now Pfizer). SS was involved in a stakeholder roundtable on biosimilars sponsored by Amgen, Pfizer and MSD, and has participated in an advisory board meeting for Pfizer. SS currently works with Pfizer, and works with Celltrion as a consultant, to carry out biosimilar research. AV is involved in consulting, advisory work and speaking engagements for a number of companies, a.o. AbbVie, Accord, Amgen, Biogen, EGA (now Medicines for Europe), Pfizer/Hospira, Mundipharma, Roche, Sandoz.

EM and HB declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. At the time of publication, HB was employed full-time by Select Projects.

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