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ORIGINAL RESEARCH ARTICLE

Evolving Biosimilar Clinical Requirements: A Qualitative Interview Study with Industry Experts and European National Medicines Agency Regulators

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Abstract

Background A biosimilar is a biological medicine highly similar to another already approved biological medicine (reference product). The availability of biosimilars promotes competition and subsequently lower prices. Changing the current biosimilar clinical comparability trial requirements may lead to lower biosimilar development costs that potentially could increase patients' access to biologics.

Objective The aim was to determine the perceptions of industry and medicines agency regulators regarding the value, necessity, and future developments of the European biosimilar clinical comparability trial requirements for establishing biosimilarity.

Methods Semi-structured interviews were conducted with eight European national medicines agency regulators and 17 pharmaceutical company employees or consultants with experience in biologics between September 2018 and August 2019. Data were subjected to content analysis.

Results In general, the participants expected that clinical comparability trial requirements will continue to be reduced, in particular based on advancements in analytical testing and knowledge generated from prior biosimilar approvals. However, there are also competing issues at play, such as competition, physician's trust, and ethical considerations. Participants also reported that any new initiative to reduce or waive biosimilar clinical requirements needs to be scientifically sound and could potentially lower biosimilar development costs.

Conclusion The main findings are that biosimilar clinical comparability trial requirements are likely to change in the near future. Clarity is needed on how to ensure adequate correlation between physicochemical data, pharmacokinetic/pharmacodynamic studies, and the drugs' performance in the clinic, as well as how to continue sufficient immunogenicity assessment. Obtaining this clarity can facilitate regulatory assessment of the next biosimilars.

1 Introduction

The regulatory approval of biosimilar medicinal products in the European Union (EU) is still evolving. One changing aspect is the requirement for the clinical trials to establish comparable efficacy to the reference product. Such trials can now be excluded under specific conditions for biosimilar insulins, low-molecular-mass heparins, and (peg)filgrastims [1]. By contrast for biosimilars of more complex molecules such as monoclonal antibodies, the European Medicines Agency (EMA) recommends that product developers conduct clinical comparability trials without exception (see Table 1) [1]. Overall, for biosimilar development the EMA suggests a step-wise approach and use of state-of-the-art methods [2] to achieve highly similar quality, safety, and efficacy between reference product and biosimilar. The demonstration of biosimilarity is based on the same scientific principles as for comparability of a biological product upon changes in their manufacturing process [2, 3]. Inherent in this is the understanding that biological products have natural variation and that some variation is acceptable [4, 5]. A biosimilarity demonstration requires extensive physicochemical and biological characterizations, non-clinical comparisons of biosimilar and reference product (for example by using cell-based assays), and *if necessary* also clinical studies [6, 7]. However, in practice, only four out of

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Key Points

The participating EU national medicines agency regulators and industry experts in general expected that clinical comparability trial requirements will continue to be reduced, in particular based on advancements in analytical testing and knowledge generated from prior biosimilar approvals.

Competing issues at play to reduce biosimilar clinical comparability trial requirements include competition, physician's trust, and ethics.

Clarity is needed on how to ensure adequate correlation between physicochemical data, pharmacokinetic/pharmacodynamic studies, and the drugs' performance in the clinic, as well as how to continue sufficient immunogenicity assessment. Obtaining this clarity can facilitate regulatory assessment of the next biosimilars.

66 approved biosimilars (two with pegfilgrastim, one with enoxaparin and one with teriparatide as active substances) were EMA-approved solely on the basis of clinical data on pharmacokinetics (PK) and/or pharmacodynamics (PD); i.e., comparable safety/efficacy studies in humans were not performed [8].

The potential lower cost of biosimilars compared to the reference product can relieve health system budgets, and entries of biosimilars on the European market have fostered competition and subsequently lower prices. So far, price per treatment day decreases between 3 and 39% across therapeutic classes have been obtained, although price reductions are country specific [9]. At the same time, biosimilars are more time-consuming and expensive to develop than small-molecule generics. Biosimilar development costs are estimated to be approximately US$100–300 million compared to US$1–3 million for generics (in cases without clinical trials) [10, 11]. A large part of these additional costs arise from biosimilar clinical comparability trials [10]. The high development costs [12] and/or insurmountable price pressure on the biosimilar can prevent development of potential biosimilar entrants. The price pressure can become insurmountable if the price of the reference product is substantially lowered close to the market launch of the new biosimilar.

There is an ongoing debate about the biosimilar clinical data requirements. Allocati et al. (2020) and Frapaise (2018) [8, 12] have encouraged reassessment of the current clinical requirements for biosimilar approval. They questioned what value the biosimilar comparability studies add and stressed that biosimilar approvals without these studies may lead to better access to medicines for patients. Further, Webster et al. (2019) suggested a new model for biosimilar approvals that relies on "confirmation of sufficient likeness" [13]. They argued that the current regulatory framework for biosimilars does not take the current level of knowledge of biosimilar and reference products into account [13]. In their proposed model, clinical comparability trials would not be required routinely, but only conducted if prompted by the initial tests such as from analytics [13]. Furthermore, Wolff-Holz et al. (2019) argued that scientific advancements in PD markers can play a role to further reduce the clinical data requirements for biosimilar approvals [1].

Changing the biosimilar clinical requirements may increase access to biological medicines and lower healthcare costs, i.e., decreased biosimilar development costs could increase market competition and lower prices [12, 13]. Moreover, conducting comparability clinical trials when not strictly scientifically justified raises ethical concerns [14]. It is at present unclear to what extent a further reduction of clinical comparability requirements would be acceptable, and therefore, the research question of this study was as follows: what are the views of industry and national medicines agency regulators regarding the European biosimilar clinical comparability trial requirements for establishing biosimilarity? In asking this question, there was a focus on the value and necessity of the requirements as well as future developments that would have to be considered. This study is part of a larger research project on stakeholder perspectives on the regulatory landscape of biosimilars, where a subset of the findings on challenges with establishing biosimilarity as well as legal perspectives on trade secrets and patents have already been reported [15].

2 Methods

We applied a qualitative approach using semi-structured individual interviews [16] because this would allow collection of expert knowledge; quantitative surveys are inappropriate due to the limited population size of eligible respondents.

2.1 Recruitment

Purposeful recruitment was carried out using networking and snowballing. Eligible participants currently or formerly worked as either an EU or US medicines agency regulator or in (or as consultant to) a pharmaceutical company with EMA/Food and Drug Administration (FDA)-approved originator biologic product(s), biosimilar product(s), or both types of products. Recruitment aimed to include participants with experience with biologics, but for company participants, also with different expertise (regulatory affairs; regulatory policy; law; chemistry, manufacturing, and control [CMC]). The participants were approached either in-person

Table 1 Characteristics of the European biosimilar clinical comparability requirements [7]

Term	Description
Clinical biosimilarity establishment	A stepwise procedure to demonstrate clinical biosimilarity in the order: PK and, if feasible, PD studies Clinical efficacy and safety trial(s), or In certain cases, confirmatory PK/PD studies
PK studies	PK studies are used to detect possible differences between reference and biosimilar products regarding their interactions with the body The preferred study design is a single-dose, cross-over study including the late elimination phase of the medicine Parameters typically investigated are C_{max}, t_{max}, volume of distribution, and AUC
PD studies	Whenever feasible, PD markers should be added to the PK study. The PD markers must be relevant for the clinical outcome A comparative efficacy trial might be unnecessary if confirmatory PK/PD studies are sufficient for establishing biosimilar comparability. For this, certain conditions must be met such as: The PD marker is an accepted surrogate marker that predicts the clinical outcome and reflects the pharmacological action and concentration of active substance The PD marker, along with human PK studies and physicochemical, structural, and in vitro biological assays, provides sufficient robust evidence for comparability between reference and biosimilar products
Clinical efficacy	If necessary, a clinical trial can be used to demonstrate comparable clinical efficacy between reference and biosimilar products Study design: Equivalence testing is preferred, but non-inferiority design can be accepted if justified on the basis of strong, scientific rationale Randomized, comparative, parallel group design using efficacy endpoints Preferably double blinded Needs to be adequately powered and conducted in a representative population reflecting an approved indication of the reference product
Clinical safety	Safety of the biosimilar is captured during PK and/or PD studies and in the comparable clinical efficacy trial The types of adverse events known from the reference product must be compared to the biosimilar in terms of type, severity, and frequency. Additionally, possible safety concerns arising from manufacturing differences between reference product and biosimilar must be described
Immunogenicity	Testing for immunogenicity needs to be conducted in accordance with current EMA guidelines Higher immunogenicity of a biosimilar compared to the reference product can question biosimilarity; however, lower immunogenicity might not preclude biosimilarity
Post-authorization safety follow-up	Clinical safety of biosimilars must be monitored post-approval to ensure a continuous positive benefit–risk assessment. The measures should include monitoring of immunogenicity

EMA European Medicines Agency, *PD* pharmacodynamic, *PK* pharmacokinetic, *AUC* area under the curve, C_{max} maximum serum concentration, t_{max} time at which C_{max} is observed

or by email contact. The participants received information about the study prior to participation and were not given any token of incentive. A total of 29 invitations were sent, with a maximum of two subsequent reminders for a reply. All participants included in the study provided written informed consent. All participants are anonymous, and all material is stored confidentially. The Faculty of Health and Medical Sciences at the University of Copenhagen approved the study (journal no.: SUND-2018-09).

2.2 Interview Guide

The interview guide was developed from informal meetings with both regulators and pharmaceutical industry representatives as well as inspiration from the interview guide used by Hoekman et al. (2015) [17]. The interview guide was designed by LCD, ABA, HH, MLDB, MvdW, and TM. The interview guide aimed at studying the appropriateness of the European regulatory framework for assessing recombinant protein biosimilars and was developed in two versions: for regulators and company participants, respectively (see the Electronic Supplementary Material); the focus of the present study is on one subset of the data. Open-ended questions and extensive probing were used during interviews to allow participants to elaborate on their answers and thus to enable capturing unforeseen aspects relevant for the research question.

2.3 Interviews

The interviews were conducted individually (or in pairs if requested by participants) face-to-face or by audio call

between September 2018 and August 2019 by LCD. All participants voiced their personal perspectives (i.e., opinions and views) and did not participate as formal representatives from their current or former workplaces. The interviews were transcribed verbatim either by LCD or a research assistant at the University of Copenhagen under the same confidentiality as LCD or by using NVivo automated transcription software (QSR International, https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/about/nvivo/modules/transcription). LCD validated all transcripts by reading each transcript while listening to the respective recording.

2.4 Analysis

Content analysis was used on the textual data in transcripts and notes from the interviews [18]. Two analysts (LCD using NVivo, and SKS on hardcopy; NVivo, version 12.6, https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home) coded parts of the data independently (18 transcripts) and then compared them in consensus meetings to arrive at categories. Subsequently, LCD re-coded all 23 transcripts accordingly and made a preliminary analysis of the categories. This along with several transcripts was audited by ABA for verification that the analysis reflected the data [18]. Thereafter, LCD, ABA, and SKS discussed the analysis until they reached consensus.

3 Results

Twenty-five persons participated in 23 interviews; of these, 17 were company participants and eight EU national medicines agency regulators; see Table 2 for participant characteristics. No EMA or FDA regulators were able to participate. The median interview time was 1 h and 2 min.

The overall analysis showed that the participants had different and highly nuanced perceptions of the biosimilar clinical trial requirements.

3.1 Summary of Stakeholder Perspectives on European Biosimilar Clinical Trial Requirements

The main concern expressed by originator company participants was whether biosimilars are sufficiently tested to provide scientific certainty that any differences between biosimilars and the reference product could not cause safety issues. Moreover, they stated that clinical data are needed for such reassurance. By contrast, biosimilar company participants considered clinical comparability trials to be suboptimal as a research tool for investigating biosimilarity because physicochemical analytics are more sensitive as a research method.

Regulators expressed a need for more scientific certainty before changing clinical data requirements for additional molecule classes than those already having reduced requirements. Overall, they believed that clinical requirements were a useful tool to study the safety of biosimilars. All participants seemed to trust the robustness of the European regulatory framework for biosimilars. Participants indicated that decisions on biosimilar approvals are science based and made using a precautionary principle; however, they also stated that scientific considerations for how to appropriately assess biosimilar marketing authorizations need to be evaluated because science evolves.

3.2 The Changing Tides for European Regulatory Requirements for Biosimilar Clinical Comparability Data

The majority of participants (regulators and companies with biosimilars) expressed that there has been a tendency for recent decisions on biosimilar approvals to rely more heavily on physicochemical data than clinical data compared to when biosimilars were introduced into the European regulatory system in 2005. Further, they stated that advancements in analytical testing of recombinant proteins and the knowledge generated from biosimilar approvals have fueled a discussion on how much clinical comparability efficacy data

Table 2 Type of workplace and expertise of participants

Type of workplace	Number of workplaces	Number of participants	Primary expertise of company participants		
			Regulatory policy/affairs	CMC	Legal
EU national medicines agencies	7	8	N/A	N/A	N/A
Companies with originator products	2	5	2	2	1
Companies with biosimilar and originator products	2	4	3	0	1
Companies with biosimilar products	7	8	5	1	2
Total	18	25	10	3	4

CMC chemistry, manufacturing, and control, *N/A* not applicable

are needed for approving biosimilars in the EU. Already, the regulatory knowledge gained from approval of some less complex molecule classes (such as filgrastims) using both analytics and comparable efficacy trials have led to waiving the comparability efficacy trials for these product classes. Both regulators and biosimilar company participants stated that physicochemical analytics have shown the ability to measure minor molecular differences in products that do not translate to detectable clinical differences in practice. The debate is highlighted in the following quote:

> "We are now also ready to move for some more innovative approaches and that we can skip most of the comparative phase three clinical trials and focus more on the physicochemical characterization. So I think that will be our next challenge for discussion." (EU national medicines agency regulator)

Regulators appeared to be open to investigating possibilities of when and how to reduce further or waive clinical trials for comparable efficacy. However, they also emphasized that these discussions did not include reduction or waiver of PK/PD studies, but that these still will be required in the foreseeable future. Several participants (both regulators and company participants) mentioned different strategies for reducing or waiving biosimilar clinical requirements. These included (1) reducing the clinical study size, and thus cost, by replacing equivalence margins with non-inferiority margins (non-inferiority trials use only one, lower or upper, margin and not two as in equivalence trials, which typically leads to studies with fewer enrollees [19]); (2) clinical data should only consist of the results from PK/PD studies and a small immunogenicity trial; or (3) expanding the pre-clinical data with more biofunctional assays and advancing these assays' abilities to predict clinical performance.

Different opinions existed on whether a further decrease in biosimilar clinical comparability trial requirements can be scientifically justified. Some regulators and originator company participants believed that the field is not there yet and emphasized the need to increase the knowledge obtained from analytical and biofunctional analyses. Other regulators said that the biosimilar requirements could change in the near future. Biosimilar company participants considered physicochemical analytical science as sufficiently established. But added that a wider regulatory acceptance of the method is lacking.

> "[A]t certain point in time, we have to think about the clinical trials, whether they always are necessary or not. That of course depends very much on the analytical capability or capabilities, so what we can make sure of on the analytical side. I am not sure whether we are there or not at the moment yet, but I think we should go in that direction. Try to cut down on the clinical side and increase the knowledge that we gain from the analytical and functional side." (EU national medicines agency regulator)
>
> "I think that the techniques are available today, well now in 2019, what is missing is what methods are really accepted and to find a consensus on this what is accepted." (Biosimilar company participant)

Three upcoming challenges were identified by the participants regarding further reducing the clinical comparability trial requirements: (1) how to appropriately reduce the requirements for complex biologics such as monoclonal antibodies; (2) taking a position on biosimilar development for orphan diseases; and (3) ensuring sufficient testing of immunogenicity resemblance. Some regulators expressed concern about sufficient testing of immunogenicity resemblance because of the difficulty in predicting this from quality data (i.e., analytical and biofunctional data). All types of company participants agreed on the need for certainty regarding immunogenicity for biosimilar approval, even though this is investigated post-approval similarly to other products. An originator company participant stressed that immunogenicity must be tested in long-term real-world data through post-marketing surveillance of biosimilars because currently it is measured inadequately in clinical trials pre-approval. However, biosimilar company participants highlighted that no immunogenicity issues have occurred for the already approved biosimilars and that one could use real-world experiences with the reference product to make immunogenicity predictions for a biosimilar candidate. This is apparent from the quotes of these participants from different stakeholders:

> "[T]he immunogenicity side is very difficult to predict from the quality data." (EU national medicines agency regulator)
>
> "[T]he highest level of uncertainty is still around the impact of immunogenicity issues to patients. That is the only concern I would say that exists… it is still difficult to explain also some immunogenicity issues that patients experience." (Originator company participant)
>
> "[T]he other aspect which is still missing is then immunogenicity and this depends now from product to product… if it has high risk of immunogenicity then I would say a certain confirmation in clinic is required… this is known from the experience with the reference medicine… from published clinical trials, from the real-world evidence that was collected." (Biosimilar company participant)

Regulators described that for biosimilar approval requirements to change they need to trust and be convinced that further reduced clinical data requirements will continue to

result in products with highly similar quality, safety, and efficacy compared to the reference products.

3.3 Opportunities and Challenges with Changing Biosimilar Clinical Trial Requirements for Biosimilar Developers

Biosimilar company participants expressed it as a challenge to develop PD markers, which was perceived as required by regulators to make the conduct of clinical trials for comparable efficacy unnecessary. Development of PD markers was explained as challenging for biosimilar developers because it could be as expensive as conducting a clinical trial showing comparable efficacy, as highlighted in this quote:

> "I don't think [that] companies are willing to invest the time and effort needed to develop a brand new validated PD marker because it would probably take just as long as the clinical efficacy program." (EU national medicines agency regulator)

A biosimilar company representative expressed that PD markers are a barrier for biosimilar development. Nonetheless, company participants also saw opportunities for innovation in physicochemical characterizations to replace PD markers for establishment of biosimilarity. Further, this scenario was argued to potentially render clinical comparable efficacy data unnecessary.

> "The barrier is the regulatory requirement to have a qualified biomarker… they [regulators] don't accept for example a very thorough, accurate in-vitro or functional characterization as a surrogate for this biomarker. I think this is the discussion we will need to have in the future… So that they [regulators] can gain trust in this characterization." (Biosimilar company participant)

A biosimilar company participant expressed that innovation in physicochemical characterizations (assuming no change in quality, safety, and efficacy) could be incentivized if companies had the potential to avoid biosimilar clinical trials for comparable efficacy. Consequently, this could encourage new companies, or re-attract existing companies, to develop biosimilars. All biosimilar company participants predicted that biosimilar development costs would decrease if regulators waived or reduced the requirements for clinical trials for comparable efficacy. Biosimilar company participants described that lower development costs could incentivize further biosimilar development. Moreover, it could ease the current difficulties in obtaining return on investments for biosimilars. Further, a biosimilar participant specified that lower development costs would make more biologicals (and not only blockbusters) attractive for biosimilar development:

> "[I]f you can cut this safety [and] efficacy trial requirements and pharmacodynamics requirement… this will make biosimilar development much more efficient. Maybe you can develop it at much lower costs so other biologics… will become attractive for biosimilar sponsors to develop a biosimilar variant." (Biosimilar company participant)

3.4 Competition and Trust of the Physicians

The participants expressed that the scenario of reducing or waiving biosimilar clinical trials for demonstrating comparable efficacy was not only a scientific question, but also included aspects related to competition, ethics, and physicians' trust in biosimilars.

Firstly, according to a participant from a company with both originator and biosimilar products, it would be too easy to introduce competitor products in the EU if the biosimilar approval requirements were too low (even if scientifically sound). In turn, this would signal to the originator industry that the EU is willing to introduce competition at originator companies' expense. Originator company participants expressed that the EU needs to balance this. However, a biosimilar company participant said that keeping unneeded requirements could lead to conduct of scientifically unnecessary clinical trials, which would be unethical. Further, the residual uncertainty regarding biosimilarity is expected to be low if there is evidence for comparability from physicochemical and in vitro tests.

Secondly, some biosimilar company participants specified that they did not believe that lower development costs would lead to lower prices on biosimilars in general. This would be because prices are not primarily based on development costs. Further, biosimilar companies would still have to do clinical trials for comparable efficacy for other markets, for example, the USA, even if the EU decided to reduce or waive their requirements. As highlighted by this quote:

> "[Y]ou have to do it not just for Europe, but you're doing global development. So even if Europe says 'oh I don't need clinical trials', well guess what the Chinese do, and so do the Americans, so you're going to end up doing it. These are really expensive, so if at the end of the day you're getting no money back on your investment, this is not a good life." (Biosimilar and originator company participant)

Lastly, participants (all types) expressed that physicians' trust in the safety and efficacy of biosimilars is just as essential as the regulators' trust. Regulators told of a need to be attentive of a potential decrease in physicians' trust in biosimilars if less clinical data would be required for approval, but that this is an educational task if approval requirements are changed. Both company participants and regulators

perceived that physicians in general are uncomfortable with biosimilars, although acceptance is on the rise. Several participants argued that this uneasiness with biosimilars is rooted in the physicians' training, i.e., to review clinical data when evaluating which products to use, and that they lack training in assessing physicochemical characterizations. Hence, physicians could hesitate to prescribe biosimilars, as it could be seen as a lack of evidence if approved 'only' with PK/PD data. This is illustrated by this quote:

> "There are at the moment already a lot of physicians, who are not comfortable to prescribe biosimilars, because they are used to use products with full clinical studies… and suddenly they have [biosimilar] products, which only have clinical data in one indication… Imagine what is going to happen if you get rid of that clinical requirement." (Originator company participant)

A few participants (regulator and biosimilar company participants) also mentioned that originator companies previously spread what was termed as misinformation about biosimilars being inferior to the reference product.

> "[A] lot of misinformation has been put out there, so there was a huge resistance from big pharma, from the doctors from the beginning… only [one] originator company that does not do biosimilars, everyone else… they do originator products and also biosimilars. Which of course has given a change in, how the story is told." (EU national medicines agency regulator)
>
> "You also hear stories that they clinically do not work as well as the originator. So I think some of these misinterpretations are due to campaigns that the originators have started, obviously again not to lose the market shares of their own products. So it is a dirty game." (EU national medicines agency regulator)

Further, it was stated this alleged spread of misinformation has caused skepticism amongst physicians regarding the safety and efficacy of biosimilars. A regulator stated that physicians' acceptance and trust will be a bigger challenge compared to the scientific questions related to reducing clinical comparability trial requirements. To facilitate physicians' trust, some regulators argued that there is a need for medicines agencies to clearly communicate and justify biosimilar approval requirements to physicians, if biosimilar clinical trials for comparable efficacy are to be waived or reduced. A regulator describes this as:

> "I think we as regulators should very well explain to the general public, to physicians, pharmacists, patients, the reasons why we are not asking for phase three comparative clinical trials anymore... so it's more for acceptance and trust in biosimilars than for very important scientific reasons." (EU national medicines agency regulator)

4 Discussion

The main findings of this study are that the participating medicines agency regulators and industry experts predict that biosimilar clinical trial requirements for comparable efficacy will be further reduced in the foreseeable future. Participants indicated that decisions on biosimilar approvals are science based, and that methods to assess biosimilar marketing authorization applications continue to be evaluated as science evolves. Advancements in analytical testing of recombinant proteins and the knowledge generated from former biosimilar approvals are fueling the discussion. However, participants' views varied on how this should happen, and scientific, economic, and ethical aspects were raised as relevant for the discussion. The participants' arguments for reducing the requirements included (1) analytics and science being sufficiently developed, (2) lower biosimilar development costs, (3) making it attractive to develop biosimilars for more originator biologics, and (4) clinical trials would be unethical if not scientifically justified. The arguments against reducing the requirements related to (1) necessity to use clinical trials for establishing comparable efficacy and immunogenicity, (2) dis-incentivizing originator companies by introducing competition too easily, and (3) concerns that physicians could become more reluctant to prescribe biosimilars. According to the participants, any new initiative to reduce or waive biosimilar clinical requirements could lower biosimilar development costs but needs to be scientifically sound.

Changes in the European regulation of biosimilars seem even more probable after the EMA in its regulatory science strategy [20] has put forward an aim to develop the biosimilar clinical requirements and after the UK medicines agency (Medicines & Healthcare products Regulatory Agency [MHRA]) recently issued guidance stating that comparable efficacy trials are most often not considered necessary [21]. Selected scientific, ethical, and political aspects of the findings on biosimilar clinical trial requirements are discussed in the following.

A part of the scientific debate is the focus on the question of the role of PD markers, and there are nuances in opinions on this. European regulators, both from present results and Wolff-Holz et al. (2019) [1], argue that PD markers can play a role in waiving biosimilar clinical comparability trials. Regulators from MHRA state in a recent scientific publication that they find comparable efficacy trials to provide little additional evidence for demonstrating biosimilarity,

but that a framework without such trials would encounter problematic cases with complex biologics and the typical lack of PD markers [22]. Webster et al. (2019) [13] also see a role of PD markers as confirming the likeness acquired by analytical similarity. Based on a recent review of the clinical evidence used for biosimilar approvals, Schiestl et al. (2020), who are affiliated with various pharmaceutical companies, further suggest to continuously require clinical PK and immunogenicity studies, whereas they argue that PD studies as well as comparable safety and efficacy trials should only be required if prompted by previous evidence [23]. It is unknown if PD markers will remain a requirement or whether more reliance on analytics will shape the future of biosimilar approval requirements in the EU. However, when looking to the UK, their newest guidance for biosimilar approvals recommends inclusion of PD markers if available [21].

Another aspect that needs to be carefully considered concerns the ethical implications of reducing or waiving biosimilar clinical trial requirements. Referring to the ethical principle of justice, Beauchamp and Childress [24] argued that it would be more just if it is possible for patients to take part in clinical trials to gain earlier access to treatment. For biosimilars, this would only apply if the originator is unavailable to patients, for either regulatory or financial reasons. One should then also consider if the limited access in the framework of a clinical trial weighs up against the fact that the trial in itself is unethical when not scientifically justified because a trial must contribute with answering a research question that is not possible to answer by other means [14]. Furthermore, there is a question whether reduced or waived biosimilar clinical comparability trial requirements will lead to faster development of biosimilars and with lower development costs. If prices do not decrease as a result of lower development costs, it is not certain that more patients will gain access to biologic treatments. Obtaining faster access to biosimilars could lead to an increase in beneficence [24], both as active actions to prevent or remove harm and to do or promote good. Furthermore, it needs to be considered whether there will be the same residual uncertainty about biosimilarity after changing the requirements as compared to before such change. If it is known with absolute certainty that different methods can provide the same evidence with the same level of certainty, this means that the safety would be the same for patients and thus the same beneficence and risk regardless of which of the two methods are used to demonstrate biosimilarity. However, if there is a larger residual uncertainty associated with one method, i.e., that patients would be exposed to an unknown risk, this could lead to a reduced beneficence if harm was not prevented [24]. Ethical considerations such as these are important as part of the evaluation of biosimilar clinical trial requirements.

A third part of the debate is political. It is important to realize that while biosimilars are considered different from generics in regulatory frameworks, they still need to be promoted similarly to originator products. This can be challenging since biosimilars by law are not substitutable by pharmacists in most parts of the EU [25]. The findings suggest that communicative initiatives are needed to ensure that physicians retain their current confidence in biosimilars if reducing the biosimilar clinical trial requirements. While our findings point to regulators and industry participants seeing physicians as largely uncomfortable about biosimilars, recent studies show that physicians' attitudes vary; either physicians are very confident in prescribing biosimilars [26] or cautious about biosimilars [27], or physicians view biosimilars as second- or third-line treatment options, and primarily for use in biologic-naïve patients [27, 28]. Some studies report that physicians are increasingly familiar with biosimilar products [29, 30], and others [27, 31–33] indicate that there is a need for further education of physicians regarding biologics to enable a higher acceptance of biosimilars. Further, clinical specialty can potentially also have an influence [26]. These aspects should be taken into account in the communication and collaboration of medicines authorities with the wider stakeholder groups such as physicians and payers, including known frequent concerns [34]. Since use of medicines is a national matter in the EU, collaborations between the EMA, national medicines authorities, and physician associations could be a feasible way forward for educational and communication strategies.

This study is strengthened by the different types of expertise held by the participants that allows for a nuanced insight into the field of biosimilars and the clinical comparability trial requirements. However, as previously mentioned, the participants were interviewed for their personal perspective on the topic, and not as formal representatives of their current or former workplace. Furthermore, it is unknown if the participants are using scientific arguments to advocate their workplaces' best interests or if the opinions stated are their own. The workplaces of the participants may or may not have competing commercial interests. Furthermore, there can be vested interests among the company participants, and it is unknown whether scientific arguments were used to support their interests rather than being "truly" scientific [35]. There is differing expertise among the participants, however, all participants are very knowledgeable in their respective area of either regulatory affairs/policy, CMC, or legal affairs. The interviews with participants who currently or formerly worked in originator companies discussed biosimilar clinical trial requirements less extensively compared to participants from other companies. This is probably because the originator company perspective on biosimilars is, from its outset, on competitor products, without large in-house experience with biosimilar development. However, these participants also

applauded the EMA for designing a regulatory framework for approving biosimilar products of high quality, safety, and efficacy.

It is not possible to evaluate if saturation was reached [36]; thus other aspects of biosimilar comparability clinical trial requirements may or may not have emerged if more or other participants had been recruited. In addition, the findings reflect the participants' opinions at the point in time when data were collected. However, the results are saturated in the data in the sense that there were extensive examples of the reported results. Content analysis was applied inductively to analyze the data in an iterative manner, in contrast to using a theoretical deductive analysis. Building on the quality criteria by Malterud [37], it was a strength of the current study that the authors have different competencies and backgrounds that allow for a higher degree of reflexivity and nuanced reflections on the complex topic. The authors have a background in regulatory science, law, protein analysis, and social and clinical pharmacy. Regarding the transferability of the study, it is expected that the results are applicable to other jurisdictions. The European regulators are in the forefront of the field of regulations of biosimilars, and if they find a way to reduce or waive the biosimilar clinical comparability trial requirements, it is likely that other jurisdictions will look into doing the same.

5 Conclusion

The main findings are that the participating medicines agency regulators and industry experts predict that European biosimilar clinical trial requirements for comparable efficacy will be further reduced in the foreseeable future. However, the results also indicate a need to clarify how adequate correlation between physicochemical data, PK/PD studies, and the drugs' performance in the clinic can be ensured, as well as how to continue sufficient immunogenicity assessment. Obtaining this clarity can facilitate regulatory assessment of the next biosimilars.

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Declarations

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Conflict of interest LCD was funded by a PhD fellowship grant to the University of Copenhagen from LEO Pharma A/S. LEO Pharma A/S was aware of, but had no decisive role in, the design or conduct of the study, collection, management, analysis, or interpretation of data, or the decision to submit the manuscript for publication. At the time of the study, MLDB was an employee of the Copenhagen Centre for Regulatory Sciences (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring Pharmaceuticals, LEO Pharma) as well as patient organizations (Rare Diseases Denmark). The center is devoted to the scientific aspects of the regulatory field with a patient-oriented focus; its research is not company or product-specific; and it has received funding from LEO Pharma A/S for this project, as well as from Novo Nordisk, Ferring Pharmaceuticals, and Lundbeck for other projects not related to this study. Currently, MLDB is employed by Utrecht University as a senior researcher conducting research under the umbrella of the Center for Pharmaceutical Policy and Regulation. This center receives no direct funding or donations from private parties, including those in the pharmaceutical industry. Research funding from public–private partnerships, e.g., IMI, The Escher Project (http://escher.lygature.org/), is accepted under the condition that no company-specific product or company related study is conducted. The center has received unrestricted research funding from public sources, e.g., World Health Organization (WHO), Netherlands Organization for Health Research and Development (ZonMW), the Dutch National Health Care Institute (ZIN), EC Horizon 2020, the Dutch Medicines Evaluation Board (MEB), and the Dutch Ministry of Health. TM's work is supported by the Collaborative Research Program for Biomedical Innovation Law, a scientifically independent research program supported by the Novo Nordisk Foundation (Grant NNF17SA0027784). TM is a scientifically independent IP Advisory Board Member of the Danish Life Science Company Chr. Hansen A/S. The company had no role in the design or conduct of the study, collection, management, analysis, or interpretation of data; or the decision to submit the manuscript for publication. SKS, MvdW, HH, and ABA declare that they have no conflict of interest.

Ethics approval No ethics approval was required according to Danish law (*Act on Research Ethics Review of Health Research Projects*, 2011, https://en.nvk.dk/rules-and-guidelines/act-on-research-ethics-review-of-health-research-projects); however, ethical considerations were met. All participants are anonymous, and all material is stored confidentially. All data collection and processing were carried out in compliance with the *European General Data Protection Regulation* (GDPR). The Faculty of Health and Medical Sciences at the University of Copenhagen approved the processing of personal data in the study (journal no.: SUND-2018-09).

Consent to participate All participants included in the study provided written informed consent.

Consent for publication Not applicable.

Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by LCD. Analyses were performed by LCD, SKS and ABA. The first draft of the manuscript was written by LCD, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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