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Community pharmacists' preparedness for substituting biologics and dispensing biosimilars – Lessons learned from a multinational survey

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ABSTRACT

Interchangeability between biological medicines and biosimilars, and subsequent substitution by pharmacists represent an important opportunity for costs savings for health care systems. Because biological medicines are complex products, the expert role of the pharmacist to inform patients and support physicians is indispensable. However, regulations on substitution of biosimilars differ around the globe, such that a substitution that is allowed in one country may be forbidden in another. Overall, pharmacists' knowledge of biosimilar medicines is incomplete and hesitancy to engage in substitutions is perceptible. As counter-balancing remedy, continued education about biosimilars is needed among practicing community pharmacists.

1. Introduction

Biopharmaceutical products (or biological medicines) are derived from living systems and produced in biotechnological processes.[1] The natural microheterogeneity of biologicals makes it impossible to create identical copies.[1] Consequently, a copy version of a biological medicine, called a *biosimilar*, is not identical, but highly similar to the original reference biological medicine (also called a *reference product*) in terms of structure, pharmaceutical quality, biological activity, efficacy, safety and immunogenicity.[2–4]

Biosimilars have been authorized for marketing in the European Union (EU) since 2006, in Australia since 2010, in the US since 2015 and in Thailand since 2017.[5–8] As biosimilars are predominantly sold at lower prices compared to their reference products, they are recognized as an important opportunity for cost savings for health care systems.[9] Even if several factors influence the true savings, estimates for the US market mention a reduction of direct spending on biological medicines by $54 billion from 2017 to 2026, which corresponds to 3% of total estimated biologicals spending over that period.[10] By 2020 in Europe, the expected savings in health care costs through the use of biosimilars have been estimated to reach up to €33 billion.[11] However, market uptake of biosimilars varies across countries and regions, and acceptance among stakeholders is a topic of debate.[12,13]

An interchangeable biosimilar is expected *"to produce the same clinical results as the reference product in any given patient"*.[14] Interchangeable products may thus be exchanged for the reference product.[14] Interchangeability is an important issue for health care professionals, but regulatory agencies across the globe approach guidance on interchangeability differently between reference products and biosimilars, or between one biosimilar and another biosimilar of the same reference product.[7,15] Varying definitions and regulations across the world lead to ambiguous practices. Within the EU, interchangeability is considered at a national or local level,[7] while in the US, interchangeability assessment is part of a dedicated regulatory

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pathway. An interchange made by a physician is called a *switch*, whereas an interchange by a pharmacist without knowledge or prior explicit consent of the prescribing physician is called a *substitution* or *automatic substitution*.[7,9] Laws on substitution of biosimilars also differ across jurisdictions. In the EU, substitution practices are determined nationally.[16] Substitution of biologicals is currently not permitted in EU member states, Switzerland and Thailand.[15,17,18] One exception in Germany is the presence of an agreed list of interchangeable biologicals called "bioidenticals" that are produced on the same production line and have the same application form. As a result, these are identical products, not similar products. Germany has provided guidance for physicians since 2020 on how patients should be switched to save costs.[19] In a further step, substitution of biosimilars on the pharmacy level will be introduced in Germany in 2022.[18,19] In France, community pharmacists are allowed by law to perform automatic substitution when patients start a biological treatment for the first time, and must dispense a product from a national biosimilar register.[20] In Denmark, all patients undergoing treatment with a biologic medicine are switched to the biosimilar treatment 12 weeks after the European Medicine Agency EMA authorizes the biosimilar.[10] In Finland, automatic substitution of biologic medicines at the pharmacy level is not recommended[21] even if no risk of serious adverse effects has been reported.[22–24] In the United States, for biosimilars fulfilling the US Food and Drug Administration's (FDA) requirements regarding interchangeability, substitution of a biosimilar for a reference product or automatic substitution are a matter of state pharmacy law.[14,25] The perspective of some stakeholders such as physicians, specialists or hospital pharmacists has been explored,[26] but research on community pharmacists practices is scarce.

Community pharmacists can play a prominent role in enabling safe and cost-effective biosimilar availability to the patients both as a dispenser of medicines and as an educator about these products. Hence, it is important to explore community pharmacists' current knowledge and attitudes regarding biosimilars.[27–29] The aims of this international research project were (i) to evaluate how well community pharmacists are informed about biosimilars and the substitution of biologicals, and (ii) to explore their attitudes toward biosimilars.

2. Material and methods

We developed an original survey in English based on a review of the literature to self-administer. Eleven questions covered the definition of biosimilars; frequency of dispensing biologicals and biosimilars; attitude toward biosimilars; substitution and interchangeability, and information sources on biosimilars. Translations were performed with cross-cultural adaptation. Five countries were purposively selected from the European Union (Belgium, Finland, Germany) and non-EU regions (Switzerland, Thailand) to represent different health care systems with different community pharmacists' roles.[30] The survey was piloted in Belgium with two pharmacists to test feasibility and in Finland with pharmacists to test face validity (acceptance and comprehensiveness). Surveys were prepared on different online platforms (SurveyMonkey™ for Belgium; REDCap™ web application for Germany and Switzerland; eLomake™ for Finland, and Google Forms™ for Thailand). Dissemination occurred through community pharmacists' associations in the respective countries by means of an email. There were no financial or other incentives provided to participants. There was no sampling strategy. Recruitment lasted between 3 weeks (Finland) and 7.5 months (Thailand; Table 1).

3. Results

A total of 916 community pharmacists was surveyed across the five countries, from which 466 complete datasets were analyzed (Table 1). When asked about the definition of '*biosimilar*', 56.1% of all respondents gave a correct answer (range: 41.7% in Germany to 71.8% in Thailand). Respondents generally did not feel sufficiently informed about biosimilars (range: 15.4% in Thailand to 44.1% in Germany). Concerning the substitution of biologicals in the respective countries, the correct answer was given by a mean of 36.7% respondents (range: 20.5% in Thailand to 73% in Finland). However, most Thai respondents answered "don't know" (58.9%). Training on the topic of biologicals was obtained in the process of professional development, after initial professional education and licensure, by a mean of 35.4% of respondent (range: 13.2% in Thailand to 48.8% in Germany), but the large majority of respondents would be interested in receiving additional training on that topic (83.3% in Germany to 97% in Finland).

Table 1
Distribution of the survey among community pharmacists in five countries and resulting participation numbers.

Country	Belgium	Finland	Germany	Switzerland	Thailand
Start date	01.11.2018	23.09.2019	07.05.2020	24.02.2020	16.03.2020
Duration	3 months	3 weeks	6 weeks	4 weeks	7.5 months
Number of participants	177	190	134	256	159
Number of full datasets	113	168	84	62	39

4. Discussion

Pharmacists are expected to be 'the expert on medicines'. For complex products such as biological medicines, the expert role of the pharmacist to inform patients and support physicians is indispensable. However, the results of this multinational survey indicate a clear lack of knowledge of community pharmacists on the definition of biosimilars. Further, a clear need for education about biosimilars and substitution practices for community pharmacists in the different surveyed countries seems to exist. A survey in France with 178 responses from community pharmacists showed that 77% answered they had "little knowledge" and 12.4% "no knowledge" on biosimilar medicines, and 50% felt "not at all" informed about biosimilars.[31] Inversely, a survey in Ireland with 125 responses received from community pharmacists showed that 75.2% were familiar with the term biosimilar, but 21% thought a biosimilar was the same as a generic medicine.[32] A survey in Karachi, Pakistan, with 305 completed responses among community (39), academic (85) and clinical (54) pharmacists and recent pharmacy graduates (127) showed 81.6% of respondents with good knowledge about the interchangeability concept, while 15.1% and 2.4% of respondents had fair and poor knowledge, respectively.[27] The community and academic pharmacists were less knowledgeable than the clinical pharmacists.[27] Our results are in line with these various rates around the globe, which probably reflects the variability of use, and the constantly evolving regulatory guidelines and standards for biosimilars. In addition, requirements on if and how the prescriber and patient should be notified in case of substitution differ between countries and evolve continuously. Globally, the patient will need to consent to a substitution, just like generic substitution of bioequivalent medicines. For biologicals however, in the US since 2015, and in the European countries that permit substitution of biologicals, the prescriber and individual patient must be notified about the biosimilar dispensed when a substitution or a switch has been made at a pharmacy, and pharmacist and physician must retain records of substituted biologic medicines.[20,33] In Australia, the pharmacist can only interchange with a biosimilar if the prescriber has not indicated "Brand substitution is not permitted" but notification to the prescriber is not needed. The pharmacy will need to retain records of what was dispensed as they would with all other medicines.[34]

The need for continued education about biosimilars appears to extend beyond practicing community pharmacists. In most countries, biological products have been included in the pharmacy curriculum with some hours of lecture. Results from exploratory surveys in both Denmark and Belgium show unsatisfactory levels of knowledge on biosimilars among near-graduated pharmacists. Data from Denmark showed that 39% of pharmacy students in their last year of the 5-year studies at the University of Copenhagen "strongly disagree" about considering biosimilars and generic medicines being the same, and only 46% agree that they felt sufficiently

informed about biosimilars.[35] A majority of students (76%) would be interested in receiving additional training on biological medicines. A recent survey among Belgian pharmacy students revealed that only 44% of master students feel well prepared to work with biologicals including biosimilars in the future.[36] In the US, neither the American Association of Colleges of Pharmacy's (AACP) Center for the Advancement of Pharmacy Education (CAPE) Educational Outcomes[37] nor the US Accreditation Council of Pharmacy Education's (ACPE) Accreditation Standards[38] specifically address preparing pharmacy students with regards to knowledge on biosimilar medications. ACPE is embarking upon an update to their accreditation standards, which will provide accreditors and pharmacy education programs in the US the opportunity to better address how pharmacists are prepared in their knowledge on biosimilar medications.[39]

5. Conclusions

Our international survey revealed a partial lack of knowledge among community pharmacists regarding the definition of biosimilars and the legal situation for the substitution of biologicals, independently of the country they live in and the current law. As experts of medicines with important role in medicine use, especially in the context of biosimilars, additional training is essential to equip community pharmacists with the necessary knowledge about biosimilars, especially in case substitution may become legal.

Informed consent

Although informed consent was not required for the purpose of this survey, written consent was obtained from all participants to use data in anonymized format for publication. Participation was voluntary.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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