Title

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Journal

Journal of Oncology Pharmacy Practice, 26(3_suppl)

ISSN

1078-1552

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Publication Date

2020-04-01

DOI

10.1177/1078155219897959

Peer reviewed

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Commentary

J Oncol Pharm Practice
2020, Vol. 26 3(Supplement) 33–39

DOI: 10.1177/1078155219897959
journals.sagepub.com/home/opp
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Proceedings of the biosimilars workshop at the International Symposium on Oncology Pharmacy Practice 2019

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Abstract

The International Society of Oncology Pharmacy Practitioners organized a workshop to create learning opportunities on biosimilars in pharmacy practice on 10 October 2019. The topics that were covered included (i) the development and testing of biosimilars, (ii) the challenges of bringing biosimilars to market, and (iii) real-world data on patient safety and perceptions during biosimilar implementation. The development of biosimilars can take up to eight years and the extensiveness of the process depends on several factors, such as the complexity of the production process and regulatory requirements. Compared to generic products of small-molecule drugs, there is a higher barrier to market entry for biosimilars, explaining the small number of biosimilars in the market. Appraisal of biosimilars for inclusion in hospital formularies is also different from the review process of originator biologics, where the former is usually institution-led and has fewer restrictions on use. When several biosimilar products are available, factors that should be considered besides cost are licensed indications, supply chain confidence, clinical data, and product attributes. Real-world data have shown that biosimilars are well-tolerated and have safety data that are comparable to that of the originator product. Oncology pharmacists from the United Kingdom, Kenya, and Canada also presented their respective experiences with biosimilar use. Different countries at varying stages of biosimilar implementation faced distinct challenges. Nevertheless, resources to assist biosimilar implementation can potentially be shared between different regions. International Society of Oncology Pharmacy Practitioners is well-positioned to foster professional cooperation at an international level to drive biosimilar implementation.

Keywords

Biosimilars, workshop, International Society of Oncology Pharmacy Practitioners

Date received: 20 November 2019; revised: 8 December 2019; accepted: 9 December 2019

Background

As part of the society's efforts to create learning opportunities relating to biosimilars in pharmacy practice, the International Society of Oncology Pharmacy Practitioners (ISOPP) organized a four-hour workshop during the International Symposium on Oncology Pharmacy Practice on 10 October 2019. This document reports on the proceedings of the workshop, sharing key learning points and discussion themes and providing an educational resource for ISOPP members.

Welcome and introduction

The workshop was opened by Emma Foreman, Consultant Pharmacist, The Royal Marsden National Health Service (NHS) Foundation Trust as the chair of the ISOPP Biosimilars Taskforce. In her opening remarks, Emma highlighted that the workshop aimed to provide an opportunity for ISOPP members to learn about biosimilars, which corresponded to the objectives of the Taskforce.

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The results of two surveys carried out by the ISOPP Biosimilars Taskforce were presented. Both surveys were open to both ISOPP members and non-members around the world. The first survey attempted to identify the educational needs of pharmacists on biosimilars. A total of 86 responses were received. While most respondents reported being well-informed about biosimilars, three key areas were highlighted as training and education gaps: (i) the evaluation of the comparative efficacy of biosimilars against originator products, (ii) practical guidance on managing the switch to biosimilar products, and (iii) medication safety. These topics were chosen as the focus of this Biosimilars Workshop. The second survey, which aimed to describe biosimilar implementation practices around the world, received a total of 90 responses; 74% of the respondents reported the use of biosimilars in their institutions. Among respondents who reported no use of biosimilars, 45% stated that the introduction of biosimilars was being considered. The main barriers to the use of biosimilars included the unavailability of biosimilars, clinician resistance, and issues with purchasing contracts or procurement arrangements.

How are biosimilars developed and tested?

Paresh Patel, Senior Biosimilar Business Development Manager, Accord Healthcare, provided an overview of the development pipeline of new biosimilars. Biosimilars are defined as biological medicines that have been shown to have no clinically meaningful difference from the originator product in terms of quality, safety, and efficacy. Nevertheless, due to differences in the production process, it is unlikely to produce identical copies of the originator product. The term "bio-better" was also briefly introduced where the new biological product may be superior to the originator. However, "bio-betters" may be subject to different evaluation pathways by regulatory authorities and no clear guidance has yet been established.

The development of biosimilars, which may take up to eight years, begins with the determination of Critical Quality Attributes (CQAs). CQAs refer to physical, chemical, biological, or microbiological properties that should fall within an appropriate limit, range, or distribution to ensure the desired product quality.[1] Examples of CQAs are product potency and purity. The determination of CQAs is a crucial step in the developmental process as CQAs of the biosimilar have to match those of the originator product. Once analytical and functional assays have established that the biosimilar is sufficiently similar to the originator molecule, preclinical studies, phase I studies, and phase III studies can be conducted to demonstrate the absence of any clinically meaningful differences from the originator product.

The comprehensiveness of the development process hinges on several factors and increases with the complexity of the originator molecule or production process. The study design and outcomes of downstream pre-clinical and clinical studies also depend on how closely the biosimilar matches the originator products in analytical and functional assays. Regulatory approval requirements, such as the need for pre-clinical animal studies, will also influence the development strategy of biosimilars. While regulatory requirements in different regions may differ, the developmental strategy is usually based on the most stringent requirements if the biosimilar is planned to be marketed at a global level to avoid delays in launching the product.

The extrapolation of biosimilars approval for other indications of the originator product can lead to reduced developmental cost and increased access to the biosimilars. Nevertheless, extrapolation should be justified based on the totality of evidence, including the mode of action of the originator product, characterization of the biosimilar molecule, and pharmacokinetic and pharmacodynamic similarities between the biosimilar and originator product.

Simon Cheesman, Lead Hematology Pharmacist at University College London Hospitals (UCLH), described the evaluation of biosimilars when making formulary decisions. The implementation process of biosimilars is different from that of originator products. Compared to originator products, the introduction of biosimilars is usually institution-led, rather than clinician-led and currently lacks clear commissioning guidance. Biosimilars are also usually listed in the formulary for a broad range of indications with fewer restrictions on use. When introducing biosimilars, a switching strategy for existing patients should also be considered and planned.

Various parties may serve as the appraisal authority, ranging from national regulatory agencies to regional purchasing groups, each with a different set of priorities to consider. It is recommended for the appraisal process to begin 3–6 months before biosimilar availability to avoid delays in the introduction and uptake of the biosimilar product, which can lead to missed opportunities for cost-savings (refer to the Cancer Vanguard website[2] for recommended implementation timeline). A range of information sources can be utilized in the appraisal process, such as the summary of product characteristics, European Public Assessment Reports, and manufacturer's information. Clinical trial publications are useful to provide detailed clinical evidence to support the implementation of biosimilars.

There may be more than one biosimilar product to choose from. Establishing a clear criterion to differentiate between different biosimilars of the same biologic can be challenging, but all considerations should embed the concept of selecting the "best value biologic". There is a possibility that the originator product is the best value biologic. Several factors that should be considered are:

1. Market authorization:
   The biosimilar selected should ideally be licensed for the desired indications in the relevant jurisdiction.

2. Supply chain confidence:
   To avoid disruption of supply, especially during the early phases of the implementation, the manufacturer should ideally be a reputable biotechnology company, have sufficient manufacturing sites, have a minimal history of shortages, and provide strong customer support. While an important factor to consider, accurate information on the reliability of suppliers may be difficult to ascertain.

3. Clinical data:
   Clinical data supporting the use of the biosimilar should be drawn from studies with relevant study populations and endpoints. Studies on biosimilar switching will also provide useful data to guide change to the biosimilar among existing patients. Furthermore, pharmacovigilance data or plans for post-marketing surveillance should be available to collect long-term safety data for comparison against the originator product.

4. Product attributes:
   The formulation and presentation of the biosimilar should not lead to additional barriers to adoption. For example, the packaging should be clear and compliant to the European Union Falsified Medicine Directive.[3] Other relevant product attributes to be scrutinized include shelf-life, storage, vial sizes, in-use stability data, administration devices, and excipients.

5. Price:
   The price of the biosimilar should be taken into consideration to maximize savings.

Several systemic or pathway barriers may hinder the implementation of biosimilars. For example, originator biologics may have enhanced stability data, evidence-backed rapid infusion schedules, off-label indications, or more convenient routes of administration. Reluctance to switch to biosimilars may also stem from the provision of funds by the pharmaceutical industry to carry out research or healthcare services.

Case studies—Comparing experiences of biosimilar implementation around the world

Jatinder Harchowal, Chief Pharmacist and Clinical Director, The Royal Marsden NHS Foundation Trust, United Kingdom (UK), shared the experience of UK hospitals in the implementation of the rituximab biosimilar. When infliximab and etanercept biosimilars were previously introduced in the UK, uptake was shown to be inconsistent due to a lack of national incentive or drive. The subsequent availability of a biosimilar for rituximab, which could potentially result in a high amount of savings for the healthcare system, presented an opportunity to establish system-wide changes to improve biosimilar uptake and design strategic pathways for future biosimilar implementation.

The implementation project was carried out across three hospital systems—The Royal Marsden, UCLH, and The Christie Hospitals—with Sandoz collaborating in a non-commercial capacity. Key stakeholders in the implementation process, including clinicians, pharmacy personnel, patients, and professional groups, were engaged. Education sessions were conducted for healthcare professionals to improve their understanding and confidence in the use of biosimilars. Patient education resources were also developed jointly with patient groups such as the Lymphoma Association. To assist in biosimilar implementation at an institutional level, policies were also developed for local NHS trusts with institutional approval.

Among the most critical steps in biosimilar implementation was the development of a central repository of information relevant to the introduction of the rituximab biosimilar. This repository was hosted on the Cancer Vanguard website[2] to provide accessible resources across the UK, which could be easily adapted for use in local settings. Examples of resources found on the Cancer Vanguard website included the process timeline for biosimilar adoption, guidance documents for biosimilar implementation, and education materials for healthcare professionals and patients.

At The Royal Marsden and UCLH, the switch to the rituximab biosimilar occurred in July 2017. Eligible patients were also assigned to rapid rituximab infusions as per protocol. Only grades 1 and 2 infusion reactions were reported, at rates comparable to the originator product. No practical problems were observed during the implementation phase. Learning from this experience, similar strategies were adopted in the implementation of trastuzumab and adalimumab biosimilars,

resulting in even higher uptake rates of the biosimilar products.

Nevertheless, the implementation of biosimilars should also take into account the patient experience. Using rituximab as an example, patients who were on single-agent rituximab regimens remained on the originator product formulated for subcutaneous administration to avoid unnecessary intravenous infusions, even after the biosimilar was introduced.

Winnie Mwangi, Oncology and Clinical Pharmacist, Meru Teaching and Referral Hospital, Kenya, provided the Kenyan perspective on biosimilars. In Kenya, cost is a key consideration. As the national health insurance coverage is usually inadequate for oncology patients, substantial out-of-pocket expenditure can impose a financial burden on impoverished patients. Therefore, the affordability of treatment is an important consideration. Consequently, biologics with first-line indications are often used as second- or third-line treatments and patients may not be able to complete all treatment cycles required.

In Kenya, biosimilars are not supplied by the national procurement agency that distributes medications to all public healthcare facilities. Purchase of biosimilars at the hospital level is allowed but rarely occurs due to stringent procurement guidelines. As a result, biosimilar uptake rates are low at approximately 20% in public hospitals. The usage of biosimilars is possibly higher in private hospitals.

Currently, there are no clear guidelines in Kenya on the implementation of biosimilars. While regulatory guidelines are available for the registration of biosimilars, biomimics (replica medicines of biotherapeutic products that do not meet regulatory requirements of biosimilarity to the originator product[4]) are introduced to the Kenyan market via special import permits or parallel imports and are assumed to be equivalent to biosimilars. Due to resource constraints, biomimics are often the only treatment option available to patients. As such, the role of biomimics is being heavily discussed in Kenya.

Clinicians and healthcare workers treat biosimilars similar to generics. Biologics are prescribed using the International Nonproprietary Name without specification of the brand name while automatic substitution of originator products with biosimilars, or even biomimics, is routinely carried out based on costs and availability at the discretion of the pharmacist. Moving forward, a crucial gap to address would be the education of healthcare professionals on what biosimilars are, and biosimilar switching. There is also a critical need to enforce existing regulations on biosimilars and establish guidelines on biosimilar implementation.

Glenn Myers, Clinical Pharmacist, The Moncton Hospital, Moncton, Canada, talked about the state of biosimilar implementation in Canada. Compared to the UK, biosimilars are relatively new in Canada with Grastofil–filgrastim being the first biosimilar to be approved for use in 2018. An evaluation pathway for biosimilars remains to be established.

Health Canada is the agency responsible for regulatory review and approval of drugs in Canada. Once approved, oncology drugs undergo health technology assessment by the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee, which provides recommendations on drug reimbursement. However, the pCODR Expert Review Committee does not evaluate biosimilars, but instead, a rapid response team established by pCODR reviews evidence on biosimilar switching and interchangeability between biosimilars and originator biologics. The team also provides input to supplement price negotiation for group purchasing.

To ensure appropriate implementation and cost-effective use of therapeutic oncology biosimilars across Canada, the pan-Canadian Oncology Biosimilar Initiative (pCOBI) was established. The main focus of pCOBI is on the development of educational materials and implementation guidelines. Clinical guidance, reimbursement, evaluation, and reinvestment of savings serve as secondary priority areas.

Lessons that were extrapolated from the introduction of Grastofil–filgrastim include:

1. Greater transparency on approval date to ensure that front-line healthcare professionals are adequately prepared for biosimilar implementation.
2. Clearer guidance for biosimilar switching.
3. More education for healthcare professionals to correct misperceptions, such as biosimilars being associated with higher adverse event rates, and improve uptake.
4. Streamlining of inpatient and outpatient access to biosimilars.

During the panel discussion, it was emphasized that biosimilar uptake around the world has been inconsistent despite the potential savings associated with biosimilar use. International collaboration is crucial to promote the use of biosimilars. Implementation pathways and resources developed by countries with experience in biosimilar implementation can be successfully adapted for use in other settings. Canada, for instance, has benefitted from tools and resources provided by the Cancer Vanguard project in the UK. This example highlights the importance of sharing information and experience on biosimilar implementation at an international level.

However, different countries are at different stages in the trajectory of biosimilar implementation and thus,

face different barriers in the introduction of biosimilars. For example, Kenya, Nigeria, and other African countries have erratic drug distribution channels and lack confidence in the quality of biosimilars/biomimics that are available in the region. To resolve this concern, regional collaboration between healthcare professionals, led by professional organizations, can help to convince policymakers of the importance of biosimilars in generating savings for the healthcare system and the need for clear implementation guidance. Furthermore, national or regional supply chains need to be set up to procure products approved by regulatory agencies, such as the United States Food and Drug Administration or European Medicines Agency, to ensure consistency in the quality of biosimilars procured. Other countries that have initiated but are in the early phases of biosimilar implementation may be more concerned with issues related to educating patients and healthcare professionals as well as handling biosimilar shortages.

Challenges of bringing biosimilars to market

Enrico Bovi, UK Oncology Biosimilars Director, Pfizer, discussed the importance and challenges of bringing biosimilars to the market. Compared to launching a generic version of a small-molecule drug, the process of marketing a biosimilar is more complex and poses more risks to the pharmaceutical company. Proof of quality and pharmacokinetic bioequivalence is usually sufficient to demonstrate equivalence to the originator product for new generics. However, new biosimilars also require data on molecular similarity and clinical data on efficacy and safety. This higher barrier to market entry explains the low average number of biosimilars for biological medicines in the market in contrast to the large number of generics for small-molecule drugs.

Nevertheless, it is important for the pharmaceutical industry to invest in biosimilars as they allow quicker and wider patient access to biologics at more affordable prices. Furthermore, the acceptance of biosimilars has been increasing. Pharmaceutical companies also have well-established production facilities that can ensure a reliable and affordable supply of biosimilars.

Biosimilars uptake has grown in the UK with increasing price erosion as more biosimilars are launched. This trend has shaped a positive landscape in the UK for biosimilar manufacturers. The commissioning framework for biological medicines published by the NHS aims for 90% of treatment-naïve patients and 80% of existing patients to be prescribed the "best value biologic" within 3 and 12 months of biosimilar launch,[5] respectively. Existing data show that the speed of biosimilar uptake has increased from 2015 to 2018, driven by price erosion and well-established implementation pathways.

As more biosimilars are introduced, further price erosion may threaten the market sustainability of biosimilars. Pharmaceutical companies should consider targeting a sustainable price and providing valuable services rather than charging a higher price while cornering the market to recoup costs within a short amount of time.

In addition to providing more affordable access to biologics, biosimilar manufacturers should also consider crucial issues such as maintaining a reliable supply chain, as switching between different biosimilars is difficult and complex. Biosimilar companies should also provide reliable stability data and aim for reasonable and convenient storage conditions. Unmet needs that biosimilar manufacturers should consider tackling in the future include simplifying intravenous infusion processes and evaluating the possibility of homecare delivery.

Administration and patient safety

Geoff Saunders, Consultant Pharmacist, The Christie Hospital, UK, presented data on patient safety and perceptions during the implementation of a trastuzumab biosimilar. Real-world data on patient safety and perception is crucial to improve the acceptance of biosimilars among clinicians. A pharmacovigilance audit was carried out by The Christie Hospital, UK, to document adverse drug reaction (ADR) rates of a trastuzumab biosimilar during the first six months of biosimilar implementation. Any adverse event that occurred within 48 h of biosimilar administration was documented. Out of the 1000 trastuzumab doses that were administered over six months, a total of 25 ADRs were documented with only eight attributable to the trastuzumab biosimilar (Table 1). All related ADRs were known side effects of trastuzumab, and occurred at rates comparable to the originator product.

Table 1. ADRs attributable to trastuzumab biosimilar during pharmacovigilance audit.

ADR	Number of cases	Treatment cycles
Infusion reaction	5	Cycle 1 (all trastuzumab-naïve patients)
Injection site pain	1	Cycle 9
Extravasation	1	Cycle 12
Heart failure	1	Cycle 20

ADR: adverse drug reaction.

The audit results increased the confidence of clinicians to switch to biosimilars.

Data on patient perceptions were also collected during the introduction of the trastuzumab biosimilar. While the majority of the patients did not recall any discussion about biosimilars, those who did were able to demonstrate a good understanding of biosimilars. Most patients did not have further questions on biosimilars but wanted reassurance that biosimilars were as effective as the originator biologics. These observations indicate that drug efficacy remains the main priority of patients regardless of which product is used. Furthermore, patients also overwhelmingly agreed that it was important that the use of biosimilars would allow the reallocation of NHS resources for newer cancer treatments.

The use of rapid infusion protocols allows patients to receive biologics at an accelerated rate after tolerating the initial cycle with no infusion reactions. To reduce chair time, The Christie Hospital aimed to continue the use of rapid infusion protocols with biosimilars, where only treatment-naïve patients will be offered prolonged infusions at conventional rates and extended monitoring time. During the implementation of the trastuzumab biosimilar, none of the patients who transited from the originator product experienced infusion reactions. In the case of rituximab, only one patient developed tachycardia after switching from the originator product to a biosimilar. Data from both the trastuzumab and rituximab experience show that the rapid infusion protocols can be safely used to administer biosimilars without the need to re-challenge patients at conventional infusion rates. A rapid infusion protocol for bevacizumab has also recently been published.[6] Anticipating the launch of a new bevacizumab biosimilar, the current discussion revolves around the timing of rapid infusion protocol implementation—whether it should be implemented immediately whilst still using the originator product or after the switch to biosimilars has been completed.

Confusion between the originator product and the biosimilar may occur during prescribing, dispensing, or ADR reporting during the early stages of biosimilar implementation. These potential errors may be avoided by keeping only the biosimilar product in the inventory. If electronic systems are involved, only the biosimilar option should be retained. Keeping both the originator biologic and the biosimilar is unnecessary since equivalence has been demonstrated between the two products and may lead to medication errors or introduce unnecessary complexity in operating procedures. Exceptions may arise if the biosimilar is not licensed for all indications or routes of administration of the originator biologic.

Emerging issues

Reinvestment of savings from biosimilars

Savings from the use of biosimilars can be reinvested in new cancer treatments, such as chimeric antigen receptor (CAR) T-cell therapy or to expand biologics access to more patients. Quantifying and publicizing these outcomes will be helpful to demonstrate to the public the importance of implementing biosimilars. Patients who have switched to biosimilars will also understand how they have helped to reduce the financial burden imposed on the healthcare system, possibly leading to patient empowerment.

Private hospitals

Private care providers also face challenges in biosimilar implementation. Private practitioners value their autonomy in prescribing and often prefer originator products. Pharmaceutical companies also do not engage private providers in implementation projects due to low volumes of biosimilar sales.

However, experience with clinicians who manage private patients has been favorable in public hospitals, where education and training have helped to drive acceptance of biosimilars among both clinicians and patients. Establishing clear and consistent guidance in the selection and approval of formulary items may help private providers in introducing and increasing the usage of biosimilars.

Re-evaluation

The lower prices conferred by biosimilars provide an opportunity to review the economic appraisal of biologics previously found to be not cost-effective, possibly leading to the re-evaluation of the role of biologics in therapy. This re-evaluation is especially important with the emergence of new but more expensive treatments. For example, the economic evaluation of bevacizumab in ovarian cancer should be reviewed with the launch of a more affordable biosimilar, especially as poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as new but costly treatment options.

Summary

Biosimilar implementation will lead to a significant amount of savings in the healthcare system. Nevertheless, biosimilar uptake remains inconsistent around the world. Collaborations between different countries and industry partners are pivotal in driving biosimilar implementation through the sharing of experience and readily accessible resources. Engagement of stakeholders, including patients, and education of

patients and healthcare professionals have been shown to be critical steps in the process. To further improve biosimilar implementation, data on patient outcomes and experience should also be collected to refine the process and convince health systems that biosimilars and originator products are clinically equivalent. Harnessing the collaborative power of pharmacists from different countries and its role as an international professional organization, ISOPP is well-positioned to assist in the distribution of information and resources to lobby for and drive biosimilar implementation. Efforts include the publication of a position statement and the dissemination of a biosimilar education toolkit.

Acknowledgements

We thank the ISOPP Biosimilars Taskforce and workshop speakers, without whom the workshop would not have been successful. We are also grateful to Emma Foreman for her valuable feedback on the workshop proceedings.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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