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Review

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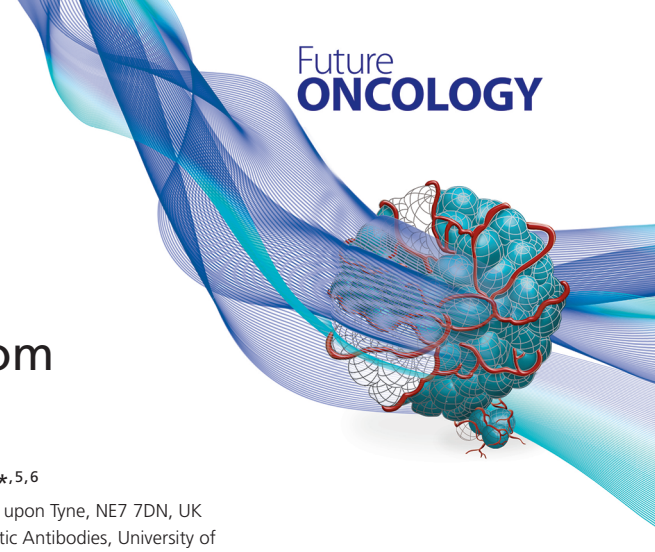

The rise of oncology biosimilars: from process to promise

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Biosimilars are biologic products that are highly similar to, and have no clinically meaningful differences from, the approved originator molecule. They are poised to play an increasingly central role in cancer treatment, helping to improve access by driving down costs. Regulatory bodies have set out robust mechanisms for the approval of biosimilars, based on comprehensive and rigorous analytical and nonclinical comparisons with the originator. Product attributes (e.g., post-translational modifications) that are important to the function of the molecule must be similar between biosimilar and originator. This should be followed by a robust clinical development program, assessing pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity. Equivalence in one indication might allow extrapolation across all the indications of the originator biologic. The recent approval of several trastuzumab biosimilars provides an example of how this process can work in practice for the benefit of patients, clinicians and payers.

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Keywords: biologic • biosimilar • breast cancer • SB3 • trastuzumab

Biologics are an increasingly central element of the cancer treatment armamentarium. Unlike traditional pharmaceuticals, which are usually small molecules, biologics are large compounds derived from living organisms, or recombinant proteins produced by cells transformed with the genetic information encoding the corresponding protein [1]. Typically, they are protein based, with inherently complex sequences and 3D structures. Unlike small-molecule drugs, they cannot be manufactured chemically. Instead, living host systems are required, which are typically human or animal cells; the process is inevitably harder to control than the process of chemical synthesis.

The importance of biologics in oncology is exemplified by the fact that the three biggest selling cancer drugs of 2015 were all monoclonal antibody-based biologics: rituximab, bevacizumab and trastuzumab [2]. At that time, all three remained under patent protection. However, since then, the patent protection for these biologic agents has expired and biosimilar forms of each drug are now available. This represents the beginning of a new era in oncology.

It is important to understand what biosimilars are, and what they are not. According to the US FDA, a biosimilar is a biologic product that is highly similar to, and has no clinically meaningful differences from, the approved reference originator product [3]. The EMA provides a similar overarching definition [4]. It is important to note that biosimilars are not generics, because it is not possible to make an identical biochemical entity, due to the inherent complexity of these molecules and their production processes. Instead, while a biosimilar has to be highly similar to the originator product, minor differences in clinically inactive components are allowed, as long as there are no clinically meaningful differences in purity, potency or safety (USA [3]), or quality, safety and efficacy (EU [5]) compared with the originator.

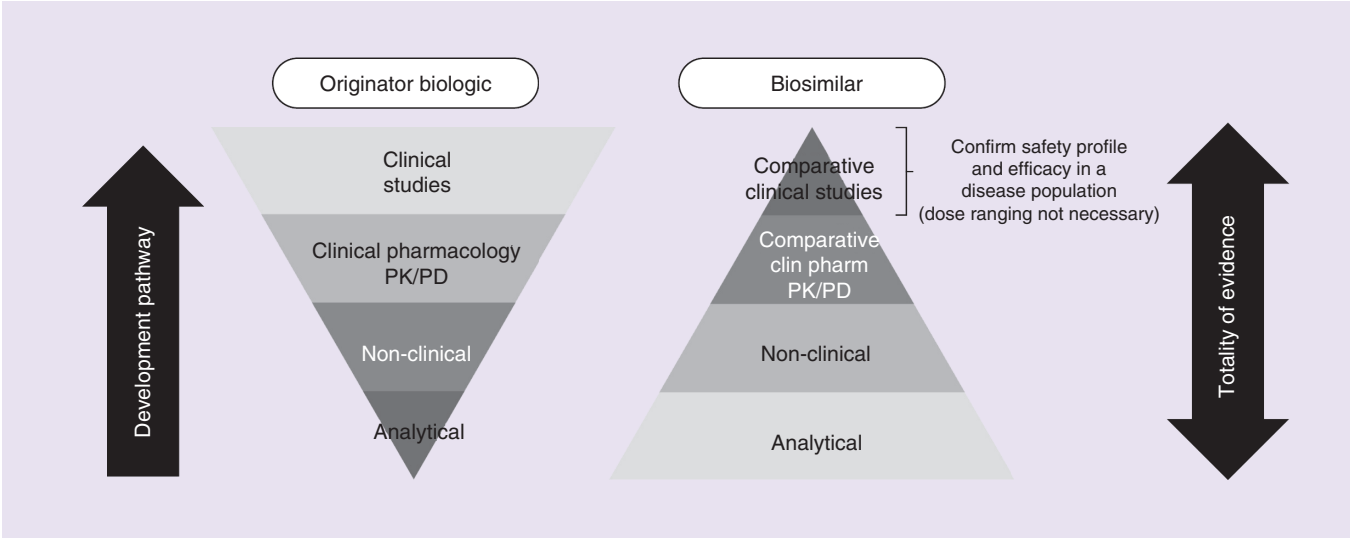

Figure 1. Development pathways for originator biologics and biosimilars.
PD: Pharmacodynamic; PK: Pharmacokinetic.
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The advent of biosimilars has created opportunities for all key stakeholders in oncologic medicine. For payers, they provide potential cost savings as more biosimilar products are brought to market, leading to increased competition and hence lower prices. For clinicians and patients, these cost savings may free up funds to improve access to (often expensive) novel treatments. For manufacturers, the loss of patents on originator biologics drives fresh innovation, and also provides opportunities for other companies to enter the oncology space.

Furthermore, thinking beyond the developed world, the approval of biosimilars may allow biologic therapies to be prescribed in less wealthy countries, where costs had previously been prohibitive. This will drive access to essential medicines: of the top three cancer drugs from 2015, two (trastuzumab and rituximab) were included on the WHO Model List of Essential Medicines for oncology [6]. However, the advantages of biosimilars can only be fully realized in the developing world if regulatory requirements are sufficiently rigorous [7]. Poor-quality copies that do not meet the highest standards – and would therefore not be approved in developed regions such as the USA and the EU – have been associated with compromised patient safety in parts of Asia and Latin America [7,8].

Even in developed countries, there has been understandable anxiety around the use of biosimilar medicines because they are 'similar' but not 'identical' to the originator. Better understanding of the rigorous process of developing and approving biosimilar medicines, and increasing experience of their use, should eliminate this anxiety. In this review, we describe this development and approval process. We limit the scope to biosimilars in therapeutic cancer care, using trastuzumab as an exemplar. Nonetheless, lessons can be learned from previous experience with biosimilars in supportive cancer care.

Overview of the development pathway for biosimilars

The development pathway for a biosimilar is very different from that of an originator biologic (Figure 1 & Table 1). An originator product requires a long basic research path, the establishment of a production and purification process (including analytics), and demonstration of proof of concept (including efficacy and safety), followed by an extensive clinical trial program, particularly in Phase III development; for each indication, the drug usually requires a separate, large, multicenter, randomized, controlled trial that is of appropriate registration standard. By contrast, for biosimilars, the bulk of the work is in the development of an appropriate production and purification process, and the requirement for an extensive physicochemical and *in vitro* functional comparison with the reference product [9]. Nonclinical and clinical evaluation is less extensive because the data proving efficacy and safety in one indication may be extrapolated across all other indications of the originator product (Table 1) [3,4,9]. For example, the first trastuzumab biosimilar (SB3; Ontruzant®) was approved based on comparisons with the originator in the neoadjuvant setting, in combination with chemotherapy [10,11]. This allowed approval of the biosimilar product

Table 1. Requirements for the approval of biosimilar products.

Characteristics	US FDA and EMA requirements	
Primary amino acid sequence	Needs to be identical	
Potency	Must match the originator product	
Route of administration	Must be the same as the originator product, although the administration device may be different	
Higher-order structures, post-translational modifications and other potential variants	Must be as similar as possible to the originator product, with adequate analyses to demonstrate that any observed difference does not affect clinical efficacy, safety or immunogenicity	
Clinical study parameter	**US FDA**	**EMA**
Pharmacokinetic studies	Comparative human studies	Single dose, comparative human studies
Pharmacodynamic studies	Comparative human studies, where clinically relevant measures are available	Combine with PK studies where a clinically relevant PD end point is available
Efficacy	At least one adequately powered equivalence trial	Highly sensitive, dose-comparative PD studies may be sufficient; otherwise, at least one adequately powered equivalence trial
Safety	At least one adequately powered trial; postmarketing surveillance	At least one adequately powered trial; postmarketing surveillance
Immunogenicity	At least two comparative trials, one pre- and one postmarketing	Must be assessed during the safety trial

PD: Pharmacodynamic; PK: Pharmacokinetic.

across all of the trastuzumab indications in early breast cancer (neoadjuvant or adjuvant setting) and in metastatic disease, as well as in metastatic gastric cancer [12].

Given this extrapolation of safety and efficacy data, post-marketing surveillance is therefore particularly important with biosimilars. Both the FDA and the EMA require that manufacturers put in place an appropriate pharmacovigilance system to ensure that safety monitoring continues after registration [3,4]. An important consequence of this is that biosimilars must therefore be prescribed by brand so that safety can be appropriately tracked. This contrasts with the recommendation to prescribe by International Nonproprietary Name for generic drugs.

Science behind product manufacturing

With biologics, 'the product is the process'. This applies equally to originator and biosimilar products. Because of their intrinsic heterogeneity, it is not possible to fully and unambiguously characterize each molecular variant of a complex molecule like a monoclonal antibody, and hence manufacturers must ensure that the production process remains largely consistent over time to ensure product consistency and quality.

The key first step is to establish a well-characterized production cell line. Initially, this is done on a small scale (perhaps in milliliter volumes) with a relatively small number of cells. However, to produce the biologic on an industrial scale, the cells have to go through many consecutive rounds of multiplication until they can be cultured in large bioreactors with volumes as large as tens of thousands of liters. From these cells and/or culture medium, the biologic has to be purified using various filtration and chromatographic techniques [14]. Rigorous testing is required across all the steps involved, from the development of the cell bank through process validation to bulk production and final batch assessment.

For any biologic, whether originator or biosimilar, there will inevitably be different forms of the protein even within the same batch. Although the amino acid sequence of the protein itself will remain the same, post-translational modifications may differ substantially. For example, the glycosylation pattern (addition of sugar molecules) will vary. This can have a marked impact on various properties of the protein, such as stability and solubility, and on its intrinsic functional properties [15]. Other types of post-translational modifications that may vary include phosphorylation, acetylation and sulfation [16]. All are enzymatically controlled within the cell and will therefore be dependent on the cell type and culture conditions. Furthermore, during purification and then storage, the protein may be subject to chemical modifications, such as oxidation and deamidation. These changes will be dependent on external factors such as pH and temperature. Based on all of these potential modifications, it has been estimated that around 100 million molecular variants are theoretically possible for any given monoclonal antibody [17].

In practice, it is clear that large numbers of variants will always be present. Even with sensitive analytical tools it is impossible to identify all of these unambiguously. Therefore, reproducibility can only be guaranteed by consistency in the production process. However, changes are sometimes required, often many times over – even with originator

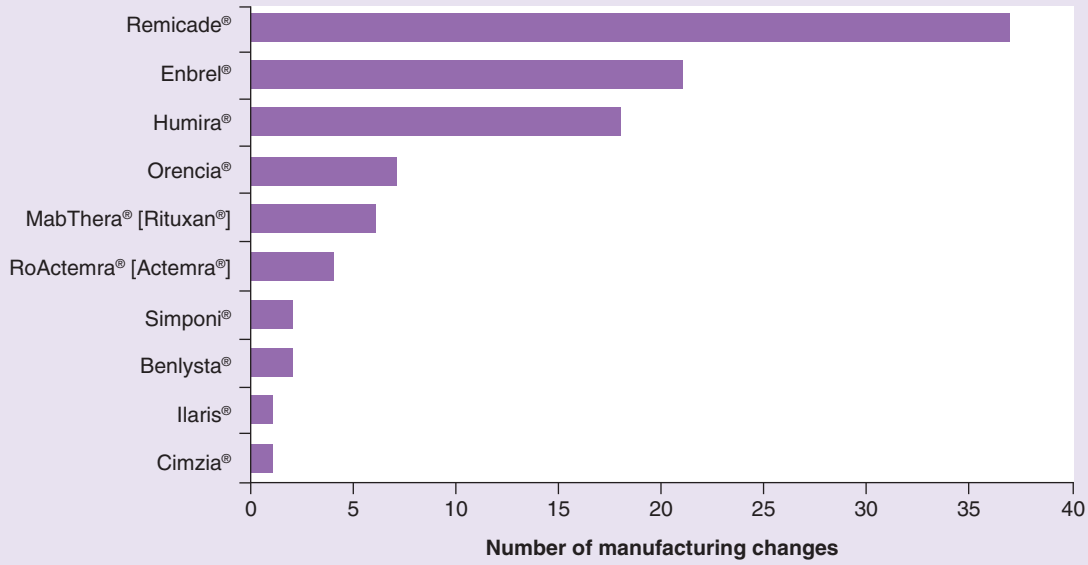

Figure 2. Postapproval changes in the manufacturing process of originator biologics.
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biologics (Figure 2) [18]. These changes must be shown to have no impact on the efficacy, safety or immunogenicity of the product [19], and tight quality control is an essential prerequisite.

With biosimilars, the same overarching principles apply. These products require the same rigorous oversight of the manufacturing process as originator biologics. Of course, a biosimilar must have an identical amino acid sequence to the originator. However, even when the originator product is off patent, its manufacturer will not share their cell line or details of the production process. Hence, the manufacturer of a biosimilar version will have to 'reverse engineer' these elements by developing their own cell line and production procedures, aiming to obtain a drug product that is sufficiently similar to the reference product. Although they will have to employ the same underlying principles to achieve this as were used for the originator biologic, the final manufacturing process will always be somewhat different. Inevitably, this will result in microheterogeneity of the protein population – not only within each product but also, more importantly, between each product (originator and biosimilar).

Hence, for both originator biologics and biosimilars, it is important to understand the range of variation in quality attributes that does not affect their safety or efficacy. Furthermore, because any biologic has many different product attributes, it is necessary to know which are relevant to product quality, pharmacokinetics (PK), efficacy and safety.

For a biosimilar to be approved, quality attributes that are important to the function of the molecule are required to be highly similar to those of the originator; minor differences are acceptable only in quality attributes known to be unimportant to function [3,4]. With monoclonal antibodies, a good example of a critical attribute is the degree of fucosylation (the enzymatic addition of fucose sugars to the protein) within the Fc region of the antibody, which can have a significant impact on antibody-dependent cell cytotoxicity (ADCC). Antibodies that have been afucosylated typically show greater ADCC [20]. In a human breast cancer cell line, changes in fucosylation across different batches of originator trastuzumab were associated with corresponding effects on ADCC activity [21]. This may have a meaningful clinical impact. In a mouse model of breast cancer, afucosylation of trastuzumab doubled the median progression-free survival compared with conventional trastuzumab [22]. Hence, fucosylation must be tightly controlled and analyzed in both the originator and biosimilars of trastuzumab.

Overall, for any new biosimilar, comprehensive characterization and demonstration of analytical similarity is the basis for establishment of biosimiliarity [3,23]. All of this testing must be applied in a comparative manner – that is, in parallel for both the biosimilar and the reference, originator medicine – to show comparability [23]. Essential requirements for the approval of biosimilars include: an identical primary amino acid sequence to the originator; matching potency; and higher order structures, post-translational modifications and other potential variants that

are as similar as possible to the originator product (Table 1) [9]. Hence, prescribers should have no doubt about the pharmaceutical quality of an approved biosimilar. This comprehensive analytical dataset effectively justifies a reduced clinical development program for regulatory approval (Figure 1).

Importantly, because analytical properties are always assessed relative to the originator and never relative to another biosimilar, the range of values for any given critical quality attribute will necessarily overlap significantly with that of the originator, but may theoretically overlap little (or even not at all) with another biosimilar. This adds a further rationale for always prescribing a biosimilar according to brand name and minimizing the number of times that patients are switched from one brand to another.

Clinical development of biosimilars

Analytical and nonclinical assessments (e.g., in cell lines and animal models) constitute the bulk of the work required in the development of a biosimilar and are fundamental to regulatory approval (Figure 1). However, for a prescriber, it is the clinical assessment that is perceived to be most critical. The FDA explicitly states that the approval of a biosimilar must be based on the totality of evidence provided, based on a stepwise approach that includes clinical assessment at the end of the process [3]. The EMA also favors a stepwise approach to the development of new biosimilars [4]. Essential elements include PK, pharmacodynamics (PD), efficacy, safety and immunogenicity [3,4]. Overall requirements are similar within the US and EU regulatory systems, but there are important differences in specific stipulations (Table 1).

During their clinical development, new biosimilars are always compared against the originator and not against another biosimilar [3,4]. For any given parameter, it is often possible to calculate a ratio of the final outcome with the two forms of the drug. An example might be the ratio of the response rate with the biosimilar divided by the response rate with the originator. Ideally, this ratio should be as close to 1 as possible. To prove equivalence from a statistical perspective, the ratio – as well as its 95% CI – should remain within predetermined equivalence margins. These are conventionally set at 0.80 and 1.25 [4]. This is an example of symmetric margins, which are equal, in relative terms, on both sides of 1, thereby demonstrating that the biosimilar is both 'noninferior' and 'nonsuperior' to the originator product for the given parameter. 'Superiority' of the biosimilar would inherently imply that it is not, in fact, similar, and this might be associated with dose-related effects such as toxicity [3]. Symmetric margins are often preferred but, in some cases, it may be appropriate to use an asymmetric interval with a larger upper than lower bound – for example, if the dose used is near the plateau of the dose–response curve and hence there is a low probability of dose effects. This typically allows for a smaller sample size than would be required with tighter, symmetric margins [3].

The clinical development program of a biosimilar typically begins with a PK comparison versus the originator product. This must be performed in a sufficiently sensitive and homogeneous study population, which could potentially be either healthy volunteers or patients with a relevant disease [24]. Factors that influence this decision include prior clinical experience with the originator product, and the sensitivity within candidate populations to detect differences and variability in PK. If safety differences relative to the originator biologic are not a major concern, healthy subjects are often preferred because there are fewer outside variables – such as disease status and concomitant medications – that might affect PK [24]. Key parameters that are typically compared include maximum serum concentration and the area under the concentration–time curve. For example, in a PK study, the trastuzumab biosimilar SB3 showed equivalence with originator trastuzumab when administered as a single dose to healthy volunteers (Figure 3) [25]. Ratios of area under the concentration–time curve and maximum serum concentration for the biosimilar and originator were close to 1 and the CIs were within the prespecified equivalence margin of 0.8–1.25.

PD markers should also be assessed whenever feasible, and these are particularly valuable if they are sensitive enough to detect small differences between originator and biosimilar [4]. Ideally, PD markers should be accepted surrogates for patient outcome; if not, they should at least have a clear dose– or concentration–response relationship [4]. An example of a good PD marker is B-cell count in the assessment of the anti-CD20 monoclonal antibody rituximab [26]. With trastuzumab biosimilars, human PD data are typically not included within the regulatory approval packages, owing to a lack of specific, surrogate markers [27,28].

The final step in demonstrating bioequivalence with a biosimilar drug is to examine its efficacy and safety in a Phase III trial. When designing such studies, there are at least three key considerations:

- Statistical design;

- Study population; and
- Study end points.

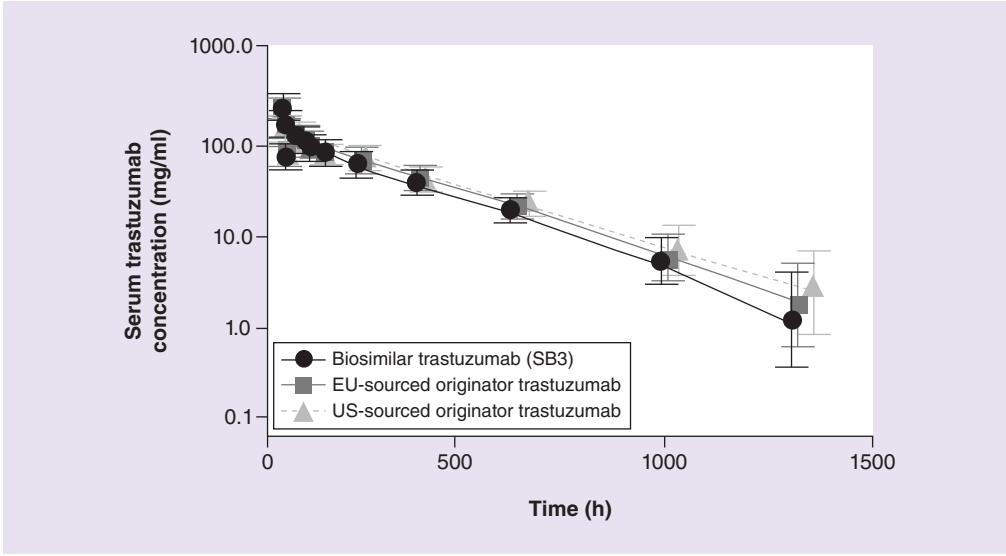

Figure 3. Mean serum concentration–time profiles of biosimilar and originator trastuzumab.
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With regard to statistical design, this is typically based around equivalence testing. As with PK assessment, equivalence is more commonly assessed based on relative rather than absolute differences between the originator and biosimilar, with the effect ratio ideally being as close to 1 as possible. Differences in absolute measures are sometimes used but can be subject to greater heterogeneity in effect estimates [29]. Comparability margins should be prespecified and justifiable based on both statistical and clinical considerations from the data of the originator product [4]. Ideally, these margins are derived from estimates of the treatment-effect size of the originator product with regard to the chosen end point, evaluated using historical data that isolate the specific contribution of the originator product alone (e.g., comparing it to placebo) [30,31].

With respect to the study population, this is particularly important with biosimilars because proof of efficacy and safety in one indication might, under particular conditions, be extrapolated across (all) other indications of the originator product. Hence, only one Phase III trial of the biosimilar versus the originator may be required. Guidance from the EMA and the FDA states that the most homogeneous and sensitive patient population should be selected to maximize the likelihood that any product-related differences will be detected [3,4]. Using trastuzumab in breast cancer as an example, a neoadjuvant study in a homogeneous trial population with early, operable disease might be a better setting than metastatic disease, where there may be multiple confounding factors – such as number and type of previous therapies, performance status and disease burden and distribution [32]. Pathologic complete response (pCR) in early breast cancer has been validated as an appropriate clinical end point for biosimilar development, which can be assessed reproducibly in every patient and is a surrogate for longer term progression-free and overall survivals. In general, pCR in breast is favored over pCR in breast and axilla in this clinical setting because of the uncertainty regarding axillary disease burden at baseline. Early breast cancer may also be the best setting for immunogenicity assessments, owing to increased sensitivity during the treatment-free phase following adjuvant treatment [33].

Applying these principles to the development of a biosimilar trastuzumab, SB3 was assessed in a Phase III study of 875 patients with early HER2+ breast cancer randomized to neoadjuvant treatment with originator trastuzumab or the biosimilar, SB3 [10]. The primary end point was breast pCR, with equivalence established if the 95% CI of the SB3/originator pCR ratio was within the predefined range of 0.785–1.546, or the 95% CI of the difference was within ±13%. In this study, an asymmetric equivalence margin was allowed because the dose level used was near the plateau of the dose–response curve, making dose-related toxicity unlikely. The adjusted ratio of breast pCR was 1.259 (95% CI: 1.085–1.460), which remained within the equivalence margins. The adjusted absolute

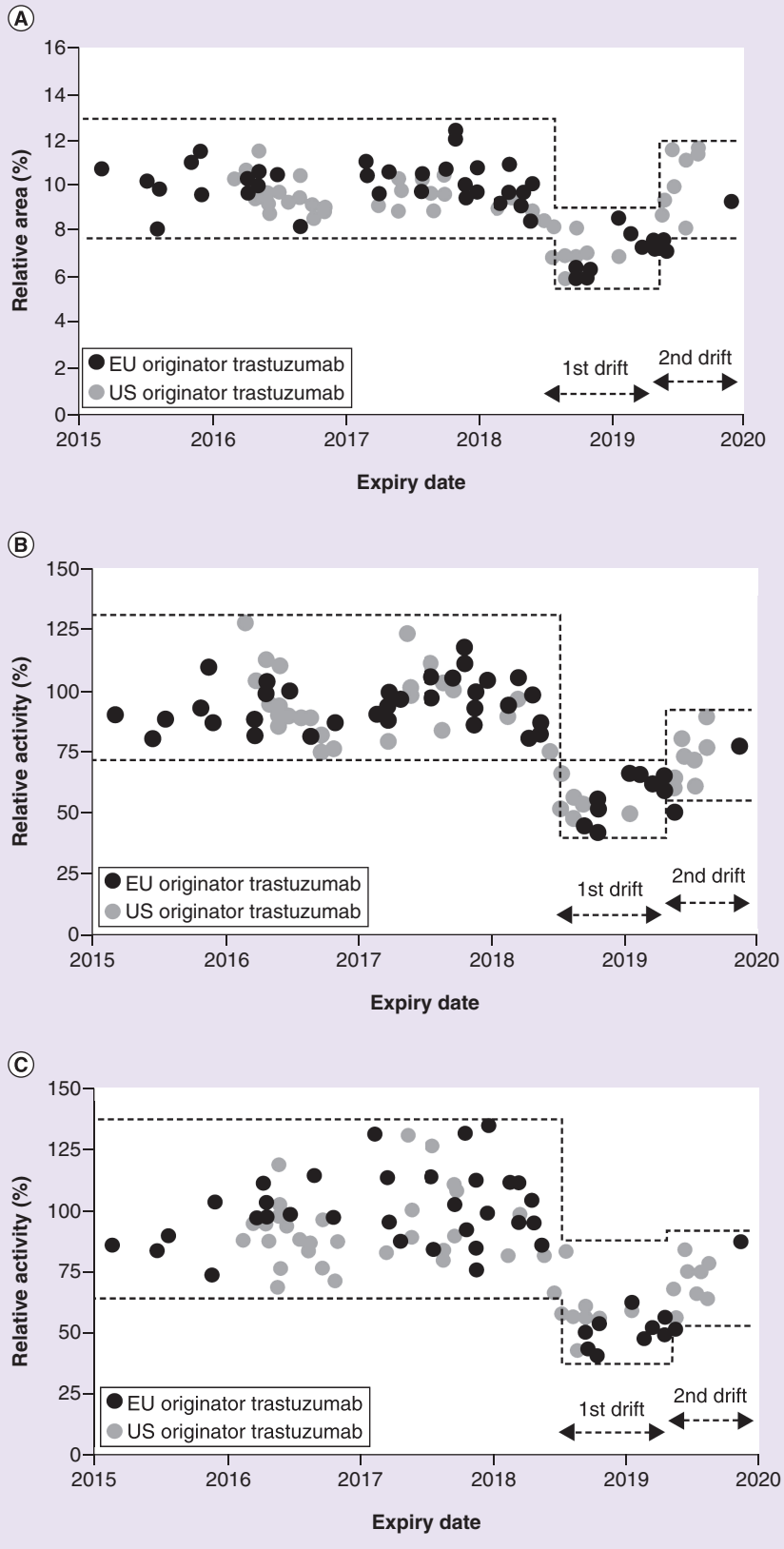

Figure 4. Drift in antibody-dependent cell cytotoxicity-related quality attributes with originator trastuzumab batches. Range of glycosylation (% afucose + % high mannose) **(A)**, relative FcγRIIIa binding activity **(B)** and relative antibody-dependent cell cytotoxicity activity **(C)**.

difference was 10.70% (95% CI: 4.13–17.26%), with the upper limit being outside the equivalence margin [10], suggesting superiority of SB3. However, this was attributed at least partly to the observation that some batches of the originator trastuzumab used in the study had reduced ADCC activity (Figure 4) [27]. Hence, in assessing SB3, the EMA considered that the true difference was likely to fall within the equivalence margins, and they concluded that SB3, ". . . is not considered superior to Herceptin (originator trastuzumab) in terms of efficacy and equivalence in efficacy is considered sufficiently established" [27].

Importantly, secondary efficacy end points relating to survival (both overall and event free) were comparable between groups [11]. Key safety data, including treatment-emergent adverse events (TEAEs) and immunogenicity, were also comparable, further supporting the biosimilarity of SB3 and originator trastuzumab [10,11].

Hence, in November 2017, SB3 became the first trastuzumab biosimilar approved for use by the EMA. It was also approved in the Republic of Korea during the same month.

Other trastuzumab biosimilars have subsequently been approved in the EU, the USA and elsewhere in the world. In December 2017, trastuzumab-dkst (Ogivri™) became the first biosimilar to be approved by the FDA, primarily on the basis of the Phase III HERITAGE trial, which compared trastuzumab-dkst to originator trastuzumab in 500 patients with previously untreated HER2+ metastatic breast cancer [34]. All participants also received a taxane. The primary outcome was overall response rate (ORR) at 24 weeks, which was 69.6% with trastuzumab-dkst and 64.0% with the originator trastuzumab. The ORR ratio (1.09) and 90% CI (0.974–1.211) were within the predefined equivalence boundaries of 0.81–1.24. The ORR difference (5.53; 95% CI: -3.08 to 14.04) was also within the predefined boundaries (-15 to 15, including the 95% CI). There were no significant differences between groups in secondary efficacy end points relating to overall or progression-free survival and time to progression. In addition, there were no notable differences in the type, incidence and severity of treatment-emergent adverse events, immunogenicity or PK profile [34].

Conclusion

Biosimilars will play an increasingly important role in the treatment of cancer, decreasing the associated costs and potentially improving access. The complexity of the manufacturing process means that strict quality control remains essential – as with any drug and particularly any biologic. Regulatory bodies have put in place robust mechanisms for the approval of these products, based on comprehensive and rigorous analytical comparisons with the originator, allied to an abridged nonclinical and clinical development program.

Future perspective

Monoclonal antibodies form the backbone of therapy for an increasing number of both solid tumor and hematologic malignancies. We have become used to branded innovator products, and their development and testing in individual treatment indications. However, the acquisition costs of these drugs are becoming increasingly challenging, even in the most affluent regions of the world. Biosimilars provide meaningful cost savings compared with originator products, although these can never meet the percentage cost reductions from generic small molecules. However, they make a vital contribution to cost-effective healthcare and to improving access to the most effective medicines in less wealthy parts of the world. Clinicians are understandably cautious when making substitutions for their familiar branded products, but the rigorous regulatory pathway for biosimilars should reassure them that biosimilars are appropriate across the range of approved indications. We all need to become confident when prescribing biosimilars, but the overwhelming likelihood is that their use will become an accepted part of routine care in the near future.

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Executive summary

Background

- A biosimilar is a biologic product that is highly similar to, and has no clinically meaningful differences from, the approved reference originator product.
- Biosimilars provide potential cost savings that may improve access to novel biologic therapies.

Overview of the development pathway for biosimilars

- The majority of the work in bringing biosimilars to market involves development of the production and purification processes, and an extensive physicochemical and *in vitro* functional comparison with the originator product.
- Nonclinical and clinical evaluation may be less extensive because the data proving efficacy and safety in one indication can sometimes be extrapolated across all other indications of the originator product.
- For example, the first trastuzumab biosimilar was approved based on comparisons with the originator in the neoadjuvant treatment of breast cancer, which allowed approval across all trastuzumab indications.

Science behind product manufacturing

- Biosimilars require the same rigorous oversight of the manufacturing process as originator biologics.
- Comprehensive characterization and demonstration of analytical similarity is the basis for establishing biosimilarity. Testing must be applied in a comparative manner (i.e., in parallel for both the biosimilar and originator) to show comparability.
- Essential requirements for the approval of biosimilars include: an identical primary amino acid sequence to the originator; matching potency; and higher order structures, post-translational modifications and other potential variants that are as similar as possible to the originator product.
- Inevitably, there will be microheterogeneity of the protein population, both within each product and also between each product (originator and biosimilar).
- For both originator biologics and biosimilars, it is important to understand the range of variations in quality attributes that do not affect safety or efficacy. Attributes that are important to molecular function must be highly similar to those of the originator; minor differences are only acceptable in attributes that are unimportant to function.

Clinical development of biosimilars

- This typically begins with a pharmacokinetic comparison versus the originator product, either in healthy volunteers or patients with a relevant disease.
- Equivalent efficacy and safety to the originator biologic must be established in a Phase III trial with an appropriate statistical design, study population and study end points.

Conclusion

- Regulatory bodies have put robust mechanisms in place for the approval of biosimilar drugs, based on comprehensive and rigorous analytical comparisons with the originator, allied to an abridged nonclinical and clinical development program.

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