

Regulatory complexities and challenges of biosimilars

This continuing professional development (CPD) supplement focuses on the regulatory complexities and challenges associated with biosimilar products and their development. Although biosimilar products have been registered and approved for use in the EU for more than a decade, there is increasing speculation and excitement on the potential for biosimilars with increasingly complex structures, eg, multi-subunit, extensively post-translationally modified, and lipid-containing products.

KEYWORDS: Biopharmaceutical; Biosimilars; Switching/interchangeability; Similarity; Data requirements; Clinical development.

The European Medicines Agency (EMA) describes biosimilar medicines as “a biological medicine that is similar to another biological medicine that has already been authorised for use”.¹ Similarity is evaluated and established against other, EU-registered and established biopharmaceutical products. These are referred to as reference medicinal products. The reference product must have been authorised for at least ten years before a biosimilar being made available, enabling a robust and extensive clinical and adverse events profile to be established.

By their very nature, biopharmaceuticals are intrinsically variable. Therefore, biosimilars cannot be referred to as generics, a term applied to pharmaceutical products denoting “sameness” between products. There are, nevertheless, a number of other terms that are more widely accepted descriptors of biosimilars, including: follow-on biologic (FOB), follow-on protein (FOP), and subsequent entry biologic (SEB) that are favoured by other regulatory bodies.

Given the complexities of these biological molecules, it is important to highlight and address these

complexities and their impact on manufacturers and patient groups. In particular, this article considers some of the anticipated limitations when moving beyond the currently registered products into more complex molecules. Although no complex biosimilars are yet approved, they are in development and will need to be understood in the context of what the current frameworks require.

Background and history

The complex nature and batch-to-batch variability of biological quality attributes within acceptable ranges is very well known. Manufacturers and regulators appreciate and accept that the manufacturing process, controls, limits and specifications will vary due to harnessing living cells to manufacture a target molecules, the associated intrinsic variability of the manufacturing process and have expectations set accordingly. Given their unique properties for treatment of serious diseases, many biological products have attracted a premium price in terms of reimbursement for patient care costs, consequently making them attractive to be copied (following patent expiry). Their high value has also made these products less available to a wider population

Biosimilars cannot be referred to as generics, a term applied to pharmaceutical products denoting “sameness” between products

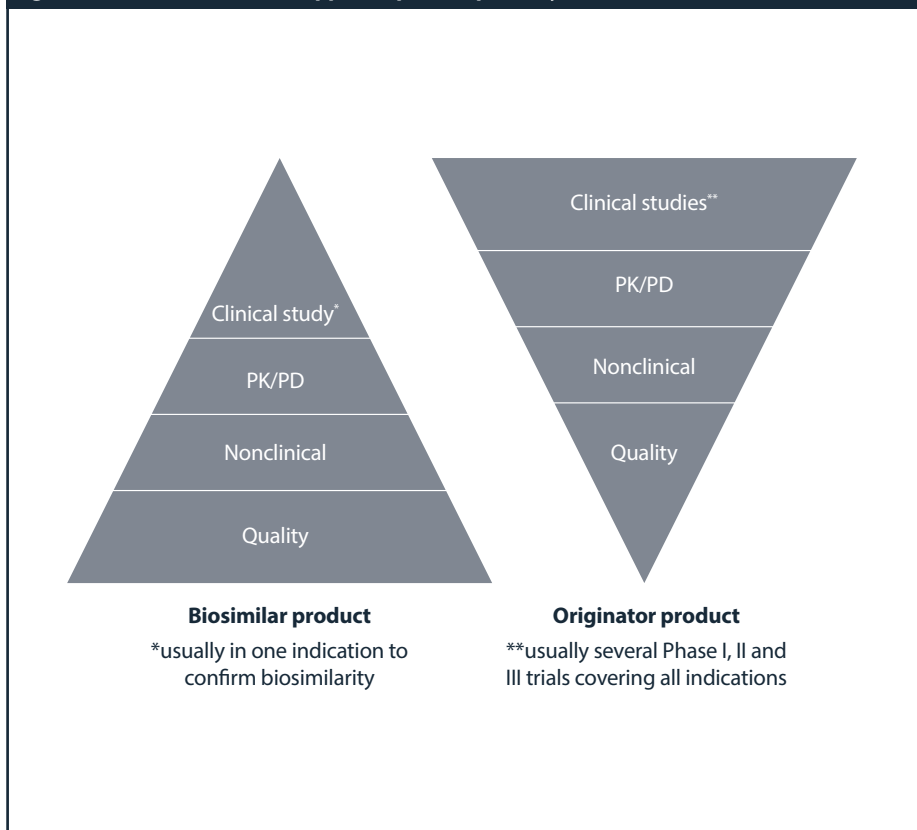
of patients and furthermore is another driver of the biosimilars market. Consequently, there are a disproportionately high number of manufacturers in south Asia and the Far East who are singularly driven to produce biosimilars. During the late 1980s and 1990s, a range of biological products based around growth hormones and monoclonal antibodies (mAbs) were developed and successfully registered. Given their novel, proprietary and often complex manufacturing processes and applications, the intellectual property (IP) around many of these products was protected by various patents.

However, due to this relatively new pharmaceutical landscape, the biosimilars industry is confronted with a constantly evolving regulatory environment. The first biosimilars guidelines were issued by the EMA in 2005;² additional EMA guidance has since been released and some of the initial guidelines have even been revised.¹ Thereafter, other highly regulated countries followed (Japan in 2009, Canada in 2010) and in 2012, the US FDA released its first draft biosimilar guidelines.³⁻⁵ Thus, in this constantly evolving regulatory environment, the biosimilars industry needs to ensure that its ongoing and planned developments comply with the criteria in the regulations and guidelines.

KEY LEARNING POINTS

- Biosimilar medicines are defined as a biological medicine that is similar to another biological medicine that has already been authorised for use.
- The manufacturing process, controls, limits and specifications will vary due to the intrinsic variability of the manufacturing process but controlled within defined ranges.
- The terms interchangeability, substitution, and switching generally refer to the practice of using the originator biologic and changing to an approved biosimilar, or changing from one approved biosimilar to another approved biosimilar (albeit theoretically at this stage).
- Extrapolation is the term used to describe the use of a biosimilar for an indication approved for the reference product, but not for the biosimilar. Some bridging clinical data will always be required.
- The biosimilar approval and review process is underpinned by an evaluation against the innovator/reference product using a totality-of-evidence approach.
- Qualitative or quantitative variability may at best result in loss of biological function or, in worse cases, severe (potentially unknown) adverse events.

Figure 1: The submission and approval process pathway



Changes in the regulatory landscape included the development of guidance for “well-characterised” (later renamed “well-specified”) biologics in the US, “comparability protocols, and “equivalence protocols” in the EU. Although these changes in the regulatory requirements were intended primarily to support and facilitate changes to biologics manufacturing processes, they triggered the evolution of the concept of the biochemical bridge, whereby a comprehensive analytical (biochemical and biophysical) comparative testing programme for structural and functional characteristics could form the basis of the justification for demonstration of similarity.

The biochemical bridge easily lent itself to the analysis of other “similar” biologics and to start to define differences and correlate to physiological and clinical effects. Clinical differences should be avoided, however. Some differences are expected, and hence dose alignment and management in reference to biosimilar switching might be required. More recently, manufacturers have been encouraged and guided to assess the “totality of evidence” when making evaluations on the similarity of biological products. The FDA has published all available data for biosimilars assessment since around 2012. The concept of “totality of evidence” seeks to encompass and assess a wide range of parameters and attributes that may not have traditionally been included as part of product release. For example, the methods of manufacture can play a significant role in the quality of a biological product, thus the evaluation of manufacturing data and controls can play a part in product assessment. These concepts have formed a pivotal part of the biosimilars registration framework, and continue to underpin the development and registration of these products.

“First wave” biosimilars

Biological products are generally more complex than pharmaceutical preparations that result from chemical synthesis. The complexity of biological products compared with small molecules results from a number of factors unique to biological molecules, including:

- Molecular mass (typically 10kDa or more)
- Composition (protein, carbohydrate, lipid, nucleic acid, cell debris)
- Higher order structure (rendering biological function)
- Complex manufacturing operations/ processes
- Formulation, including the use of adjuvants

Given these and many other limitations (related to IP, manufacturing complexity issues, etc), the first wave of approved biosimilars were relatively simple biological molecules with limited (often just glycosylation) post translational modifications. They were still, nevertheless, vastly more complex than small molecule pharmaceuticals. These limitations should also not be considered individually because, often, they are interwoven or interlinked, particularly for more complex biosimilars such as Remsima (infliximab, a chimeric entity). As such, progress with the development and registration of biosimilars is generally hampered by a number of aspects, including:

- Complexity regarding the innovator molecules:
 - IP
 - Demonstrating equivalence with intrinsically variable innovator, and showing batch-to-batch variability due to its natural structure and biological function
- Limitations placed on biosimilar interchangeability, substitution, switching,

and extrapolation of indication

- Complex multi-subunit or multimodal biologics (eg, antibody-drug conjugates [ADCs], vaccines)
- Data requirements for registration (analytical and biochemical, nonclinical, clinical)
- Other “unknown” considerations, typically where the issue has not arisen or has not been identified yet for this class of molecules (keep an open mind when looking at the apparent totality of data).

Data requirements

Based on these special properties and criteria, a generic development and approval (ie, demonstration of bioequivalence with the reference product by bioavailability studies) is therefore not sufficient. Instead, full quality development complemented by a comprehensive comparison of the physicochemical and biological parameters with the reference product is required. At the physicochemical level and due to the comparative testing and characterisation, the biosimilar developer is required to provide sufficient quality data to demonstrate parity with the originator. The extent and nature of the nonclinical and clinical data package should be tailored to detect potential differences between the biosimilar and the reference product. Hence, demonstration of patient benefit per se is not the only scope, but to establish similarity to the reference product and consequently, to allow partial reliance on efficacy and safety data collected for the reference product. Figure 1 shows a high-level comparison of the requirements for a biosimilar versus originator/reference product development. Understanding these regulatory requirements and trends in biosimilar development is crucial for a successful registration.

Additionally, the data required during the review and approval of biosimilar products will vary considerably on the type of biosimilar product. Although these data will be assessed holistically during the review process, it is helpful to ensure they are determined and reported in an easy-to-understand pieces. The data may therefore be classified in a number of ways, regardless of the data is reported in common technical document (CTD) module 3.2.R, which aids comprehension of the data. This may be done by detailing and analysing the constituent components of the molecule:

- Protein
- Lipid
- Carbohydrate
- Nucleic acid/others (cell debris).

By reporting the structure of the molecule:

- Primary
- Secondary
- Tertiary
- Quaternary.

By type of testing, including functional stepwise assessments:

- Analytical/biochemical/biophysical
- Biological and immunochemical
- Nonclinical
- Clinical.

Switching

The terms interchangeability, substitution, and switching generally refer to the practice of using the originator biologic and changing to an approved biosimilar, or changing from one approved biosimilar to another approved biosimilar. Extrapolation is the term used to describe the use of a biosimilar for an indication approved for the reference product, but not for the biosimilar. There is no provision for automatic extrapolation and prior approval and sound scientific justification is required before a biosimilar may be extrapolated to other indications approved for the reference product.

Following the approval of a small molecule or pharmaceutical product, being able to switch (or substitute) between pharmaceutical drug products is a well-established and extensively used phenomenon and is typically implemented at the pharmacy level. In addition to restrictions against biosimilar extrapolation, this type of switching and interchangeability requires approval at the national level. There are a number of considerations that must be taken into account as part of interchangeability, switching, and substitution.

The biosimilar approval and review process is underpinned by an evaluation against the innovator/reference product using a totality-of-evidence approach. Following its approval, the biosimilar receives its own marketing authorisation (MA) number and becomes a product in its own right, with no requirement to continue to demonstrate biosimilarity post approval. Although this is perfectly sensible, the longer term acceptability of such an approach becomes more challenging in the post-approval period. Following the approval of a biosimilar (which may be viewed as a “similarity snapshot” in time), both the biosimilar and the reference product can embark on different post-approval pathways, which may result in significant differences in their composition, structure, biological effects and, possibly in the future as manufacturers wish to capitalise on returns, expanded clinical use (eg, Botox). This potential divergence could place considerable strain on the extrapolation of the clinical and chemistry, manufacturing and controls (CMC) data reviewed at the time of biosimilar approval.

There are a wide range of analytical procedures that may be applied to biosimilars and these are well documented by others. State of the art analytical methods should indeed be used for testing and characterisation. The specifications for biological molecules typically encompass two types of variability: intrinsic variability resulting from the natural variability of a class of products, and analytical test variability resulting from the assays used to test the product. This intrinsic variability can result in specifications for the target molecule (reference product and biosimilar) that may be viewed as being “wide”.

This supplement offers regulatory professionals an accessible way to use Regulatory Rapporteur as a starting point for recording their LLL hours and help gain or maintain MTOPRA status.

Supplements will be archived online and will build up to become a repository of CPD exercises – pitched at different levels of regulatory experience – that members can access free as and when they require them.

Being able to switch (or substitute) between pharmaceutical drug products is a well-established and extensively used phenomenon and is typically implemented at the pharmacy level

In actual fact, it is the intrinsic variability that makes biosimilarity challenging. In addition to analytical and extensive characterisation data for the bulk and finished product, biosimilar analysis profiling should also include in-process data (and specifications) and stability data (comparative, during storage, in-use, and accelerated) because this totality of evidence will be used to determine biosimilarity. For global submissions, reference product from different jurisdictions should be sourced and analysed. If the variability is wide, this may be because of low number of lots tested. However, manufacturers of biologics may use different assays for activities rather than interchangeable methods, which adds to the complexity.

Conclusion

The approval of the current crop of biosimilar products is, without doubt, a great achievement that has enabled greater patient access to medicines with high medical need and remains a major milestone in pharmaceutical development. With these achievements come greater challenges, not only maintaining diligence and patient safety with the currently approved products, but to develop biosimilar registration packages for biological products of increasing complexity. The difficulties in surmounting the next challenges are significant, and include detailed understanding of the structure and function relationships of biological molecules that are comprised of more than one protein molecule, complexed branched sugar chains, lipid bilayer components, and the possibility of nucleic acid and cell debris (sometimes deemed to be an impurity). Qualitative or quantitative variability in any of these components may, at best, result in loss of biological function or, in worse cases, severe (potentially unknown) adverse events.

References

1. European Medicines Agency. *Multidisciplinary: Biosimilar*. Available at: <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar> (accessed 1 January 2019).
2. European Medicines Agency. *CHMP/437/04 Rev 1. Guideline on similar biological medicinal products*. October 2014. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf (accessed 8 January 2019).
3. PMDA. *PFSB/ELD Notification No_0304007. Guideline*

for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009. Available at: <https://www.pmda.go.jp/files/000153851.pdf> (accessed 8 January 2019).

4. Health Canada. *Fact Sheet: Biosimilars*. Available at: <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologicals-radiopharmaceuticals-generic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html> (accessed 1 January 2019).

5. FDA. *Biosimilars – Guidances*. Available at: www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm290967.htm (accessed 1 January 2019).

Acknowledgements

The content of this CPD article is drawn from:

- Ash Ramzan, Principal Consultant, Woodley BioReg Ltd, UK. ‘The future of biosimilars – monoclonal antibodies and beyond’ *Regulatory Rapporteur* 2015;12(9):5–9.
- Manfred Kurz, Global Regulatory Affairs, Senior Manager, Eisai Limited, Hatfield, UK. ‘Lighting the path through biosimilar clinical development’ *Regulatory Rapporteur* 2017;14(1):4–7.
- Claudia Sailer, Team Leader Regulatory – Oncology II, Global Regulatory Affairs Biopharmaceuticals, Sandoz GmbH. ‘Investigating biosimilar development and registration: A –Figrastim case study – Part 1’ *Regulatory Rapporteur* 2016;13(6):23–27.
- Claudia Sailer, Team Leader Regulatory – Oncology II, Global Regulatory Affairs Biopharmaceuticals, Sandoz GmbH. ‘Investigating biosimilar development and registration: A Filgrastim case study – Part 2’ *Regulatory Rapporteur* 2016;13(7/8):19–23.

We thank the authors for their permission to use their content for this CPD supplement.

Quiz: Test your knowledge

Now you have read the supplement, complete the self-assessment exercise at topra.org/CPDSupplements and answering the questions online.

Successful completion and submission of the assessment form means that you can claim your lifelong learning (LLL) hour for the task, which members can add to their CPD recording tool.

Case study:

Getting biosimilars onto the market

Lowering healthcare expenditures is a major objective in many countries, and one cost-saving strategy is the introduction of biosimilars to replace expensive innovator biological medicines. This case study focuses on key aspects and prerequisites of comparative biosimilar clinical development, including associated regulatory hurdles along with benefits and obstacles of global development.

Depending on the source of the comparator (EU versus US) and whether they are required for EU or US trial purposes, documentation requirements will differ, eg, summary of product characteristics (SmPC) or a quality assurance (QA) statement (see Table 1).

Challenges with EU trials

Key challenges in the EU relate to inconsistent penetration of standard of care and country-specific treatment regimens, which can impact CTA approvals in certain member states, along with availability of patients. For instance, an innovative new anti-HER2 mAb (pertuzumab) was approved in the EU, targeting a different epitope from that of trastuzumab, and impacting the standard of care in this oncology setting (breast cancer).

According to the EU SmPC: "Perjeta (pertuzumab) is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease".

In view of this, pertuzumab, in combination with trastuzumab and docetaxel, in first-line treatment of patients with advanced cancer provides benefit and is the best available therapy. Enrolment in a biosimilar study with trastuzumab only would interfere with current standard of care. Some member states may be reluctant to authorise a biosimilar clinical trial designed for demonstration of therapeutic equivalence against the single agent trastuzumab.

Furthermore, an innovative fixed-dose subcutaneous formulation was approved allowing subcutaneous delivery of trastuzumab (Herceptin SC 600mg/5ml solution for injection)⁴ containing hyaluronidase. Benefits include less complex handling, no need for dose calculation, faster administration, and convenient cartridge administration systems using single-use injection vial. Again, patients should be made aware

of the possibility of subcutaneous administration of trastuzumab, which may impact recruitment, and differences may exist across EU member states.

Implications and learnings

Although an EU approval might be supportive, it is not sufficient for registration in other highly regulated markets. Most additional requirements are due to the need to establish biosimilarity to the national reference product. However, a clinical programme acceptable in one jurisdiction might not be sufficient in others. Nevertheless, an EU approval is the gateway for many registrations in emerging markets and Australia. Biosimilars developers should have a clear idea of where they want to register their products and what could be a common target product profile and clinical programme. This should take into account the greater regulatory flexibility in EU, Canada and Australia but also the more stringent requirements in US or Japan. Integrating feedback from key regulatory authorities is essential to allow for a global development from the beginning.

Although there are now opportunities to bridge to other reference products scientifically, what is the nature of these studies? Is it really necessary to conduct multiple pharmacokinetic/pharmacodynamic (PK/PD) studies to compare all reference products against each other, or will evaluations on the quality level suffice? On the quality level, the development is likely to remain quite extensive when developing different presentations or strengths; multiple comparability exercises with multiple reference products are needed to meet national regulatory requirements. However, if bridging studies are limited to the quality level, this is still inexpensive compared with conducting clinical studies.

Clinical trials in non-EU countries

Conducting biosimilar clinical trials in non-EU countries offers access to large, ethnically diverse, treatment-naïve patient populations in significantly reduced clinical trial cost environments compared to the EU.⁵⁻⁷ However, moving to non-EU countries may be accompanied with complications: emerging countries may have poorly defined regulations, overlapping authorities, ill-defined administrative processes, long and unpredictable approval times, or frequent reorganisation of legislation. Sometimes Court rulings may affect CTA decisions (eg, in 2013 the Indian court ordered

re-examination of clinical trials approved earlier).⁸ Differences in standard of care and medical practice may exist. Additionally, a lack of locally generated data including EU patients may be viewed detrimentally by the Committee for Medicinal Products for Human Use (CHMP) during marketing authorisation application (MAA) review.

Logistical and clinical trial management is certainly more challenging in a global biological trial and includes concerns relating to transportation, cold chain capacities, specialised equipment and instruments at the clinical sites. Import licences are needed for comparators and co-medication. A limited number of sites and investigators may be familiar with good clinical practice (GCP) and activation times for sites can be long, requiring frequent monitoring visits.

There can also be difficulties with export of human biological samples (blood or biopsies samples) from patients to the central lab for analysis (eg, pathology, PK). Sometimes investigators require certain qualifications depending on the indication studied. Sites may be geographically distributed in a country and designated as government or non-government institutions. Occasionally some countries may request a good manufacturing practice (GMP) compliance certificate from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use/pharmaceutical inspection convention (PIC) authority. The EU system of quality person release of IMP may not be accepted. Also, the sponsor may have to commit to file an MAA on completion of the clinical trial.

CPD Supplement

Editor

Davina Stevenson,
*Deputy Editor of Regulatory
Rapporteur*

Publisher

Jenine Willis,
*Communications and
Publishing Director, TOPRA*

Benedict Lam,
*Acting Managing Editor,
TOPRA*

Table 1: Comparators used in biosimilar clinical trials – EU versus US

	Comparators used in biosimilar clinical trials to meet EU regulatory requirements	Comparators used in biosimilar clinical trials to meet US regulatory requirements
EU-approved reference product (ie, non US-approved comparator)	Reference should be made to the current version of the summary of product characteristics (SmPC). The investigational medicinal product (IMP) must have a marketing authorisation (MA) in an EU member state and it must be used in the same form, for the same indications and with a dosing regimen as defined in the SmPC. Often a certificate of analysis (CoA) is supplied by the wholesaler. The EudraCT number must be obtained and a clinical trial application (CTA) must be submitted to EC and CA.	The US FDA regards EU-sourced material as IMP and an investigational new drug (IND) application is needed for importation into the US. This can be based on information in the public domain, eg, European public assessment reports. “Summary basis of approval” information can be filed as an amendment to the IND for test product. Limited information may be accessible, but this should satisfy FDA expectations. It must be acknowledged that neither the biosimilar developer has access to confidential regulatory files of the innovator company nor is the FDA regulator allowed to cross-refer to registration documentation. An EU-approved comparator can be included in the 1571 IND application form to assure this comparator IND is evaluated under the same IND as a test product.
US-approved reference product	US-approved products must be purchased from the US market, where normally no CoAs are available. In such cases, a quality assurance (QA) statement (“pedigree certificate”) may be acceptable as a proof of origin. This document contains information on drug sales and distribution, such as the lot number and quantity, repackaging and an ownership history from the manufacturer name to the wholesaler that purchased the drug from manufacturer to re-packager. Regardless of the pedigree certificate, the company may for reasons of enhanced quality standards decide to re-test the US material and issue a company CoA.	US comparator must be purchased from the US market. In general, lots used in the clinical study should be specified in the IND application. Reserve samples must be retained as per the applicable FDA conditions. ¹ In addition, if using US-approved reference product according to FDA guidance there is a simplified procedure for bioavailability and bioequivalence studies ² which exempts clinical investigation of a marketed drug from IND requirements if the product is not a new chemical entity; radioactive labelled; cytotoxic; or the administered dose does not exceed the maximum dose as specified in the label.

Case Study References

1. FDA. *New and revised draft Q&As on biosimilar development and the BPCI Act (revision 2): Guidance for industry.* Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm273001.pdf> (accessed 8 January 2019).
2. FDA. *Guidance for clinical investigators, sponsors, and IRBs investigational new drug applications (INDs) — determining whether human research studies can be conducted without an IND.* Available at: www.fda.gov/downloads/drugs/guidances/ucm229175.pdf (accessed 8 January 2019).
3. EMA. *Perjeta.* Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/perjeta> (accessed 8 January 2019).
4. EMC. *Herceptin 600 mg Solution for Injection in Vial.* Available at: www.medicines.org.uk/emc/medicine/28179/SPC/herceptin+600+mg+5+ml+Solution+for+Injection/ (accessed 8 January 2019).
5. Pharm-Olam. *Reconsidering India as a clinical trial location.* Available at: https://cdn2.hubspot.net/hubfs/4238150/PharmOlam_March2018/PDF/pharm-olam_india_clinical_trials_white_paper_1.pdf?t=1533489754586 (accessed 9 January 2019).
6. *Bioprocess technology process.* *Biopharma Processing Journal Winter 2013/2014.*
7. PPD White Paper. *Developing biosimilars in emerging markets: Regulatory and clinical considerations.* March 2013. Available at: www.healthtrustpg.com/biosimilars/pdf/ppd.pdf (accessed 8 January 2019).
8. LiveMint. *SC directs health ministry to re-examine 157 clinical trials.* October 2013. Available at: www.livemint.com/Industry/XQvYs3BcDWU3nZ95ZEaeaL/SC-directs-health-ministry-to-reexamine-157-clinical-trials.html (accessed 8 January 2019).