The future of biosimilars – monoclonal antibodies and beyond

Abstract
Although biosimilar products have been registered and approved for use in the EU for more than a decade, the recent approval of the first biosimilar product in the US has added to the already heightened interest in this class of product. While many of the currently approved molecules fall into one or two therapeutic categories, there is increasing speculation and excitement on the potential for biosimilars with more complex structures.

This article seeks to assess the limitations and concerns surrounding the currently approved biosimilars, and look ahead to the potential added complications and concerns with multi-subunit, extensively post-translationally modified, and lipid-containing products. Recognising that it is too soon to provide strict guidance on how these new products should be developed, specified, and delivered, some general points have been included for consideration.

Introduction
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”. Similarity is evaluated and established against other, already 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 prior to a biosimilar being made available.

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).

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 will consider some of the anticipated limitations when moving beyond the currently registered products into significantly more complex molecules.

Background and history
The complex nature and batch-to-batch variability of biological products is very well known; manufacturers and regulators alike appreciate and accept that the manufacturing process, controls, limits and specifications will vary due to the intrinsic variability of the manufacturing process and have expectations set accordingly. For a number of reasons, not least the cost and complexity of their manufacture, this class of products has been the reserve of specialist pharmaceutical companies (typically referred to as biotech companies). Given their unique properties, 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 of patients and furthermore drives the biosimilars market. Consequently, there are a disproportionately high number of biosimilars manufacturers in south Asia and the Far East.

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. Following the expiry of IP protection, others have sought to manufacture and register these products; this has triggered the refinement of existing, and the development of new, legislation encompassing the need to demonstrate biochemical and biophysical equivalence in addition to a highly similar physiochemical and biological profile.

During the same period, 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. While 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 could be used as part of the justification for demonstration of equivalence or 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. 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 on its expectations for the evaluation of all available data for biosimilars assessment since around 2012. These concepts have formed a pivotal part of the biosimilars registration framework, and continues to underpin the development and registration of these products.
**“First wave” biosimilars**

Biological products are generally more complex than pharmaceutical preparations that result from relatively simple chemical reactions. The complexity of biological products compared with small molecules results from a number of factors unique to biological molecules. These factors include:

- Molecular mass (typically 10 kDa 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.

The complexity of demonstrating equivalence for biosimilars is further compounded by the fact that the reference medicinal product (the innovator’s product) — against which a biosimilar will ultimately be assessed — is also intrinsically variable, showing batch-to-batch variability due to its natural structure and biological function.

Given these and many other limitations (related to IP, manufacturing complexity issues, etc), the first wave of approved biosimilars were relatively simple biological molecules; they were still nevertheless vastly more complex than pharmaceutical preparations. Some examples of early biosimilars include growth hormone and mAbs. Figure 1 summarises some of the early biosimilars that are now considered to be reaching middle age, as well as more recent approvals.

This development of “relatively simple” biosimilar molecules has continued over the past decade and Table 1 summarises selected EU approved biosimilar programmes since 2006. It is clear from this summary that all of the currently developed and marketed biosimilar products are from a handful of product types/therapeutic areas. Although many of these molecules (including mAb approval) resulted from a breakthrough in the approval of “complex biosimilars”, they are all also “relatively small” biological molecules with limited (often just glycosylation) post translational modifications.

**Current limitations facing biosimilar products and manufacturers**

Progress with the development and registration of biosimilars is generally hampered by a number of aspects, including:

- IP surrounding innovator molecules
- Limitations placed on biosimilar interchangeability, substitution, switching, and extrapolation of indication
- Complex multi-subunit or multimodal biologics (e.g., antibody–drug conjugates (ADCs), vaccines)
- Data requirements for registration (analytical/biochemical, nonclinical, clinical)
- Other “unknown” considerations, typically where the issue hasn’t arisen or hasn’t been identified. These issues are expected to be faced at some time in the future and be addressed.

Each of these aspects, along with potential options to overcome them, are discussed further in the following sections. The reader should note however that these limitations should not be considered individually as very often they are interwoven/interlinked.

It should also be noted that there are early signs that more complex biosimilars are on the horizon; Remsima being a good example of a “breakthrough” complex biosimilar registration.

**Intellectual property limitations**

It is the author’s opinion that patents and IP protection, coupled with exclusivity after marketing application approval, are important and essential provisions that facilitate and support new drug/therapy development and should be maintained (and in some instances strengthened) to continue to encourage innovation and development. However, while it is often legitimate to extend patent protection and

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**Figure 1: Summary of the development and approval of biosimilars.**

![Figure 1: Summary of the development and approval of biosimilars.](image-url)
data exclusivity through real advancements in technology and know-how, there are increasing numbers of patent extension attempts that have been engineered as a means of preventing competition and maintaining market share; for example, Amgen’s recent patent extension application for Enbrel. Although this is seen as being justified and commercially essential to encourage innovation, this approach obviously limits the provision for biosimilars – seen as competitors of the originator. These “protectionist” provisions have in some instances resulted in local legislation being passed that allows manufacturers to manufacture and supply local patents with immunity from IP litigation; India has passed such laws locally, granting 12 compulsory licences between 1995 and 2011.

Alternative, more enlightened approaches should be considered that allow the patented technology to be either de-protected before patent expiration, or used under licence. There are already relevant examples where innovators have agreed a licence arrangement with potential manufacturers to enable the use of proprietary methods and know-how. For example, the move away from in vivo testing for potency to in vitro testing has been supported (and encouraged) by the willingness of approved in vitro test IP-holders to licence the technology to their “competitors”. This approach may also be extended to other areas of proprietary information, including cell banks and recombinant clones and manufacturing technologies which could potentially deliver accelerated product development pipelines, ultimately resulting in a greater number of patients receiving treatment with biological/biosimilar products.

**Interchangeability, substitution, switching and extrapolation**

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 evidence.

**Table 1: Summary of selected EU biosimilars programmes since 2006.**

<table>
<thead>
<tr>
<th>International nonproprietary name (INN)</th>
<th>Biosimilar</th>
<th>Company</th>
<th>Reference</th>
<th>CHMP opinion</th>
<th>EU approval</th>
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<td>Celtrion</td>
<td>Remicade</td>
<td>Jun 2013</td>
<td>Sep 2013</td>
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</table>
Focus – Biosimilar medicines

justification is required before a biosimilar may be extrapolated to other indications approved for the reference product.

Following the approval of a small molecule/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. While 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 also clinical use. 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.

Although there may be many (elaborate) ways of controlling this divergence, at the simplest level, consideration should be given to “tethering” the biosimilar to the reference product to ensure there remains a resemblance in terms of composition profile and clinical use/application; this may well be an interim measure while additional data are generated and assessed. Tethering may be achieved by including the national competent authorities (NCAs) in the EU as part of the review/approval of change control requests and/or licence variation applications for the biosimilar. As these NCAs would be able to review the available data and any planned and implemented variations for the reference product, a knowledge and risk-based assessment of the proposed biosimilar product change would be possible. While potentially costly and requiring significant changes to the way change controls and variation applications are reviewed and assessed, this approach would ensure that impact assessment covered not only patient safety and product efficacy, but also ongoing consideration against the reference product. It is too early to say whether this concept of tethering would result in the need for more substantial data submission prior to variation approval, or an elevated risk of rejection. The author is aware that aside from the approved legislation for licence variations, further discussion and consultation is required before this (and other) concepts are trialled to assess their utility to provide ongoing assurance post biosimilar approval.

This level of controls is a very “new and potentially contentious” area for discussion and, if not handled and managed carefully, could result in unforeseen adverse events.

Complex multi-subunit biologics

Table 1 summarises some of the current biosimilar products, and as already discussed, while these are large multi-component molecules, they still represent the less complex forms of biological products spectrum.

There have been some successful developments of biosimilar products, for example the “biosimilar” form of Allergan’s Botox has been developed in South Korea demonstrating that large, complex proteins that are not mAbs may also be developed and commercialised as “biosimilars”. What is notable is that the South Korean version of botulinum toxin has been manufactured following the isolation of the original Hall Strain, thus circumventing the technical, commercial and IP challenges faced by many potential biosimilars.

The next generation (perhaps even the third or fourth wave) of biosimilars will be more complex, and potentially multi-subunit molecules; vaccines may be considered under a separate class of more complex biological molecules. Given the complex nature of these types of biological molecules, the burden of biochemical, biophysical, and analytical similarity becomes increasingly pivotal. Further compounding the technical complexities is the fact that vaccines are administered to otherwise healthy individuals, so the regulatory and safety margins for such molecules may be a factor that limits their approval as opposed to the technical/analytical abilities. At the present time, the only assured way to demonstrate the safety margins for these types of products is clinical evaluation, which is costly and lengthens the development time.

Data requirements

The data required during the review and approval of biosimilar products will vary considerably on the type of biosimilar product. The EMA and the US FDA have published detailed guidance on CMC requirements for biosimilars; these will not be described here. As discussed earlier, some nonclinical and clinical data will always be required to demonstrate biosimilarity. This article is directed to CMC requirements; clinical requirements will not be discussed further here.

The analytical/biochemical data is intended to form the major part of the package to demonstrate the similarity of a biosimilar product to the reference product. While these data will be assessed holistically during the review process, it is nevertheless helpful to ensure they are determined and reported in easy-to-understand pieces; the data may therefore be classified in a number of ways.

This may be 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 assessments:

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

There is a wide range of analytical procedures that may be applied to biosimilars and these are well documented by others. 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”; in actual fact, it is
the intrinsic variability that makes biosimilarity challenging.

In addition to analytical and 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) as this totality of evidence will be used to determine biosimilarity.

Other factors
Our understanding of the manufacture, testing, control, and administration of biosimilars is limited by what is already known about these molecules. As we are not aware of what we don’t know about these molecules, we cannot determine whether this unknown information will have a bearing on the long terms use of these products. Clearly this can only be determined with the passing of time and development/implementation of new methods of analysis and interpretation. This burden will lie on both industry and regulators to determine and manage to ensure patient safety and product efficacy.

Conclusions
The approval of the current crop of biosimilar products is without doubt a significant achievement that has enabled greater patient access to medicine. Approval of biosimilar products in the EU and, more recently, in the US, will remain a 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, complex branched sugar chains, lipid bilayer components, and the possibility of nucleic acid and cell debris. 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.

This article has sought to address some of the major areas for consideration while developing the biosimilar registration pathway for the next generation of biosimilars. With our current understanding of biological products, and the state-of-the-art analytics available to us, it is possible to start to plot a path to continue to deliver on the early success of biosimilars. It goes without saying however, that caution should be exercised throughout to ensure the correct balance between biosimilar development and patient safety.

References
1. EMA. European Medicines Agency Q&A: Similar biological products – Biosimilar medicine.
3. FDA. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products, CBER, April 1996.
4. EMA. Adapted from European Medicines Agency – European public assessment reports for authorised medicines.