Chemically synthesized proteins referencing biological medicinal products

A EuropaBio white paper

Calling for:
- Equal assessment transparency
- Equal measures for traceability and adverse event reporting
- A level playing field for market access

Executive summary

The current situation

Some proteins can be produced either by using a biological manufacturing process or through chemical synthesis.
After loss of exclusivity follow-on products could use one of the two manufacturing principles and, in EU, both chemically synthesized and biologically produced follow-ons are allowed to reference a biological originator.

EMA classifies a follow-on product as a small molecule or as a biological medicinal product[1] based on its own manufacturing process, rather than that of its reference product. This classification determines the available legal basis to be used for registration. Thus, today follow-ons produced by different methods will be classified differently, as biosimilars, hybrids or generics, even though they all reference the same biological original, and all are present on the entire, or parts of the EU market, simultaneously.

The problem

Follow-on products that have been classified differently have differing requirements for documentation, prescribing, dispensing and adverse event reporting despite referencing the same product and despite being present on the EU market simultaneously.

To address this, we suggest that all follow-on products to biological medicinal products be treated in a consistent manner following biosimilar principles for the review and registration in EU.

EuropaBio call for action

EuropaBio would welcome a dialogue with the European stakeholders on the best way of ensuring equal and transparent measures for assessment, traceability, adverse event reporting, prescribing and dispensing for all follow-ons of a biologic originator.

EuropaBio would also welcome a guideline for chemically synthesized proteins.

[1] A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Background

Biosimilars and generics, key differences

Table 1 holds a summary of the generally accepted key differences between biosimilars and generics.

Table 1: Summary of Key Differences Between Biosimilars and Generic Chemical Drugs[2]

Area	Biosimilars	Generic Chemical drugs
Chemical structure	The amino acid sequence is the same, but slight differences may occur in impurity profiles or post-translational modifications as long as there is no clinically meaningful difference to the reference product	The active drug is chemically identical to the reference product
Analytical characterization	Current techniques cannot predict if any differences detected are potentially immunogenic.	Current techniques are available to ensure that the active drug in the generic product is identical to the reference product
Manufacturing complexity	Very complex; produced in living cells and involves several stages of purification, production, and validation of the final product	Relatively simple; uses organic medicinal chemistry reactions
Impact of a change in manufacturing process	As with all biologics including the reference medicine, small changes in process may alter the final structure and function of the protein	Likely to be negligible because the end product is identical

In view of these differences, the biosimilar route was instigated, because biologics cannot be copied in the same manner as small molecules due to the impact of the manufacturing process on the end product. While small molecule generics are considered to be the same as their reference drug, biosimilars are considered versions of the active substance of the original biological medicinal product that they reference.

[2] Lee Ventola C. Biosimilars Part 1: Proposed Regulatory Criteria for FDA Approval. Pharmacy & Therapeutics 2013;38(5):270-274, 277, 287.

EU regulatory pathways for follow-on products

Table 2 Outline of the paths applicable for follow-on molecules.

	Legal basis	File type	Reference allowed	Open to
Full application	Article 8(3)	Full	To literature	Chemical entities and biologics
Generic application	Article 10(1)	Abbreviated	To reference drug file	Chemical entities[3]
Hybrid application	Article 10(3)	Abbreviated	To reference drug file	Chemical entities[4]
Similar biological application	Article 10(4)	Abbreviated	To reference drug file	Biologics only

The generic route, article 10(1), allows for maximum abbreviation. According to minutes from the CMDh Coordination Group for Mutual Recognition and Decentralised Procedures, this route is not precluded for synthetic follow-on versions of biologics.[5]. In contrast, the biosimilar route, article 10(4), is only available for biological medicinal products due to paragraph wording[6]. Article 10(3), hybrid was designed for chemical entities where abbreviation is allowed, but where the data demands of the generic route are insufficient.

The centralised procedure is mandatory for all biologics, including biosimilars, and for new chemical entities in some indications. A chemical entity that references a drug approved by the centralised procedure has automatic access to the centralised procedure, but falls outside the mandatory scope and is therefore not obliged to use it.

The teriparatide example

Teriparatide (marketed as Forsteo® in the EU) was granted marketing authorisation in the EU in 2003. Teriparatide, rhPTH(1-34), produced in *E. coli*, using recombinant DNA technology, is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone. Forsteo is registered in the EU as a biological product. Through correspondence with BfARM and CMDh, it became apparent that the decentralised hybrid application had been accepted and was under review. In October 2015, CMDh confirmed that a generic/hybrid application could be submitted for a synthetically produced follow-on teriparatide product. The product was approved in Germany and several other concerned member states in late 2016 and early 2017.

---

[3] Although the generic route is not explicitly precluded for biologics, the criteria for demonstrating "sameness" are stringent and thus this is not currently a practical route for most biological products.

[4] Although the hybrid route is not explicitly precluded for biologics, in practice a biosimilar not fulfilling generic criteria would follow the biosimilar route instead.

[5] "Some MSs [Member States] preferred to get these applications under Art. 10(3), but it was agreed that Art. 10(1) applications also have to be accepted and should not be invalidated." CMDh, Coordination Group for Mutual Recognition and Decentralised Procedures – Human, Minutes from the meeting on 22-24 June 2015, *available at* http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Agendas_and_Minutes/Minutes/2015_06_CMDh_Minutes.pdf.

[6] "*Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products,…*"

Meanwhile, other manufacturers had applied through the centralised biosimilar pathway for marketing authorisation for biosimilar versions of teriparatide. The table below represents the differences between the generic and biosimilar application assessment reports.

Table 3 Assessment reports for teriparatide follow-ons in EU

Assessment report	**Terrosa/Movymia** (biosimilar, centralised procedure)	**Teriparatide-Ratiopharm/Teva** (hybrid, decentralised procedure)
Number of pages	47	9/16*
Hybrid criteria	Not applicable	Not addressed
Clinical program	BE in 54 HV, not all parameters included unity (slightly lower)	BE in 72 HV, not all parameters included unity (slightly higher)
Immunogenicity	Not done—raised as an issue solved by offering data from 1 year comparative efficacy and safety study post-approval	Not done—not considered an issue
Risk management	Missing info, immunogenicity	Missing info, none

* Revised version published later.

4 Problem statements

Similarity vs sameness

Ensuring patient safety should be a main consideration when devising the requirements of the abbreviated routes. EMA allows both chemically synthesized and biologically produced follow-ons to reference a biological originator. A synthetically derived protein referencing an original biological medicinal product does not share the same manufacturing platform with the reference product, yet in the present system it can be treated as a generic.

Because a generic relies on the proven safety and efficacy of the reference medicinal product, clinical study data on safety and efficacy are not required. However, reliance on the findings of safety and efficacy for a reference medicinal product are predicated on the applicant being able to demonstrate that the generic product is bioequivalent and has the same active ingredient.

The difficulties in showing sameness for a biological medicinal product led to development of the biosimilar route. Article 10(4) notes that difficulties may be due in particular to differences relating to raw materials or in manufacturing processes. A synthetic follow-on of a biological medicinal product will have source and manufacturing differences. New impurities will originate from differences in the raw materials and from the manufacturing process.

For example, if a synthetically derived follow-on is manufactured through solid phase synthesis, with each amino acid synthesis step, there is the potential for

product related impurities, including deletion contaminants, addition contaminants, racemic mixtures, and other impurities.[7]
Since a chemically synthesized protein that uses a biological medicinal product as its reference product is not the same active substance, they should not be considered generics, but rather similar.
Hence, comparability should be established as for a biosimilar, regardless of the legal pathway.

The main concern regarding new impurities in proteins and polypeptides is whether they could be immunogenic. The impurity profile of the reference drug has been clinically qualified, but a generic application does not require enough clinical exposure to ensure the clinical qualification of new impurities present in the follow-on medicinal product.
Impurities in proteins and polypeptides can lead to immunogenicity related reactions even when present in very low levels. No generalised safety threshold has been defined under which the presence of a new impurity can be ignored.

For follow-ons where comparative analyses of impurities reveal the presence of even small amounts of different, unqualified impurities than those present in the reference medicinal product, additional analyses, as well as controlled clinical qualification, should be required to assess whether the observed impurities could result in immunogenicity reactions, loss of efficacy, safety issues or other adverse patient health consequences.

Consistency of review

Patient safety depends on assessment quality. While the approval standard in EU is the same regardless of procedure, the teriparatide case shows that the level of transparency is not equivalent between centralized and decentralized procedure. Such imbalances may undermine the faith in the level of scrutiny. In the teriparatide case it is e.g. not possible to determine from public records the factual causes for the different assessment of immunogenicity risk between the biosimilar and the hybrid application.

The value of a level playing field for market access

Pharmaceutical policies for the off-patent market for small molecule generics traditionally included a variety of measures related to pharmacy-level substitution, pricing, reimbursement, market entry and expenditure controls but also measures targeting distributors, physicians and patients. These policies have in common to assume that products are interchangeable. It was shown in an EBE survey performed in 2011 that most of EU countries apply a policy of generic price

[7] See, e.g., Novo Nordisk, Citizen Petition, *available at* https://www.regulations.gov/document?D=FDA-2017-P-6029-0001 (October 2, 2017); Eli Lilly and Company, Citizen Petition, *available at* https://www.regulations.gov/document?D=FDA-2016-P-2515-0001 (August 18, 2016).

linkage.[8] 23 countries surveyed use generics substitution; while 24 countries use international non-proprietary name (INN) prescribing.

The second EBE policy survey performed in 2016 on biosimilars showed that a large majority of the countries in Europe have specific policies in place reflecting the different nature of biological medicines compared with small-molecule medicines.[9] In nearly all of the countries and policy areas the treatment decision remains with the physician. Most Member States 26 (81%) surveyed do not allow automatic substitution. Pharmacy-level substitution of biosimilars can be done in Czech Republic, Estonia, Latvia, Poland and Serbia. The majority of countries surveyed, which practice internal reference pricing (IRP), exclude biologicals.

For hybrids, most countries seem to apply a case-by-case approach to pharmacy substitution.

In a situation where there are biosimilars, hybrids and generics referencing the same biological originator, there is a risk that medicinal products are treated differently, based on the regulatory pathway rather than the science motivating the current policies for biologics. This may lead to an uneven playing field for similar products as well as confusion among prescribers, pharmacists and patients.

Pharmacovigilance

6 Rules related to post-marketing pharmacovigilance differ between generics and biosimilars. The black triangle is applied to new active substances and biological medicinal products. Hence, any medicinal product classified as a biosimilar will be marked with the black triangle and be subject to additional monitoring for the first 5 years, or until the PRAC decides to remove it from the list. Generics and hybrids are not in scope for the automatic black triangle/additional monitoring. However, it is possible for PRAC to advise that a product should be added to the list.

In 2012 the European Commission issued a directive (2012/52/EU) intended to facilitate the recognition of prescriptions issued in another Member State. The Directive states that the INN or common name should be used, except for biological medicinal products where the brand name should be used to ensure clear identification.

In line with this, the EU rules on pharmacovigilance requires that suspected adverse reactions relating to biological medicinal products includes the trade name and the batch number of the product, and mandatory follow-up measures are described in GVP module VI to gain this information, where possible. No similar measures are prescribed for chemical entities, even if their approval rested on reference to a biological medicinal product.

In a situation where there are biosimilars, hybrids and generics referencing the same biological originator, it is important that traceability is maintained for all

[8] Vogler S. The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries — an overview. GaBI J 2012;1(2):93-100.
[9] Roediger A, Freischem B, Reiland J-B. What pricing and reimbursement policies to use for off-patent biologicals in Europe? – results from the second EBE biological medicines policy survey. GaBI J 2017;6(2):61-78

follow-on molecules, as well as for the originator, regardless of legal pathway, otherwise there is a risk that all adverse events are assigned to one of the products only with very limited possibility to analyse underlying product related causes.

International aspects

EMA was the first authority to issue comprehensive guidelines on biosimilarity and have been a thought leader in this field ever since. Other authorities are therefore likely to look to EMA for guidance on what the acceptable standards for approvals should be for follow-ons referencing biological medicinal products. As a stringent regulatory authority, EMA possesses the necessary expertise to do qualified case by case assessments. While the expertise on biologics in regulatory agencies not defined as stringent is improving, there is still a gap between guidelines and implementation in many countries. Permitting synthetic follow-ons as generic applications without publicly addressing the consideration where this is not appropriate could result in a situation similar to that addressed in the WHO 'Guidance on scientific principles for regulatory risk assessment of biotherapeutic products', i.e. where products become licensed using a pathway which does not follow globally agreed and relevant regulatory expectations and for which there may be concerns of safety and efficacy.

In October 2017, FDA published draft guidance[10] on their views of the requirements for allowing a generic type of application for synthetic follow-on molecules for five specific polypeptide originators composed of 40 or fewer amino acids, showing that the scientific aspects of such an approach is not without hurdles requiring consideration. The Draft Guidance provides a limit for new peptide-related impurities in the proposed generic product, beyond which FDA would not accept a generic application. Of note, in the US these five products are not considered biological products, but are regulated as drugs. This is in contrast to the EU where these peptide products are regulated as "biological products", and therefore the US approach cannot be adopted 'as is' in the EU.

EuropaBio's position & asks

A chemically synthesized protein that uses a biological medicinal product as its reference product is not the same active substance as the reference product. Because the products do not have the same active substance, they should not be considered generics or substitutable, but rather similar.

If a chemically synthesized protein uses a biological medicinal product as their reference product, comparability should be established as for a biosimilar.

[10] FDA, "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin,", *available at* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf (October 2017).

In addition, new impurities with potential for immunogenicity, not seen with recombinant products and not previously tested in the clinic, warrant clinical comparability data and immunogenicity testing. The extent of the data is dependent on the specifics of the product and the scientific understanding underlying that product.

Today the hybrid pathway is the appropriate pathway for these products since current legislation exclude chemically synthesized proteins from the biosimilar application route. We suggest that all follow-on products to biological products be treated in a consistent manner following biosimilar principles for the review and registration in EU.

EuropaBio would welcome a dialogue with the European stakeholders on the best way of ensuring equal transparency in assessment and equal measures for traceability and adverse event reporting for all follow-ons of a biological originator. One path could be to open the biosimilar route to all products referencing a biological originator. EuropaBio would also welcome a guideline for chemically synthesized proteins.

EuropaBio would also welcome dialogue at national level on prescribing and dispensing rules ensuring a level playing field for all follow-on molecules for the same originator.

EuropaBio aisbl
Avenue de l'Armée 6, 1040 Brussels, Belgium
+32 2 735 03 13 | +32 2 735 49 60
www.europabio.org | VAT: BE 0477 520 310