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How Should Synthetic Follow-Ons of Biological Products Be Regulated? What Are the Implications for Automatic Substitution?

JENS HEISTERBERG

Novo Nordisk A/S, Vandtårnsvej 108-110, DK-2860 Søborg, Denmark

Correspondence: jhir@novonordisk.com

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1. Introduction

Follow-on products referencing biological medicines have from 2005 until recently been licensed as biosimilars in the European Union (EU), because they have themselves been biological medicines.

However, synthetically produced follow-on products referencing biological medicines are now emerging. This presentation will address the EU regulatory and scientific challenges associated with these products – primarily with respect to licensing, but also in relation to allowing automatic substitution at the pharmacy level.

2. Discussion

Regulatory aspects

In the EU, a biological medicine is defined as a medicine whose active substance is produced by or extracted from a biological source (1). Examples are recombinant proteins, monoclonal antibodies, medicines derived from human blood and human plasma, immunological medicines and advanced therapy medicines. Biological medicines need for their characterisation and the determination of their quality a combination of physico-chemical-biological testing, together with the production process and its control.

Most protein-based medicines licensed in the EU are considered biological medicines because of the production method, typically using recombinant technology.

However, there has in recent years been a significant progress in manufacturing technologies using chemical synthesis. Consequently, it has now become technically feasible and economically viable to produce smaller proteins via chemical synthesis. Such products are not biological medicines under EU law.

This has led to the extraordinary situation that follow-on products that reference biological medicines are not necessarily biological medicines themselves.

If the follow-on product is manufactured using recombinant technology, it will be considered to be a biological medicine. It can only be licensed as a biosimilar product according to Article 10(4) of Directive 2001/83/EC[1]. Several biosimilar guidelines have been issued by the EMA to guide developers of these products, and the requirements outlined in these guidelines will apply (2).

However, if the follow-on product is manufactured synthetically, it will not be considered a biosimilar product. Hence, it cannot be licensed according to Article 10(4). If it is not a biosimilar product, the question then arises: How would such a product be categorised?

From a regulatory perspective, there is currently no clarity about exactly which regulatory pathway these products should follow (3). One pathway could be the so-called "hybrid" route (Article 10(3)) where results of appropriate pre-clinical tests or clinical trials shall be provided as opposed to the simple generic route (Article 10(1)).

Table 1 displays the different regulatory pathways for follow-on products that reference a medicine already licensed in the EU and the level of the required documentation compared to a full application.

Table 1 *EU regulatory pathways for follow-on products and the level of documentation compared to a full application*

Category	Legal framework	Level of documentation
Generic	Article 10(1)	Low
Hybrid	Article 10(3)	Low-medium
Biosimilar	Article 10(4)	Medium
Full	Article 8(3)	High

In contrast to requirements and decisions regarding licensing, automatic substition is solely a matter for the individual EU member states. (Please note that automatic substitution is sometimes referred to as "interchangeability", especial-

ly in a US context for biological medicines). Criteria vary considerably across member states, but – in most countries – biological medicines, including biosimilars, are not subject to automatic substitution, whereas automatic substitution for generic medicines is common.

Scientific aspects

In line with the uncertainty about the regulatory pathway, there is also uncertainty with respect to the regulatory requirements for licensing.

When establishing the requirements, it should be recognised that proteins are complex molecules and that their efficacy and safety are specifically tied to the manufacturing process. Hence, differences in manufacturing process that result from a different manufacturer producing a synthetic follow-on product may significantly alter the function of the product and could result in adverse clinical consequences.

A synthetically produced follow-on product could differ from the biological reference product with regard to impurity profile and stability, including propensity towards fibrillation.

Changes to the impurity profile, including the presence of clinically unqualified deletions, additions, and reaction products between the protein and process reagents and solvents, as well as increased fibrillation may result in increased immunogenicity.

Further, protein products are often susceptible to physical stress at larger scale manufacturing, and fibrillation may occur upon storage.

Available analytical methods are insufficient to establish the clinical "sameness" of a different manufacturer's synthetic follow-on to a biological reference product (or a recombinant follow-on produced from a different cell line or through a different manufacturing process).

Consequently, the generic route (Article 10(1)) is inappropriate for licensing synthetic follow-on products referencing biological medicines. As shown in Table 2, there are significant differences in the clinical documentation requirements for a generic product compared to a biosimilar product.

Article 10(4) will not apply for synthetic follow-on products referencing biological medicines, but at least some of the requirements for biosimilars are still relevant.

Therefore, synthetic follow-on products where the reference product is a biological medicine should only be licensed via Article 10(3), and the documentation should include the following: a) Full chemical and biophysical comparability; b) Long-term stability and absence of fibrillation issues to be shown with commercial scale batches; c) Clinical testing, including a clinical trial to evaluate immunogenicity.

Table 2 *Small molecule generics versus biosimilars: Differences in clinical documentation requirements*

	Generics Article 10(1)	Biosimilars Article 10(4)
PK	Yes (in most cases)	Yes
PD	No	Yes
Efficacy	No	Yes (in many cases)
Safety	No	Yes
Immunogenicity	No	Yes

For automatic substitution to be considered, the implications of repeated switches between the reference and the follow-on product regarding immunogenicity should be evaluated. In addition, these products are often presented in a device, and aspects related to the use of the device should be assessed in such cases.

Any follow-on product should be subject to the same pharmacovigilance requirements in place for the reference product. Requirements for naming, traceability and risk minimisation for a synthetic follow-on product should follow those of biosimilar products.

4. Conclusions

- *Synthetic follow-on products with biological medicines as reference are emerging*
- *EU regulatory framework and requirements for these products are not entirely clear*
- *Proteins are complex molecules, and differences in manufacturing process may have implications for immunogenicity*
- *A more cautious approach is warranted for the licensing of synthetic follow-on products that reference biological medicines than for generic medicines*

References

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