

IFPMA Position Paper on:

SYNTHETIC FOLLOW-ON PRODUCTS THAT REFERENCE BIOLOGICALLY PRODUCED MEDICINES

INTRODUCTION

What are these products?

Overall, medicines have different sizes and complexities – ranging from small molecules with simple molecular structures to highly complex proteins as well as advanced therapies. The focus of this paper is follow-on versions of smaller protein products developed to be marketed following expiry of patent and data protection of the reference product. They are synthetically produced while the reference product is manufactured recombinantly.

Why have these products emerged?

In recent years, significant progress in manufacturing technologies using chemical synthesis has made it technically feasible and economically viable to produce smaller proteins via chemical synthesis. This has enabled generic companies to develop synthetic follow-on versions, also in cases where the reference product is biologically produced.

Some examples

Synthetic versions of smaller proteins such as teriparatide and liraglutide have been developed and marketed by generic companies. It is expected that it will be possible to produce a growing number of smaller proteins (less than 100-150 amino acids) synthetically in the future.

What is the challenge?

In some countries, there is lack of clarity about how these products should be regulated.

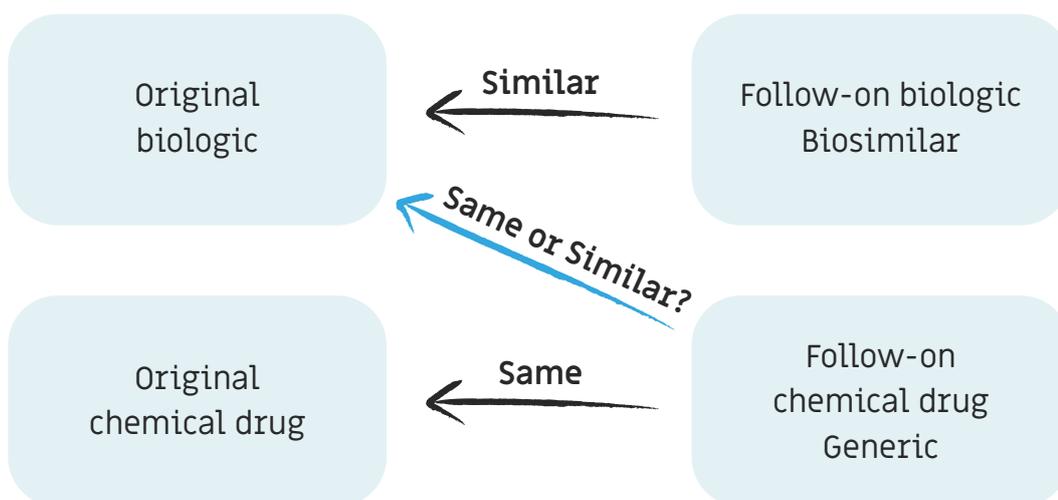
“Synthetic follow-on products that reference a biologically produced medicine are complex and should not be viewed as simple generics. Instead, they should be **evaluated following an approach more aligned with that adopted for biosimilars.**”

REGULATORY ASPECTS

Follow-on products referencing biologically produced medicines are in most cases biologically produced themselves and are thus regulated as biosimilars in many regulatory jurisdictions.

However, regulators generally do not consider synthetic protein products to be biological medicines. Synthetic follow-on products will thus not be biosimilars, even if their reference product is biologically produced. This has led to uncertainty about how synthetic follow-on products referencing a biologically produced medicine should be categorised and evaluated by regulators.

Should these products be evaluated as simple small-molecule generics or do their characteristics call for a more elaborate evaluation?



SCIENTIFIC ASPECTS

Proteins are complex molecules. Differences in manufacturing process that result from producing a synthetic follow-on product may significantly alter the properties of the product and could result in meaningful clinical consequences.

A synthetic follow-on product will likely differ from the biological reference product with regard to impurity profile and could differ with regard to stability, for example a different tendency towards fibrillation. It is important that these factors as well as the overall complexity of the product are considered in the development and subsequent regulatory evaluation.

Changes in the impurity profile may involve the presence of clinically unqualified isomers, deletions, additions, and reaction products between the protein and process reagents

and solvents¹, including increased high molecular weight protein (HMWP) formation and fibrillation. Further, protein products are often susceptible to physical stress at larger-scale manufacturing, and fibrillation may occur during manufacture or upon storage. These factors may result in increased immunogenicity^{2,3}.

Available analytical methods may be insufficient to establish therapeutic equivalence of a synthetic follow-on product to a biological reference product; this applies in particular to non-clinical models to predict immunogenicity⁴. Thus, compliance with a compendia monograph does not indicate comparability, but should be a minimum requirement.

Clinical trials should therefore be considered to establish that the same efficacy, safety and tolerability profile can be obtained with a synthetic follow-on product as compared to its biologically produced reference product.

IFPMA POSITION

Synthetic follow-on products that reference a biologically produced medicine are complex and should not be viewed as simple generics.

Instead, they should be evaluated following an approach more aligned with that adopted for biosimilars and be characterised as outlined below:



Full quality **comparability documentation**, including evaluation of biological activity using suitable assays reflecting the mechanism of action



Long-term stability and absence of fibrillation issues to be shown with several commercial scale batches, including studies that simulate in-use conditions



Clinical testing comparing follow-on and reference product to confirm safety and the absence of increased immunogenicity should be conducted unless the quality evaluation demonstrates strong comparability

In view of the complexity of the products, they should not routinely be considered for automatic substitution at the pharmacy level without an assessment of potential risks associated with unsupervised switching. Furthermore:



Any follow-on product should be subject to the same **pharmacovigilance requirements** that apply to the reference product



Requirements for **naming, traceability and risk minimisation** should follow those of biosimilar products

- 1 Staby A et al. Influence of Production Process and Scale on Quality of Polypeptide Drugs: a Case Study on GLP-1 Analogs. Pharm Res 2020;37,120
- 2 US FDA Guidance for Industry “Immunogenicity Assessment for Therapeutic Protein Products”, August 2014
- 3 Engelsman J et al. Strategies for the Assessment of Protein Aggregates in Pharmaceutical Biotech Product Development. Pharm Res. 2011;28(4):920–933
- 4 Gokemeijer J et al. How Close Are We to Profiling Immunogenicity Risk Using In Silico Algorithms and In Vitro Methods?: an Industry Perspective. AAPS 2017;19(6):1587-1592