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Commentary

Different Pharmaceutical Products Need Similar Terminology

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Abstract. In the last decade, discussions on the development of the regulatory framework of generic versions of complex drugs such as biologicals and non-biological complex drugs have attracted broad attention. The terminology used is far from harmonized and can lead to multiple interpretations of legal texts, reflection papers, and guidance documents regarding market introduction as well as reimbursement. This article describes the meaning of relevant terms in different global regions (Europe, USA, WHO) and offers a proposal for a globally accepted terminology regarding (non-) biological complex drugs.

KEY WORDS: biosimilars; generics; non biological complex drugs; substitution; terminology.

INTRODUCTION

The 1984 *Drug Price Competition and Patent Term Restoration Act*, also known as the "Hatch–Waxman Act" was the basis of the system of generic drugs in the USA (1). The Hatch–Waxman Act led to the development of a generic drug industry as a result of the regulatory policies developed by the FDA, for which the Act gave the legal basis. The basic generic approach as formulated by the FDA and later adopted by other regulatory agencies considers copies of medicinal products therapeutically equivalent to their original products if they are pharmaceutically equivalent and bioequivalent, meaning that their bioavailability (rates and extents of absorption) after administration in the same molar dose are comparable.

The determination of bioequivalence is based on a statistical comparison of log-transformed pharmacokinetic characteristics of the generic and the original preparation where both two one-sided 90% confidence intervals of the extent of drug absorption in healthy volunteers ($AUC_{0\text{-}t}$) and C_{max} are within 80 and 125% of the reference product. The pharmacokinetic approach is the most reliable and preferred way for establishing bioequivalence and is applicable for systemically active drugs.

The goal of the bioequivalence studies is to show that there is no statistically significant difference in the rate and extent of absorption between the test and reference product. When test and reference products are pharmaceutically equivalent and bioequivalent, they are considered therapeutically equivalent and therapeutically interchangeable.

However, the introduction of the concept of biosimilars for the class of large, complex, protein-based drugs manufactured through a complex and intricate manufacturing process, has led to new questions regarding the interchangeability of drugs for individual patients and reimbursement issues like reference price systems and terminology used in scientific publications. For biosimilars, non-clinical and/or clinical studies are requested in addition to physicochemical (quality) analyses. In addition, since 2010, the group of non-biological complex drugs (NBCD) has been defined: a non-biological complex drug is a medicinal product, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different (closely related and often nanoparticulate) structures that can't be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. It is also unknown which structural elements might impact the therapeutic performance. The composition, quality and *in vivo* performance of NBCD are highly dependent on manufacturing processes of both the active ingredient as well as the formulation (2).

In this paper, we provide a proposal for standardized terminology for "generic versions" [(intended) copies] of small, low-molecular weight molecules and similar biologicals and NBCD. Our proposed terminology is based on an analysis of the use of the terms in the regulatory guidance concerning biosimilars of the European Medicines Agency (EMA), WHO, and the FDA and a questionnaire we have sent to different

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stakeholders, including regulators, regulatory experts of the pharmaceutical industry, academic researchers, and trade organizations. The responses of these stakeholders in this survey were anonymized or paraphrased and were used to draft this manuscript.

Our ultimate goal is to reach a global consensus regarding the terminology among all stakeholders: innovators, follow-on manufacturers, and regulators. This could, for example, be achieved by an ICH process.

The EMA

In Europe, the EMA played a pivotal role in defining a science-based decision instrument to issue marketing authorizations for "similar biological medicinal products." The term "similar biological medicinal product" is defined in Article 10(4) of Directive 2001/83/EC, that is the legal basis of the regulatory system designed by the EMA (3), "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, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests and/or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided."

Thus, a similar biological medicinal product, also known as "biosimilar", is a product which is similar to a biological medicine that has already been authorized, the so-called "reference product." In addition to a state-of-the-art physicochemical (*in vitro*) characterization, the key to be considered as a biosimilar is the availability of sufficient data from clinical trials. This is confirmed by a recent paper by the members of the Biosimilar Medicinal Products Working Party at the EMA suggesting that "any copy version of a therapeutic protein, which has not been developed and assessed in line with the scientific principles of a strictly comparative development program against a reference product, should not be termed biosimilar. We do not wish to imply that other products are of lower quality, efficacy, or safety, but simply that they may not qualify as biosimilars according to the understanding of this term in the EU, and potentially, other regions, and thus may require different terminology to enable a clear distinction between the different products (4)."

Another important term to consider is the "therapeutic equivalence" of two medicinal products: there is no formal definition of this term in the EMA legislation. It may be understood as the equivalent of the safety and efficacy properties of two medicinal products administered at the same dose and *via* the same route.

"Traceability" is defined as the ability to trace each individual unit of a medicinal product from the source to its final destination, and *vice versa*. Directive 2010/84/EU also states that "the EU Member states shall ensure, through the methods for collecting information, and where necessary, through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number (5)."

The definitions of the terms "interchangeable," "exchangeable," "substitution(able)," and "switchable," are not provided by the EMA since the assessment of these concepts is outside the remit of the EMA. The decisions on interchangeability or substitution rely on National Competent Authorities. European National Competent Authorities have different attitudes regarding the interchangeability of innovators' products and their biosimilars. Major European Union member states (including France, Germany, United Kingdom, Italy, and Spain) rejected the practice of substitution of a biologic by the pharmacist without the physician's consent ("automatic substitution").

Finally, the answers in the survey clearly showed different interpretations by the respondents for the terms substitution (substitutable) and switchable.

The FDA

The Biologics Price Competition and Innovation Act, BPCI act, (2009) outlines the overall policy of US regulators regarding biosimilars (6). In February 2012, three draft documents were published proposing in more detail the protocols to be followed: "Scientific considerations in demonstrating biosimilarity to a reference product (7)", "Quality considerations in demonstrating biosimilarity to a reference protein product (8)," and "Biosimilars: Questions and Answers regarding implementation of the BPCI act (9)." Section 351(i) of the Public Health Service Act defines *biosimilarity* to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

The BPCI act recognizes two levels: biosimilarity and "interchangeability." For interchangeability, a higher level of evidence for similarity is requested than for biosimilarity and it gives an additional advantage to the product: "the term 'interchangeable' or 'interchangeability,' in reference to a biological product that is shown to meet the standards described in subsection (k) (4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product (BPCI act)." The product label should provide this information about being biosimilar or interchangeable with the reference product.

The terms "switchability" and "prescribability" are being used in the context of biosimilars, where switchability refers to changing the product (from reference to biosimilar or *vice versa*) in a patient during the course of treatment. Prescribability is the term used for the product options to choose from at the start of therapy (10).

Other Regions

In September 2011, an analysis by Konski *et al.* was published comparing regulatory rules in the USA, Europe, China, and India (11). The EU's biosimilar framework has been

adopted by Australia and provided foundational principles for pathways in Canada (2010), Japan (2009), Malaysia, South Africa (2010) and others.

The WHO Position

In 2009, the WHO-issued guidelines on the evaluation of "similar biotherapeutic products" (SBP) intended to provide guidance for the development and evaluation of such biotherapeutics (12). Vaccines, plasma-derived products, and their recombinant analogs are excluded from the scope of this document.

According to the WHO guidelines, a SBP is intended to be similar to a licensed biotherapeutic product for which there is a substantial evidence of safety and efficacy. The dosage form and route of administration of the SBP should be the same as for the reference biological product (RBP). Biotherapeutics which are not shown to be similar to a RBP as indicated in this guideline should not be described as "similar," nor called a "SBP." Traditionally, National Regulatory Authorities have required the use of a nationally licensed reference product for licensing of generic medicines. This practice may not be feasible for countries lacking nationally licensed RBPs. The WHO uses the following definition for "interchangeability": "An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice." No automatic substitution is mentioned.

TERMINOLOGY LIST

Our proposed terminology list is based on the analysis of the regulatory guidance in the world and the responses to the questionnaire we have sent out.

Generic Medicinal Product

A drug product that is comparable to a reference-listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use.

Biological Product

A biological product is a product derived from living material (such as cells or tissues) used to treat or cure disease. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapeutics, tissues, and recombinant therapeutic proteins. Biological products can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or maybe living entities such as cells and tissues. Biological products are isolated from a variety of natural source—human, animal, or microorganism based—and may be produced by biotechnology methods.

Biosimilar Product/Similar Biological Medicinal Product

A similar biological medicinal product (also known as biosimilar) is a biological product authorized by an abbreviated regulatory pathway requiring similarity to an already licensed biological product (the reference product) in physicochemical, *in vitro* and *in vivo* biological characteristics, and clinical data showing similarity in efficacy, safety, and immunogenicity.

A Non-Biological Complex Drug (NBCD) Product

A medicinal product, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different (closely related and often nanoparticulate (13,14)) structures that can't be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. It is also unknown which structural elements might impact the therapeutic performance. The composition, quality, and *in vivo* performance of NBCD are highly dependent on the manufacturing processes of both the active ingredient as well as the formulation (2). Examples of NBCD are, amongst others, liposomes, iron–carbohydrate ("iron–sugar") drugs, and glatiramoids.

Therapeutic Equivalent

Two medicinal products with systemic effect are therapeutically equivalent if they are pharmaceutically equivalent and if their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same. This is considered demonstrated if the 90% confidence intervals of the ratios for log $AUC_{0\text{-}t}$ and C_{max} between the two preparations lie in the range 80.00–125.00%. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

Drug products classified as therapeutically equivalent can be interchanged with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Interchangeability

Therapeutic equivalence of two different products enables the products to be interchanged. Interchangeability can be at the population level meaning both products can be used for treatment for the same condition in the same population. Interchangeability at the individual level means that in an individual patient, the products can be alternated or switched. Interchangeability at the individual level is a condition for substitution.

Substitution

A policy to allow replacement at the individual level of a medicinal product for a similar/bioequivalent product.

Switchability

Changing the product (*e.g.*, from reference product to biosimilar or *vice versa*) in a patient during the course of treatment.

Traceability

The ability to trace each individual unit of a medicinal product from the source to its final destination, and *vice versa*.

Extrapolation

The possibility to use the clinical data showing safety and efficacy in one indication (*reference indication*) to claim safety and efficacy in other indications. Extrapolation concerns the extrapolation of four different aspects: efficacy, safety, immunogenicity, and interchangeability and may concern the indication, population, or both.

CONCLUSION

The pharmaceutical "rules of engagement" are more and more becoming global in character. Common, accepted terminology is a first requirement for global harmonization of regulatory rules and actions.

It is critically important for authorities, health care professionals, scientific experts, and patients to have one unified terminology to guarantee a consistent quality and use of generic versions of complex innovator products. In this paper, we do not only define and analyze the problem, but we also provide a proposal for the terminology used. The section above offers such a terminology list.

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