

Patenting of Biosimilars?

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Abstract

Patenting biosimilars before the expiration of the original patent might raise several questions for the original manufacturer as well as the biosimilar manufacturer. In general, the most eminent questions are the drafting of the original patent in a way to be protected against a wide range of similar products and for the biosimilar manufacturer to ensure that the similar product is new and inventive. Since so far no case law exists in Europe dealing with biosimilars, both manufactures are somewhat in an unclear and ambiguous situation when it comes to estimate the scope of claims of biopharmaceuticals.

Keywords: Biosimilars; Novelty; Inventive step; Case law

Introduction

Biopharmaceuticals have proven to be useful in the treatment of many life-threatening or chronic diseases such as cancer or diabetes. Biopharmaceuticals are generally complex drugs consisting of relatively large molecules. They are in most cases biotechnologically produced proteins, including antibodies, although other large biological molecules such as DNA, RNA or antisense oligonucleotides are also used for therapeutic or in-vivo diagnostic purposes. The first such substance approved for therapeutic use was recombinant human insulin entering clinical trials in humans in 1980 [1]. The global market for biosimilars is estimated to rise to about US\$ 3.5 billion by 2016 [2].

All these large biomolecules share one common feature: they are a sequential arrangement of molecules such as either amino acids (proteins) or nucleic acids (DNA or RNA). Their nature and function in a living organism is determined by the order of the different amino acids or nucleic acids found in the sequence of these chain-like molecules. However, the sequence in these molecules is often slightly altered by nature. These small alterations might consist in a simple exchange of one link (amino acid or nucleic acid) in the chain by a different link. These exchanges create polymorph molecules that could show reduced or enhanced biological activity or have no consequences on the activity of the chain-like biomolecules. This variability in the structure of biopharmaceuticals is often a result of the production process, depending on the type or organism or the culture conditions used for the generation of the drug. Thus, several biomolecules that might be slightly different but have the same biological function can be produced by different production processes. Such molecules are called biosimilars. In fact, the WHO defines a biosimilar to be “a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product” [3] and the FDA states that “biosimilar or biosimilarity is defined in Section 351 of the Public Health Service Act to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” [4]. Similar biotherapeutic drugs are therefore not an exact copy of the

active compound of existing drugs, e.g. chemical generics. These generic drugs are in general bioequivalents having the exact same biological effect than the proprietary drug. Biogenerics, on the other hand, are not exact copies but only similar in structure and maybe biological effect and efficacy.

Are there consequences for the patenting of biopharmaceuticals, considering the special nature of biosimilars? If biosimilars, in a narrow sense, are defined as biogenerics and these similar biologic compounds may enter the market after expiration of the patent protection, no noteworthy patent-related problems need to be solved but a number of regulatory questions remain open to interpretation. However, if the biosimilars are understood in a broader sense, e.g. as inventions and patent applications based on similar biological compounds, a number of patent-related questions will arise. For example, there might be cases when patent applications for biosimilars are filed during the time the original patent is still valid rather than after the expiration of the original product protection. In this scenario, the issue for the pioneer manufacturer is to draft the claims in the original patent broadly enough to prevent biosimilars from being patented and entering the market. Thus the scope of the claims should include a very broad covering of all sequences that are at least in a range of between 80 and 100 per cent identity in comparison to the sequence of the (original) biopharmaceutical. From the biosimilar manufacturers' perspective questions will revolve around how to draft patent claims without infringing the pioneer manufacturers' patent rights and the best way to ensure that the authorities will grant the patent. Thus, for the biosimilar patent applications the questions of novelty and inventive step are in the focus. There are two possible scenarios for biosimilars differing by more than 80 per cent from the sequence of an original drug. First, we could assume that the biosimilar is only a small subsequence of the original sequence of the biopharmaceutical, but still has the same desired effect. Second, what if the biosimilar has a considerably longer sequence but contains the original sequence as a subsequence? Are the biosimilars new and inventive in these cases? In the U.S. the Biologic Price Competition and Innovation Act (BPCIA) established an information exchange and patent dispute scheme in which both, the original manufacturer and the biosimilar manufacturer, are involved. At the end of this process the biosimilar manufacturer should be certain that his product does

not infringe any patent rights and the pioneer manufacturer does not have the possibility of pursuing patent infringement.

In Europe, no case law for such biosimilars or such scenarios exists so far. However, some clues might be derived from cases that do not directly deal with biosimilars. As far as novelty is concerned, the following decisions by the Board of Appeals of the European Patent Office may be relevant. In the decision T 198/84 a number of principles for a selection invention in the field of chemistry was defined: according to this decision a sub-range singled out of a larger range is not considered new by virtue of a newly discovered effect occurring within it, but must be new per se. In T 12/90, a decision on the novelty of generically defined compounds including particular examples, the board stated that an arbitrary selection cannot be considered novel. In T 133/92 it was decided that a claimed group of compounds cannot be considered as selectively novel when it essentially resulted from omitting those parts of a larger group of compounds that a skilled person would have immediately considered as being less interesting than the remainder. As for the decision on the inventive step for enlarging the sequence by adding sequences that have virtually no function, T 72/95 says that if a known device is modified by adding a feature which has no technical function, this modification cannot contribute to the inventive step. Furthermore, in T697/92 it was held that the use of equivalent means can indicate lack of inventive step.

Due to the absence of decisions on cases involving biosimilars in Europe, case law dealing with other technical areas has to be used. Thus, there remains considerable uncertainty regarding biosimilar patent applications. The question is therefore whether a similar information exchange scheme as used in the U.S. would be a possible approach in Europe as well.

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