BIOSIMILARS AND PROTECTION OF THEIR OWNERSHIP

Gist of the news

It is reported on the website of *http://cinnagen.com*:

Signature of the first technology transfer contract in the field of biopharmaceutical production between Iran and Turkey with presence of Iran food and drug organization president.

For the first time, CinnaGen pharmaceutical company as the leading biopharmaceutical producer in Iran and the Middle East has managed to transfer the production technology of MS (Multiple Sclerosis) medicine known as **ReciGen®** from Iran to Turkey.

According to this contract, ReciGen® will be produced through the transferring process under the license of CinnaGen company with the help of specialist and researchers.

This contract is a great change in Iranian pharmaceutical industry landscape, as previously, Iranian pharmaceutical companies were license followers and this time an Iranian company is considered as the licensor and technology holder.

The technology receiver is the oldest and the biggest Turkish pharmaceutical company known as Abdi Ibrahim.

Abdi Ibrahim is famous for 100 years of activities in field of pharmaceutical research and production with 3500 employees and more than 370 pharmaceutical products in Turkey.

The above news may be considered a significant development in producing biosimilars in Iran that calls for detailed analysis. First part of our report, therefore, focuses on regulatory definitions of biopharmaceuticals. Then, we will look at the problems of patenting biosimilars. The third part of report will cover the process of patenting biosimilars and the report will come to an end with a brief analysis on registration of biosimilars in the EU, the US and Iran.

Regulatory definitions of biopharmaceuticals

Biopharmaceuticals – Ronald A Rader in his article titled "(Re)defining Biopharmaceuticals" proposes the following definition for biopharmaceuticals by referring to the EU regulations: "A protein or nucleic acid based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source".

Original (or innovator) brand - In order for the company to market and sell their product they must first gain approval from the Food and Drug Administration (FDA) by submitting a New Drug Application. In this documentation the company submits data to establish a drug's clinical safety and efficacy. Other studies determine the

characteristics of the drug dosage form, including the manufacturing process, drug stability, purity, strength, and how it dissolves. Once the drug receives FDA approval, the innovator company can then exclusively market and sell this 'brand-name' product for as long as the company has patent protection (*scientificamerican.com*).

Biosimilars – A biosimilar is a biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which 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 (*fda.gov*).

Biogenerics – A biopharmaceutical or other biological product—e.g., insulin, hGH—that has emerged from patent protection and can be manufactured by a party other than the original developer using either identical or different manufacturing processes; for FDA approval, the product must be bioequivalent or comparable to the original innovative product (*thefreedictionary.com*).

Another definition is provided by article 10, paragraph 2(b) of Directive 2001/83/EG: “generic medicinal product” shall mean a medicinal product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Reference product – According to *cbg-meb.nl*: The ‘reference medicinal product’ is a medicinal product authorized under Article 6, in accordance with the provisions of Article 8 (Article 10, paragraph 2 under a) of Directive 2001/83/EG).

Biobetters – Biobetters contain similar active ingredients, e.g. an antibody that targets the same protein as a product already on the market, but possess some molecular or chemical modification that constitutes an improvement over the originator drug, e.g. enhanced bioavailability or reduced immunogenicity (*Gabionline.com*).

In this News & Analysis report, only biosimilar products will be analyzed because they are the subject of the contract signed between CinnaGen and Abdi Ibrahim. Two main ways are available for creating and protecting ownership of biosimilars: patenting and licensing.

Patenting of biosimilars, problems to face

One of the best ways to establish, maintain and protect the ownership of a biosimilar product is to get a patent for it. The problem is that these products are highly complicated and understanding their side-effects takes time. In the case of *Lilly v Janssen*, considered by the High Court in June 2013, this issue came up. As explained on the website of *osborneclarke.com*:

There are two alternative bases on which a patent may be insufficient. The 'classical' form is that the description simply does not give the skilled person enough information for them to be able to work the invention without undue burden – essentially, requiring them to carry out them further research of their own in order to get any working product. More recently, patents have also been found to be insufficient on the basis that although the description does enable the skilled person to do some variants within the scope of the invention claimed, that does not include every possible embodiment of the claimed invention.

The second problem is that post-application developments may have an impact on validating a patent as explained in the same source:

In a dispute between Mylan and Yeda Research and Development Co ("Yeda") over the use of copolymer-1 in the treatment of multiple sclerosis, Mylan sought to invalidate Yeda's patent on the grounds that the supposed invention was not inventive, by reference to later evidence that in fact Yeda's invention did not make any difference over and above what was known in the art. The Court of Appeal agreed in principle that evidence subsequent to the filing of the patent could be admitted for this purpose.

The next issue is the so called "inventive step" (Europe) or "non-obviousness" requirement (U.S.). This issue includes, among others, the "obvious to try" and hindsight problems, but also pharmaceutical life cycle strategies and the notion of a so called “innovation gap” in the pharmaceutical sector, as explained by Timo Minssen in his doctorate thesis titled “Assessing the Inventiveness of Bio-Pharmaceuticals under European and US Patent Law.”

The Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 defines two of the above terms:

“Obvious to try” means choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

“Hindsight problems” means that “It is difficult but necessary that the decision-maker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art. ...” W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

The last problem is choosing a proper name for the biosimilars. As explained by *bioprocessintl.com*, in choosing a name for a biosimilar product, the following criteria must be taken into consideration:

a) Whether to assign either unique, similar, or generic (the same as reference product) names to biosimilars;
b) Whether and how biosimilarity relationships, structures, product class, and other information should be reflected in biosimilar names; and
c) Whether there should be any system and predictability to names.

By looking at the names of products adopted by CinnaGen company, one can observe the following raison d'être for them:

1) The name CinnoVex is close to the name of its reference product Avonex;
2) The name Zitux or Reditux is close to the generic name of Rituximab;
3) The same goes for the name of PegaGen that reflects the generic name of "pegylated filgrastim" in its first part and includes also the last part of the producer's name.
4) The name CinnaPoietin, on the other hand, includs the first part of CinnaGen's name and the second part of the generic product's name: Erythropoietin beta.

The rule adopted by CinnaGen in naming its products, therefore, is to combine part of its own name with part of the generic name of the product. This means that there is a system and predictability to names of its products. The assigned generic name is also reflected in the adopted names. In this way, biosimilarity relationship is reflected in the names of CinnaGen products. Hence, all the rules of naming biosimilar products are respected by CinnaGen.

Process of patenting of biosimilars

In his article titled "Patenting of Biosimilars?" Heinz Mueller explains that:

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.

In practice the latter case rarely happens because intellectual property lawyers draft the patent applications in a way to prevent the potential competitors from any attempt to patent their biosimilars during the time that the original patent is still valid. However, the latter group may resort to another technique by patenting "biobetters". A good example of a biobetter is Reditux that is a biosimilar of rituximab lunched in India in 2007 by Dr. Reddy. CinnaGen has also produced a biosimilar of rituximab called Zitux. Recently, some famous producers of biopharmaceuticals such as Merck & Co., Roche and Sanofi have been working on produding biobetters of rituximab, as reported by *biopharma-reporter.com*.

Registration of biosimilars in the EU, the US and Iran

According to the FDA, the Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, amends the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be "biosimilar" if data show that, among other things, the product is "highly similar" to an already-approved biological product.

In the EU, the following guidelines apply to registration of biosimilars:

- Guideline on Similar Biological Medicinal Products (CHMP/437/04, London, 30 October 2005);
- CPMP/BWP/328/99 Development Pharmaceutics for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96);
- Topic Q5C, Step 4 Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (CPMP/ICH/138/95 - adopted Dec. 95);
- Topic Q6B, Step 4 Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96 - Adopted March 99); and
- ICH Topic S6, Step 4 Note for Preclinical Safety Evaluation of Biotechnology-Derived Products (CPMP/ICH/302/95 - adopted Sept. 97)

In Iran, according to the Guidelines of the Ministry of Health and Medical Education, a biosimilar product shall be registered after a comparison is made between the product and the licensed originator product in order to establish similarity in quality, safety, and efficacy. Products should be compared in the same study using the same procedures. If the licensed originator product is not registered in Iran but it is registered by the FDA or the EMEA and has received a production or import license based on Periodic Safety Update Report (PSUR), then it could be used as a reference material for the biosimilar product.

It must be noted, however, that according to *essentialdrugs.org*:

> Despite the fact that biopharmaceuticals that were produced by the local Iranian industry in the past decade including INFs, GCSF and GH have received marketing authorization for the local market, none of them received formal evaluation according to those of international guidelines for "Biosimilars".

Conclusion

Gabionline.com reported on November 1, 2013 that:

Since 2003, Iran's national regulatory authority (NRA) has registered six copies of branded biopharmaceuticals. Another 16 are in the pipeline and are expected to reach the Iranian market in the coming years.

Trend.az also reported on February 4, 2014 that:

For the first time a biosimilar anti-cancer drug has been manufactured in Iran … The drug, named "Pegajen" [PegaGen] was publicly presented in Iran on Feb. 3. Reportedly the drug was manufactured using the latest technology for producing recombinant preparations.

The strong inclination in the Iranian market to produce biosimilars could be explained by the fact that pharmaceutical companies in Iran as a non-WTO member do not have access to the production procedures of originators including cell type, fermentation and purification procedures, as reported by *essentialdrugs.org*. The only way out of the current impasse is to find "legal" openings in the international patenting and registration system. The recent contract signed between CinnaGen and Abdi Ibrahim seems to be another step in this direction.