World Patent Information 33 (2011) 67–71

Contents lists available at ScienceDirect

World Patent Information

journal homepage: www.elsevier.com/locate/worpatin

Patent search on biologics as potential biosimilar candidates ☆

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ARTICLE INFO

Keywords:
Biologics:biosimilars:follow-on biologics
Biopharmaceuticals
FTO search
Keyword searching
Sequence searching
Semantic searching:Enbrel:patent

ABSTRACT

The biological pharmaceutical market is one of the fastest growing sectors in the health care business. Sales of biologic drugs reached $120 billion in 2008 [1] and the worldwide market of biologics continues to grow (IMS Health). As patents on first generation of biologic drugs, including epoetin, insulin granulocyte colony-stimulating factor (G-CSF) and interferon alpha, will soon expire, if they have not already, and patents on some of the second generation of biological drugs, such as antibody drugs, are going to be expire in the next few years, there exists a great opportunity in developing biosimilars, especially for large pharmaceutical companies which face great challenges in developing new blockbuster drugs. In the past few years, the United States, Canada, and Japan have debated or passed legislation on biosimilars with active involvement from top pharmaceutical and generic drug companies. The successful leader in this field will be the one that has the foresight and resources to position themselves well to gain in the future. So what are biosimilars? What are the technological differences between biosimilars and small molecule generic drugs? Finally, what are the considerations for biosimilars in terms of patent searching? An example on a biosimilar study is given here.

1. Introduction

Biosimilars have become a buzzword in recent years. When the terms of "biosimilar or follow-on bio" (truncated form of biologic) are searched for on "Google news", a Timeline bar graph shows the steep increase in the number of News Articles published form 1980 to 2009 (adjustable dates). Clicking on the blue bars brings up the collection of articles (Fig. 1).

The European Medicines Agency (EMEA) has moved ahead of the rest of the world in this area. It established a biosimilar regulatory pathway in 2004 and published the "Guideline on Similar Biological Medicinal Products" in 2005 [2]. Since then it has approved a number of biosimilar products in a declared, balanced process. The United States has been very cautious on moving in the same direction and the legislative pathway for biosimilar approval is still being debated [3]. Health Canada is working on the same issue by drafting the guidelines, called Subsequent Entry Biologics (SEBs) [4], while Japan's Ministry of Health, Labor and Welfare (MHLW) recently adopted biosimilar regulations [5] that are similar to the European Union approval system. In June 2009, Japan announced its first approval of a biosimilar human growth hormone (HGH) product [6].

So what are biosimilars? And why is there a lot of recent attention on them?

1.1. Definition of biosimilars

First, there are biologics (biologic pharmaceuticals or biopharmaceuticals). Biologics or biopharmaceuticals are a subset of drugs that are generated from biological sources and include gene therapies, vaccines, antibodies, and other therapeutic products derived through biotechnology [7]. They were "officially" introduced to the market as "biologic drug" in the early 1980s. Only in 1982 did recombinant human insulin become the first biotech therapy to earn FDA approval and arrive on the market [8], even though the first two biologics, insulin and HGH, had been on the market in the United States for a long time, simply without biologic titles.

Biosimilars, also called follow-on biologics (FOB) or Subsequent Entry Biologics (SEBs), refer to "generic" version of biologics or biopharmaceutical products that are produced and sold on the market after the patents on the innovator's biologics are expired. However, the nomenclature of biosimilars is not universal. For example:

Wikipedia definition [9]:
Biosimilars or follow-on biologics are terms used to describe officially approved new versions of innovator *biopharmaceutical products*, following patent expiry.

EMEA definition [2]:
A new biological medicinal product claimed to be "similar" to a reference *medicinal product*, which has been granted a

☆ This article has been developed from a presentation by the author at the International Patent Information Conference, IPI-ConfEx, in March 2009, in Venice Mestre, Italy.

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0172-2190/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.wpi.2010.05.001

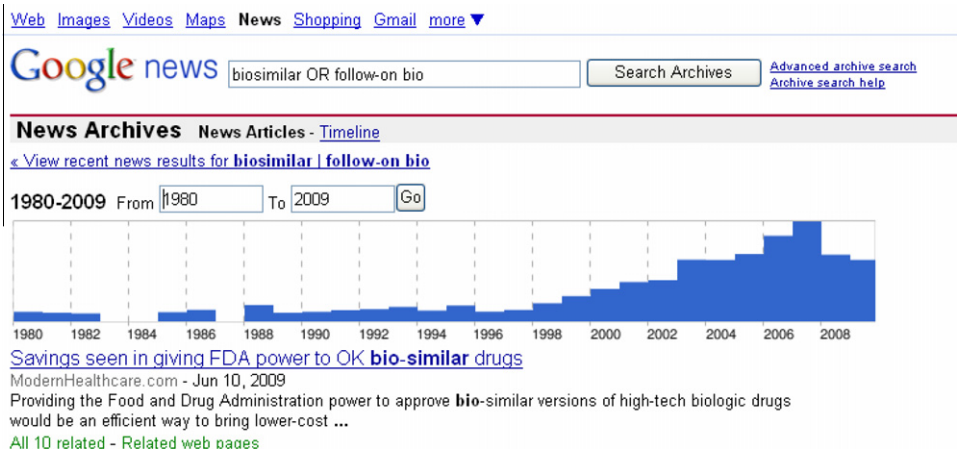

Fig. 1. Snapshot of the web site Google news for a search on "biosimilars or follow-on bio" from 1980 to 2009.

marketing authorization in the Community on the basis of a complete dossier... *e.g.: medicinal products containing biotechnology derived proteins as active substance, immunologicals such as vaccines, blood-derived products, monoclonal antibodies,* etc.

US Congress definition [3]:
The biological product:

(I) is biosimilar to the *reference product* and any biological product licensed...

(II) can be expected to produce the same clinical result as the reference product in any given patient for each condition of use prescribed, recommended, or suggested in the labeling of the reference product...

Canada Health definition [4]:
A SEB is defined by Health Canada as "a biologic product that would enter the market subsequent to, and similar to, an innovator product authorized for sale in Canada."

In summary, a biosimilar is a biological product which is similar to the referenced product "approved before" and "on market", and is expected to have substantially similar clinical results (in terms of safety profile and efficacy) of the referenced product. For more reading about biosimilars, such as related to bioequivalence, clinical safety and efficacy, regulatory, policy and legal issues, please refer to listed reviews [10–15].

1.2. Types of biologics or biosimilars

People normally think of biologics as proteins or antibodies, but biologics can be gene therapies, vaccines and other biological therapeutic products too.

The therapeutic proteins, such as epoetin, insulin, G-CSF and interferon alpha, are well known as the first generation biologics. Monoclonal antibodies are the current success stories of modern biotechnology. Availability of human and humanized monoclonal antibodies or chimeric protein-antibody has increased the success rate in clinical trials of cancer and immuno-inflammatory diseases like rheumatoid arthritis. The global sales of monoclonal antibodies were $27 billion in 2007 and $33 billion in 2008 (IMS Health data).

1.3. Biosimilars on the market

In the light of the expiration of a number of patents on first generation biologics, EMEA has approved about 13 biosimilars (related to three proteins, six drug products) so far [16]. The first two biosimilars are HGH products, Omnitrope and Valtropin. Five biosimilar epoetins products—Binocrit, Epoetin alfa Hexal, Abseamed, Retacrit and Silapo, have been approved, and six, G-CSF products have received approval from EMEA. They are TevaGrastim, GRASTIM, Filgrastim-Mepha, Grasalva, Ratiograstim, and Biograstim.

1.4. Differences between biosimilars and generic drugs

The differences are clear. Biosimilars are macro biologic molecules; have complicated primary, secondary and tertiary structures; and are expressed in living cells, and generic drugs are the low molecular weight compounds, normally synthesized by chemical reactions.

The living cells that produce biologics can be sensitive to very minor changes in the process of making the biologic. In contrary, a manufacturing process for small-molecule drugs can be altered as long as the finished product is analyzed by laboratory tests to establish that it is the same product.

For small molecules, the bioequivalence of the generic drug is demonstrated through relatively simple analyses such as blood level testing, without the need for further human clinical trials. However, current analytical methods cannot characterize these complex biological molecules sufficiently to confirm structural and functional equivalence with reference molecules; as such, interchangeability of biosimilars to the reference product is questionable [17].

2. Search on biologics as potential biosimilar candidates

Searching biologics can be difficult and time-consuming due to the complex of their biological structures and properties of macro molecules. The key considerations for such searching are:

2.1. The patent owner of a biologic drug tends to file patent applications aggressively to protect the drug. The patent family could be large containing hundreds of patent family members.
For example, a patent family (US5656272) covering Remicade (Infliximab) assigned to the New York University Medical Center and Centocor, Inc. (Johnson & Johnson subsidiary) contains 170 publications, 115 applications, and 79 priorities (INPADOC family). For US filings alone, there are 37 issued patents and 59 published applications. For patent searchers and patent analysts, the challenge is to figure out which patents cover the product and which do not.

2.2. Not only are patents on composition matters important, but patents on production methods or process of making are critical too.