Review Article

EXTENDING PATENT LIFE CYCLE: HOW FORMULATION PATENTS ARE USED TO DELAY THE ENTRY OF BIOSIMILAR PRODUCTS?

Jayanthi Murthy*
IPM Dept., Intas Biopharmaceuticals Ltd, Ahmedabad 382 213, Gujarat, India.
***Corresponding author's E-mail:** jayanthim@intasbiopharma.co.in

Accepted on: 21-08-2011; **Finalized on:** 20-11-2011.

ABSTRACT

Biopharmaceutical companies employ different patent strategies very cleverly to protect their products beyond the molecule patents expiry. Biogeneric players who want to enter into the market with biosimilar products should have to pass through the pool of patents surrounding the drug product. One such strategy is developing the new formulations and protecting the same by filing patent applications. This paper discusses about the way in which the biopharmaceutical companies used this strategy to extend the patent life of the biotech drug beyond the molecule patents expiry.

Keywords: Formulation patents; ever greening; patent life-cycle management.

INTRODUCTION

Biologics include an extensive range of medicinal products for example recombinant therapeutic proteins, peptides, nucleotides, vaccines, hormones, enzymes and antibodies created by biological processes. Biologics can be expressed by recombinant DNA technology and other biotechnological processes or it can also be isolated from microorganisms, animals or human. The cost to develop a new biologics and bring to the market is around hundreds of millions dollars. Patent protection for the basic biologics is generally sought at the infant stage of research and development process. Due to the extensive regulatory assessment period, the patent term has been lost significantly by the time the product enters into the market. One strategy of expanding patent protection and maintaining the exclusivity of the commercially successful product is to obtain additional patents that expand the exclusivity further than the expiry of original patent claiming the biologics per se. Patent life-cycle management is a well-known conception of a big biopharmaceutical companies. Innovator companies have encountered biosimilars by increasing the breadth and complexity of the patent "fence" around their crown jewels by filing patent applications on new formulations. Developing and patenting novel formulations are extensively valuable to the management of patent life cycle which maximizes the profitability of the drugs.

Patent term is limited to 20 years everywhere from the date of filing of the patent application; companies seek patent protection on other inventions which use the same biologic in an improved form. For example, a company may seek patent protection on an improved formulation using known components, including a biologic whose patent may be expiring, which provides quicker absorption into the blood. If this new patented formulation protects the marketed product, the patent protection can be extended from the date of expiration of the patent protecting biologics per se to the date of expiration of the patent covering the improved formulation, usually well after the expiration of the compound patent.

Difficulties in patenting novel or improved formulations

To extend the patent protection on the biologic, the patent claiming the new or improved formulation (second generation patents) must have a later filing date than the original patent to the biologic per se. Thus, the original patent is often prior art to the later filed application. To obtain a patent on new or improved formulation, an applicant must be able to show that the claimed subject matter is new and non-obviousness over earlier patent to biologic per se. In general, fulfilling novelty criteria is not very difficult but applicant must be careful regarding inherent anticipation and the focus should be generally on obviousness. Formulation must be more than conventional use of prior art elements.

How to rebut obviousness rejections?

- By submitting technical support that shows that the formulation claimed in a later patent could not have been envisaged to work.
- By showing that the new formulation has unexpected advantages (e.g., improved stability, efficacy etc.)
- By providing data obtained upon clinical studies are good opportunities for patenting improvements, because in vivo effects are unpredictable.

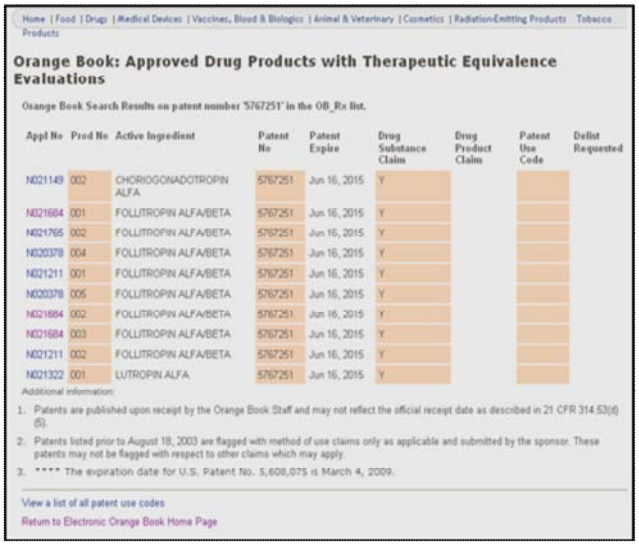
Formulations expand biologics patent protection

Biologics innovators are already applying patent life cycle management strategies to expand patent protection on their blockbuster biologics by seeking patents in new and / or improved formulations. As similar to the pharmaceutical industries, developing and protecting new or improved formulations are most popular strategy to extend the life of patents for biologics also.

EXAMPLE 1

Follitropin Alfa/Beta

Follitropin alfa/beta, is an FDA approved drug indicated for the induction of ovulation and pregnancy in the anovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure. It is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program. Follitropin alpha is produced by recombinant DNA technology. The product has been protected by US patent numbered 5,767,251 (Figure 1) owned by Genzyme Corporation now owned by Serono. The filing date of this patent is Jan. 22, 1993. This patent was granted on Jun. 16, 1998. As Pre-GATT rule applies here and the expiry of this patent is Jun. 16, 2015 (17 years from the date of grant). [7]



Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Orange Book Search Results on patent number '5767251' in the OB_Rx list.

Appl No	Prod No	Active Ingredient	Patent No	Patent Expire	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021149	002	CHORIOGONADOTROPIN ALFA	5767251	Jun 16, 2015	Y			
N021684	001	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N021765	002	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N020378	004	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N021211	001	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N020378	005	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N021684	002	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N021684	003	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N021211	002	FOLLITROPIN ALFA/BETA	5767251	Jun 16, 2015	Y			
N021322	001	LUTROPIN ALFA	5767251	Jun 16, 2015	Y			

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

View a list of all patent use codes

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Figure 1: Patents listed in Orange book for Follitropin Alfa/Beta

Liquid formulation – Gonal F RFF Pen

Gonal-f® RFF Pen is a disposable, prefilled drug delivery system intended for the subcutaneous injection of multiple and variable doses of a liquid formulation of follitropin alfa. Each Gonal-f® RFF Pen is filled with 415 IU (30 mcg), 568 IU (41 mcg), or 1026 IU (75 mcg) follitropin alfa to deliver at least 300 IU (22 mcg) in 0.5 mL, 450 IU (33 mcg) in 0.75 ml, or 900 IU (66 mcg) in 1.5 ml, respectively. Each Pen also contains 60 mg/ml sucrose, 3.0 mg/ml m-cresol, 1.1 mg/ml di-sodium hydrogen phosphate dihydrate, 0.45 mg/ml sodium dihydrogen phosphate monohydrate, 0.1 mg/ml methionine, and 0.1 mg/ml Poloxamer 188. O-phosphoric acid and/or sodium hydroxide may be used for pH adjustment.

For this formulation Ares Trading (now Serono) filed a patent application in Apr. 02, 2004 which was granted in US (US 7,741,268) on Jun. 22, 2010. This patent will expire by Apr. 02, 2024 almost 9 years later than the product patent's expiry. [8]

EXAMPLE 2

Etanercept (Enbrel®)

Etanercept is sold under the trade name of Enbrel, and is an FDA approved drug to treat rheumatoid arthritis, psoriasis, ankylosing spondylities, psoriatic arthritis, and juvenile rheumatoid arthritis. Etanercept is a fusion protein produced through expression of recombinant DNA that treats autoimmune diseases by interfering with the TNF receptor (a part of the immune system) by acting as a TNF inhibitor. The product has been protected by US patent numbered RE 36,755 owned by Immunex Corporation now owned by Wyeth. This patent expires by Mar. 07, 2012 as the term of the patent is extended (Figure 2). [9]

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

(68) PATENT NO. : Re. 36,755
(45) ISSUED : June 27, 2000
(75) INVENTOR : Craig A. Smith, et al.
(73) PATENT OWNER : Immunex Corporation
(95) PRODUCT : ENBREL® (etanercept)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. Re. 36,755 based upon the regulatory review of the product ENBREL® (etanercept) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 230 days

from March 7, 2012, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

Figure 2: Enbrel's Patent Term Extension from USPTO

Liquid formulation of Etanercept (Enbrel®)

ENBREL® single-use prefilled syringes are available in 25 mg (0.51 mL of a 50 mg/mL solution of etanercept) and 50 mg (0.98 mL of a 50 mg/mL solution of etanercept) dosage strengths. ENBREL® single-use prefilled SureClick™ auto injectors are available in 50 mg (0.98 mL of a 50 mg/mL solution of etanercept).

The solution of ENBREL® is clear and colorless, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2. Each ENBREL® prefilled syringe and SureClick™ autoinjector contains a 50 mg/mL solution of etanercept with 1% sucrose, 100 mM sodium chloride, 25mM L-arginine hydrochloride, and 25mM sodium phosphate.

For this formulation Immunex (now Wyeth) filed a patent application on Feb. 27, 2003 which was granted in US (US 7,648,702) on Jan. 19, 2010. This patent will expire by Feb. 27, 2023 almost 11 years later than the product patent's expiry. This formulation patent claims the presently marketed aqueous formulation of ENBREL®. [10]

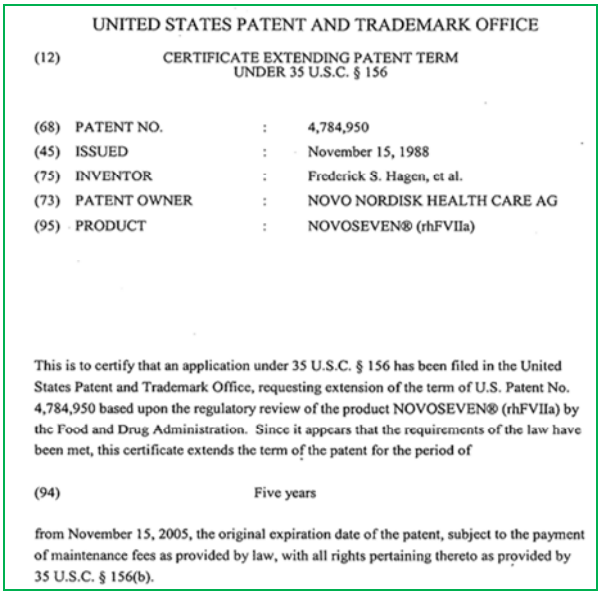
This aqueous formulation increases the sales of ENBREL® in the United States. Lyophilized formulation of ENBREL® is also marketed but the drawback of the lyophilized formulation is it has to reconstitute prior to the

administration to the patients. In view of that, a competitor could be able to develop an alternate formulation of Etanercept, including the lyophilized formulation, and enter into the market prior to the liquid formulation patent's expiry.

EXAMPLE 3

Eptacog Alfa (activated) - NovoSeven®

Eptacog alfa (activated) is sold under the trade name of NovoSeven®, and is an FDA approved drug intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade. It is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues and is structurally similar to human plasma derived Factor VIIa. The product has been protected by US patent numbered US 4,784,950 owned by Zymogenetics Inc., and the patent was expired on 15th Nov. 2010. Fig. 3 shows the extension approved for the said patent.[11]



UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	4,784,950
(45)	ISSUED	:	November 15, 1988
(75)	INVENTOR	:	Frederick S. Hagen, et al.
(73)	PATENT OWNER	:	NOVO NORDISK HEALTH CARE AG
(95)	PRODUCT	:	NOVOSEVEN® (rhFVIIa)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 4,784,950 based upon the regulatory review of the product NOVOSEVEN® (rhFVIIa) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) Five years

from November 15, 2005, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

Figure 3: Novoseven®'s Patent Term Extension from USPTO

Lyophilized formulation of Eptacog Ala (NovoSeven® RT)

NovoSeven® RT is supplied as a white lyophilized powder in single-use vials containing 1mg, 2mg, or 5mg rFVIIa per vial. The diluent for reconstitution of NovoSeven® RT is a 10 mmol solution of L-histidine in water for injection and is supplied as a clear colorless solution and is referred to as the histidine diluent. After reconstitution with the histidine diluent, each vial contains approximately 1mg/ml NovoSeven® RT.

For this approved lyophilized formulation, Novo Nordisk filed a patent application in US (US 2004/0248793 A1) on Jun. 20, 2003. If it will get granted then it will expire by Jun. 20, 2023 almost 13 years later than the product patent's expiry. [12]

NovoSeven® RT accounts for the majority of NovoSeven® RT sales in the United States. Eptacog Alfa (Activated) is also sold as NovoSeven® **-** a lyophilized formulation that is not stable at room temperature.

Liquid formulation of Eptacog Alfa (Activated)

Though liquid formulation of Eptacog alfa activated is currently not available in the market, Novo Nordisk filed a patent application for the liquid formulation also on Jun. 24, 2004 which was granted in US (US 7,790,852) on Sep. 07, 2010. This patent will expire by Jun. 24, 2024 almost 14 years later than the product patent's expiry.[13]

CONCLUSION

Patent life cycle management is the strategic use of patents to maintain product exclusivity and revenue stream over the life of commercially valuable biotherapeutic proteins. Well established biopharmaceutical companies will have fully integrated patent and product life cycle management systems. Biopharmaceutical players should consider streamlined patenting procedure both before and after marketing approval. The exclusivity can be efficiently extended by formulation patents. By careful attention to the filing timings and the content of the patent application patent life-cycle can be managed effectively.

Acknowledgement: I am grateful to Dr. Rustom S. Mody (Executive Vice President – Intas Biopharmaceuticals Ltd., Ahmedabad) for encouraging me to write this publication.

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About Corresponding Author: Ms. Jayanthi Murthy

Jayanthi Murthy is working as an Assistant Manager in Intellectual Property Management Department of Intas Biopharmaceuticals Ltd., She is a registered Patent Agent – India, and completed her Post Graduate Diploma in Patents Law from Nalsar University, Hyderabad and having 6 years of professional experience in biotech industry. She joined IBPL in 2004 and is associated with handling patent related issues of biotech products.