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The Copaxone Story in the U.S. and India

Article By:

Lisa L. Mueller

Teva Pharmaceutical Industries Ltd. ("Teva") markets **Copaxone®** (a 20 milligram daily injection) for the treatment of multiple sclerosis. The active ingredient is copolymer-1, or glatiramer acetate, which is a polypeptide product consisting of four different amino acids (alanine, glutamic acid, lysine and tyrosine). Copolymer-1 is a mixture of individual polymer molecules with different constituent ratios and thus different molecular weights. Annual sales of Copaxone® are approximately US$4.3 billon worldwide and account for more than half of Teva's profit. Copaxone® is very expensive with many patients paying over US$40,000 per year for the drug.

In 2003, Natco Pharma Limited ("Natco") began research to develop a generic version of Copaxone® in order to make a cost effective version of the drug available to patients in India. As a result of its efforts, Natco developed a novel process for producing copolymer-1 and filed patent applications covering its process. Presently, Natco's copolymer-1 product is sold in India under the mark "GLATIMER".

During the past seven years, there has been significant **patent infringement litigation** in both the U.S. and India between Teva and Natco involving Teva's patents covering Copaxone®. Most recently, on February 28, 2014, the High Court of Delhi ("High Court") dismissed Teva's lawsuit seeking an injunction to prevent Natco from exporting its generic version of Copaxone®. In view of the legal actions involving the patents covering this product we at the BRIC Wall Blog thought it would be interesting to trace the evolution of this litigation to see where Teva might go from here.

U.S. and Indian Patents

In the U.S., at least 10 patents cover Copaxone®, specifically, U.S. Patent Numbers 5,800,808 (the "'808 patent"), 5,981,589, 6,048,898 (the "'898 patent"), 6,054,430 (the "'430 patent"), 6,342,476, 6,362,161, 6,620,847, 6,939,539, 7,199,098 and 8,367,605. These patents issued between 1998 and 2013. The expiration date of the '808 patent is September 1, 2015, while the remaining nine patents expire on May 24, 2014. U.S. Patent Numbers 5,981,589 6,054,430, 6,342,476, 6,362,161 6,620,847, 6,939,539 and 7,199,098 were listed in the Orange Book for Copaxone® (collectively, the "Orange Book patents"). All the patents are owned by Yeda Research and Development Co., Ltd. ("Yeda") and exclusively licensed by Teva.

In India, Yeda filed application no. 93/DEL/2003 on May 2, 2003 for the product glatiramer acetate. A

pre-grant opposition was filed by Natco raising issues of inventive step and an objection under Section 3(d) of the Indian Patents Act, 1970 ("the Act"). The application was rejected on March 3, 2009 as (1) obvious and lacking inventive step over the prior art; (2) not constituting an invention within the meaning of Section 2[1(j)] of the Act; and (3) not constituting patentable subject matter within the meaning of Section 3(d) of the Act. Yeda has appealed this decision. Nonetheless, Yeda obtained Indian Patent Number 190759 (the "'759 patent") claiming a process for manufacturing a co-polymer-1 fraction. Claims 1-3 of the '759 patent are reproduced here:

1. A method of manufacturing copolymer-1 fraction (a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1) used in pharmaceuticals, comprising reacting protected copolymer-1 with hydrobromic acid by known methods to form trifluoroacetyl copolymer-1, treating in a manner such as herein described said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying in a manner such as herein described said copolymer-1, to result in copolymer-1 having a molecular weight of 5 to 9 kilodaltons.

2. The method as claimed in claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for 10-50 hours at a temperature of 20-28°C.

3. The method as claimed in claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for 17 hours at a temperature of 26°C.

Mylan's Agreement with Natco

On June 7, 2008, Mylan Pharmaceuticals Inc. ("Mylan") signed a license and supply agreement with Natco for generic copolymer-1 pre-filled syringes. The agreement granted Mylan exclusive distribution rights in the U.S. and all major markets in Europe, Australia, New Zealand, Japan and Canada and included an option to expand into additional territories.

As a result of its agreement with Mylan, Natco developed two different generic copolymer-1 products using two different manufacturing processes. A first copolymer-1 product is made using a first manufacturing process and is sold only within India. A second copolymer-1 product is made using a second manufacturing process that is exported to Mylan.

U.S. Litigation

On December 27, 2007, Sandoz Inc. ("Sandoz") filed the first abbreviated new drug application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and sell its proposed copolymer-1 product before the expiration of the Orange Book patents. On June 29, 2009, Mylan filed its own ANDA. In view of the ANDA submissions, Teva and Yeda separately sued Sandoz (in August 2008) and Mylan and Natco (in October 2009) in the U.S. District Court, Southern District of New York ("U.S. District Court") for infringement of the Orange Book patents as well as U.S. Patent Numbers 5,800,808 ("'808 patent") and 6,048,898 ("'898 patent"). Included among the patent claims asserted were claims 1-3 of the '430 and '898 patents, which are reproduced below.

Claims 1-3 of the '430 patent

1. Copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, prepared by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, andtreating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

2. The copolymer-1 of claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 10-50 hours at a temperature of about 20-28°C.

3. The copolymer-1 of claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26°C.

Claims 1-3 of the '898 patent

1. A method of manufacturing copolymer-1 of a predetermined molecular weight profile, comprising the steps of:

selecting a predetermined molecular weight profile, reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifluoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

2. The method of claim 1, wherein said protected copolymer-1 reacted with hydrobromic acid for about 10-50 hours at a temperature of about 20-28°C.

3. The method of claim 2, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26°C.

The lawsuits were consolidated and on June 29, 2012, the Judge found all nine patents valid, enforceable and infringed. Specifically, the Judge found Mylan had infringed seven of the patents and Sandoz infringed four patents. On July 26, 2013, the Federal Circuit ruled that four of the patents were valid but found five invalid for indefiniteness. Specifically, the Federal Circuit ruled that the claims of the five patents were indefinite because a person skilled in the art could not discern the boundaries of the claims. The patents declared invalid were U.S. Patent Numbers 5,800,808, 5,981,589, 6,048,898, 6,620,847 and 6,939,539. The patents held valid were U.S. Patent Numbers 6,054,430, 6,342,476, 6,362,161 and 7,199,098. The invalidation of the '808 patent was significant because of all the Orange Book patents, it had the longest expiration date (September 1, 2015).

On November 13, 2013, the U.S. Supreme Court denied Teva's request to stay the Federal Circuit's decision during appeal. As a result of the Supreme Court's denial, Sandoz and Mylan can launch

their respective generic versions of Copaxone® in May 2014 (rather than in September 2015).

Litigation in India

2007 Lawsuit

In 2007, Teva and Yeda filed a lawsuit against Natco in the High Court asking for a permanent injunction restraining infringement of the '759 patent as well as for a permanent injunction restraining Natco and its agents from directly or indirectly managing, selling or offering for sale, exporting, marketing, commercializing or registering copolymer-1 under the mark "GLATIMER" or any other mark. Teva and Yeda also asked for an order restraining Natco and its agents from exporting the infringing drugs, formulations or bulk drugs outside India. Additionally, Teva and Yeda sought an accounting of Natco's profits and a decree for damages in the sum of approximately US$41,000.

Natco responded by arguing that its "GLATIMER" product did not infringe the '759 patent. Specifically, Natco argued that the process used to produce its "GLATIMER" product was completely different than the process recited in the claims of the '759 patent. In addition, Natco filed a counterclaim for revocation of the '759 patent. Natco argued that the patent was invalid for several reasons, including lack of novelty and inventive step and because the patent did not meet the criteria of patentability under the Act. The issues were framed in this litigation in May 2012 and a trial is currently in process.

2012 Litigation

On November 3, 2012, Teva ,Yeda and Teva API Limited ("Teva India") filed a second lawsuit against Natco in the High Court seeking a permanent injunction to restrain Natco and its agents from directly or indirectly manufacturing, selling, offering for sale, exporting or registering the product that had been held by the U.S. District Court from infringing the '759 patent. Similar to the first lawsuit, Teva, Yeda and Teva India (collectively referred to as "Teva") sought an accounting of Natco's profits and a decree for damages. Teva argued in the complaint that the U.S. District Court decision lead to the conclusion that Natco was infringing the '759 patent based on the manufacture of copolymer-1 by Natco for export and sale to the U.S. Teva argued that "Natco's act of manufacturing the glatiramer acetate product for sale in the U.S. and elsewhere amounted to a clear infringement of the '759 patent and was, therefore, liable to be restrained by permanent injunction".

Teva argued that the High Court enjoyed jurisdiction to entertain the lawsuit because Natco was involved in a "large number of activities" that occurred in Delhi and targeted customers, consumers, suppliers and hosts of other people for various aspects of their business in Delhi. Examples given included the selling and offering for sale of products though distributors and agents in Delhi, the supply of its products to various hospitals and chemists throughout India as well as a distribution network in almost every city in India.

Natco argued that the process claimed in the '759 patent was not being practiced in Delhi as its manufacturing facilities were based in Hyderabad. Moreover, Natco agued that nowhere in its pleadings had Teva provided any evidence that there had been an infringement of the '759 patent in Delhi.

On February 28, 2014, the High Court found that it lacked jurisdiction and dismissed the lawsuit. The High Court reviewed the two processes used by Natco to manufacture copolymer-1 and noted that the present suit involved the process used by Natco for manufacturing copolymer-1 in India on behalf

of Mylan for sale outside of India (the “Mylan process”) and not the process used by Natco for manufacturing copolymer-1 in India for sale within India.

The High Court stated that the averments in a complaint alleging infringement or apprehended infringement of a process patent have to be precise. Specifically, the High Court stated:

> “…the averments in the plaint in the instant case have to be examined to ascertain if there is any specific plea that there is a violation of the process patent within the jurisdiction of this Court. The Court finds that there is no such specific averment. There is no averment that the process patent i.e. Indian patent No. 190759, or for that matter the ‘Mylan process’ is being practiced/infringed by Natco within the jurisdiction of this Court. This has also to be seen in the context of the fact that there is no denial by the Plaintiffs that there is no manufacture of the GA-second product (the Mylan process) in Delhi. There is also no denial by the Plaintiffs that Natco has at present its manufacturing facilities only in Hyderabad.

Since the suit concerns a process patent, the pleadings as regards the product being sold in Delhi or elsewhere, or the possibility of it being launched in Delhi or elsewhere cannot justify the jurisdiction of this Court. To recapitulate, in para 40 of the plaint it is averred that ‘The US Court decision leads to an incontrovertible conclusion of infringement of rights of Plaintiffs No. 1 and 2 in IN ‘759 based on the manufacture of glatiramer acetate by Defendant No. 2 for export and sale in the United States.’ In para 41 it is stated that Natco’s act of **manufacturing** the glatiramer acetate product ‘for sale in US and elsewhere amounts to infringement of the process patent. The averment is not that such manufacturing of the product for export to the US and elsewhere is happening or is apprehended to happen within Delhi. ***I****n the circumstances, the invocation of Section 48(b) of the Patents Act 1970 by the Plaintiffs to urge that the product obtained as a result of infringement of process is sold or apprehended to be sold in Delhi appears to be misconceived. The fact that Natco may have an office in Delhi or a distributor in Delhi is not relevant given the fact that the subject matter of the suit is a process patent, and the action brought forth is for alleged infringement of that process for the purposes of export to the US and elsewhere.”* (emphasis added).

Where does Teva go from here?

As part of its campaign against generic versions of Copaxone®, Teva published data in January 2014 in PLOS ONE comparing Copaxone® with Natco’s “GLATIMER” product. The data in the article demonstrates significant differences in the biological and immunological effects between the branded drug and Natco’s generic version. However, the research was carried out in mice and not in humans. Despite this, Teva’s President of Global Research and Development and Chief Scientific Officer Dr. Michael Hayden remarked that, “The data from this paper shows the possible significant ramifications of changes in physiochemical properties between Copaxone® and a purported generic GA. This study suggests a distinct potential difference in the impact of a purported generic GA on the immune system of patients, with possible implications on efficacy and safety in RRMS patients. Teva believes the only way to truly understand the impact of these differences is by conducting a full battery of clinical studies.”

Additionally, Teva has developed a new three-times-a-week 40 mg/1 mL dosing regimen. In May 2013, Teva filed a supplemental New Drug Application with the FDA for this new regimen. Additionally, Teva filed for patent protection on the new regimen. So far, two U.S. patents have

issued covering this regimen (U.S. Patent Numbers 8,232,250 and 8,399,413). These patents will expire in 2030. Moreover, a Patent Cooperation Treaty application was filed covering this dosing regimen which was published as WO 2011/022063. The national phase was entered in a number of countries, including Australia, Canada, China, European Union, India, Japan, Korea, Mexico, New Zealand and Taiwan. It will be interesting to watch to see whether Natco develops its own version of this dosing regimen.

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