Humira™ (Adalimumab) Dosage Patents in Opposition Proceedings before the European Patent Office (EPO): Originator and Biosimilar Applicant Strategies

This article picks one biologic product that is currently successfully marketed in Europe by the originator and examines how originator and biosimilar companies use the European Patent system, in particular filing and opposition strategies, in order to delay (or to speed up) the market entry of biosimilars.

AbbVie’s Humira™ (adalimumab) is a human anti-TNF antibody for treating autoimmune diseases. Humira™ was approved by the US Food and Drug Administration (FDA) in December, 2002 and by the European Medicines Agency (EMA) in September, 2003. As of November 2015, Humira™ has worldwide sales of almost 2.5 billion USD.¹ The basic patents on Humira™ expire in the US in 2016 and in Europe (EP) in 2018. A list of companies developing biosimilars of adalimumab can be found in an Generics and Biosimilars Initiative (GaBI) article posted on October 3, 2014.² Potential market entry by biosimilar makers in Europe is almost inevitably preceded by various patent disputes, in particular on the validity side.

² http://www.gabionline.net/Biosimilars/General/Biosimilars-of-adalimumab.
The validity of a patent granted by the European Patent Office (EPO)\(^3\), \textit{i.e.} an "EP-Patent", can be challenged in so-called "Opposition Proceedings." Successful Opposition Proceedings lead to the revocation of the granted EP patent and render the patent null and void for all designated member states. Opposition Proceedings before the EPO are procedurally quite distinct from IPR (Inter Parties Review) and PGR (Post-Grant Review) as available in the US, in particular due to the much longer time frame required to arrive at a final decision in EP proceedings.\(^4\) On the other hand, Opposition Proceedings before the EPO are cost effective in the sense that the focus is on the technical merits of the case, \textit{i.e.} whether a claimed biologic is novel and inventive and whether the information provided in the patent is sufficient for the skilled person to practice the claimed subject-matter over the whole range claimed. Also, opponents can challenge claims that deviate from the originally filed disclosure in the sense that technical information is included that was not clear and unambiguous to the skilled person from the originally filed disclosure. While technical experts are allowed in these proceedings, based on the fact that the members of the EPO Opposition Divisions and Boards of Appeal are predominantly technical experts themselves, expert battles, depositions, or procedural questions are either the exception or play no role at all.

A specific example is taken from the recently concluded Opposition Proceedings regarding a dosage patent based on \textit{AbbVie's Humira}\(^{TM}\). Similar to the strategy employed by pharma originators in the field of small molecules, biologics originators attempt to extend or maximize patent exclusivity of a successful biologic product by protecting specific aspects above and beyond the actual biologic, for example combination products, improved formulations and/or dosages. An exemplary "dosage patent" is \textit{AbbVie's} EP 1 406 656 with claim 1 reading:

\[^3\] The European Patent Office (EPO) and the European Patent Convention (EPC) are based on an intergovernmental treaty and are \textit{not} part of or related to the European Union (EU).

\[^4\] First instance Opposition Proceedings typically take two to three years, second instance Appeal Proceedings another one to three years, or even longer, depending on the technical complexity of the case and the number of parties involved.
A composition comprising the amount of 40 mg of an isolated human anti-TNFα antibody, for use in treating an autoimmune disorder in a human subject, wherein the composition is to be administered subcutaneously to the human subject in need thereof on a biweekly dosing regimen of every 13-15 days, and wherein the human anti-TNFα antibody neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC50 of 1 x 10^{-9} M or less, comprises a light chain variable region (LCVR) comprising a CDR3 domain comprising the amino acid sequence [...]

Apparently, this dosage patent is of particular relevance for the commercialization of the corresponding biosimilar products, since a large number of interested parties have filed an opposition against the grant of this patent. As a specific feature of validity challenges before the EPO, of the 15 opponents, only six parties have revealed their identity (Amgen Inc., Pfizer Inc., AET BioTechnology GmbH, Gedeon Richter Pharma GmbH, Mylan, and Teva Pharmaceutical Industries), while nine "strawman" oppositions are on record.\(^5\) It appears likely that companies that have announced or indicated that they have an adalimumab biosimilar program are behind most, if not all, of these strawman oppositions (e.g. Boehringer Ingelheim, LG Life Sciences, Momenta Pharmaceuticals, Sandoz Switzerland, Samsung Bioepis, Oncobiologics/Viropro).

Opposition Proceedings did commence in October of 2013, and all parties have exchanged their respective arguments. One question of particular importance in this case was the potential anticipation of the patent by the respective clinical studies conducted earlier or in parallel. In that context, the question of whether or not the Opposed Patent can validly claim its priority was of particular importance. All parties, but in particular the Patent Proprietor, have filed a large number of documents in that respect, including a large number of opinions. Not surprisingly, based on the large number of opponents and the thousands of pages of documents filed, Opposition Proceedings did not proceed in an expedited manner. However, by fall of this year, potential summons to Oral Proceedings and therefore a first indication of the Opposition Division’s opinion on material patentability questions were on the horizon. Anticipating a potential negative decision or indication on the merits, patentee has declared on November 4, 2015, that patentee "no longer approves the text in which the patent was granted". In essence, this means that the patentee abandons the patent

\(^5\) In Opposition Proceedings before the EPO, the true identity of the parties of interest does not have to be revealed, i.e. a "strawman" may file the opposition.
effective immediately. According to EPO Boards of Appeal (BoA) case law, under this scenario, the Opposition Division is not allowed to render a written decision on any of the material issues, for example entitlement to priority or relevance of the prior art on record. For the opponents, this "withdrawal" of the Opposed Patent by the patentee may be a victory of limited value, most notably because several divisional applications to the opposed (meanwhile withdrawn) patent are pending. In fact, patent proprietor has explicitly stated that essentially the same subject-matter abandoned for the parent will be pursued in a divisional application.

As illustrated by the *Humira™/AbbVie* case, the strategy of filing a cluster of patents around a certain technology, here the dosage of the blockbuster adalimumab, allows or helps to keep biosimilar competition off the market for a certain time period (even if the dosage patents or other "evergreening" patents may ultimately prove to not be patentable). Companies with adalimumab biosimilar programs have labelled this practice as an "abuse" of the European Patent System. However, under the European Patent Convention (EPC), this practice is perfectly legal. Few or no provisions exist to address potential abusive or anti-competitive behavior, partly due to the fact that the EPC is not a treaty in the framework of the European Union (which has repeatedly stated its political intention to use anti-competitive legal measures against "artificial" exclusion of competition by means of simply delaying proceedings).

In light of the fact that a biosimilar, which is costly to develop and manufacture anyway (as opposed to a generic small molecule compound), may be prevented or delayed from entering the market quite effectively by patents surrounding the originator biologic, an alternative approach chosen by the Swiss firm *Roche* appears to be quite sensible: Rather than developing biosimilars to existing originator biologics, *Roche* develops next generation versions of biologics, such as Rituxan and Avastin.⁶ This strategy not only avoids unnecessary proximity to patents for existing biologics, but also allows for building up patent exclusivity in its own right.

⁶ See last paragraph in article "Biosimilars gain market traction", in Chemical & Engineering News of November 2, 2015, page 29
**In summary:** Opposition Proceedings before the EPO provide a strong and effective instrument to challenge originator patents, in principle. However, the long duration of these proceedings and the lack of measures in the EPC to address potential anti-competitive behavior provide the patentee/originator with an at least equally strong tool to maintain patent exclusivity, for example based on potentially weaker “evergreening” patent(s), reaching beyond the patent term of a basic patent. In the present case, *AbbVie* predicts, potentially based on such a strategy, that despite the loss of patent protection for the basic patents in 2016/2018, biosimilar competition will not appear on the market until at least 2020.⁷

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⁷ *Id.*