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December 22, 2008

Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Ave., NW
Washington, D.C. 20580

Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901

Dear Sir/Madam:

We appreciate the Federal Trade Commission's interest in legislation to provide a mechanism for approval of generic biologic products as well as its sponsorship of the November 21, 2008 Roundtable discussion of the issues surrounding this legislation. We take this opportunity to provide some brief comments on the Roundtable discussion.

First, it is clear that there needs to be a pathway for the approval of biogenerics and that the pathway should include provisions to address patent resolution. As experience with the Hatch-Waxman Amendments demonstrates, the introduction of biogenerics will, without question, benefit consumers and third party payors by bringing lower-priced generic products to market. Biogeneric competition will result in significant cost savings.

Furthermore, biogeneric competition should lead to more competition and innovation in brand biologics, which will also benefit consumers. Dr. Laurence Kolitkoff showed in "Stimulating Innovation in the Biologics Industry" that Hatch-Waxman has actually encouraged brand companies to invest in research and development on new drugs as well as increasing the patenting of new drug inventions. His conclusion makes sense: monopoly protection can foster complacency as firms rely on income streams from monopoly profits rather than investing in new innovation. Generic competition provides an incentive for brand companies to branch out into new drugs, formulations and methods of treatment to obtain additional patent protection.

We disagree with the panelists who suggested that patent resolution need not be included in legislation dealing with biogeneric approval. These panelists argued that there is no such thing as launching at risk for generic companies – that is, there is no risk to generics in launching before a determination of patent validity and/or infringement. But this statement is not accurate.

Launching before certainty of noninfringement or invalidity presents huge financial risks for a generic drug company. The generic product will be priced at a discount to the brand company. Thus, if subjected to damages for the brand company's lost profits, the generic company would almost certainly make less profit on its sales than it would owe in lost profits. Add to that the risk of treble damages for willful infringement as well as the enormous investment required to develop a biogeneric product (by some estimates, 100 times as much as developing a generic small molecule product), and the incentives to bring a biogeneric to market are exceedingly limited.

Second, the Hatch-Waxman model provides a workable model to address the need for, and desirability of, a pathway to biogeneric approval that contains patent resolution provisions. While not perfect, Hatch-Waxman works well to maintain an appropriate balance between innovation and competition. The goal therefore in structuring a biogeneric program should be to maintain as much consistency between biogeneric approval and Hatch-Waxman as possible, to promote certainty in the pharmaceutical market.

We believe an exclusivity period for the first biogeneric applicant, similar to the 180-day exclusivity period in Hatch-Waxman, is an important component to ensure incentives for generic companies to develop these expensive products. We therefore disagree with the panelists who argued that an exclusivity period for the first biogeneric applicant is unwarranted. The 180-day exclusivity period in Hatch-Waxman has proven to provide a substantial incentive for generic drug companies to promptly file ANDAs. Biogenerics are substantially more expensive to develop than small molecule generics and therefore such an incentive is perhaps even more important for biogenerics. While an exclusivity period should be a component of biologics legislation, that period should be relatively brief and commensurate in scope to the 180 days of exclusivity under Hatch-Waxman to foster rapid entry from subsequent biogeneric applicants.

In contrast to Hatch-Waxman, however, we believe three additional patent listing requirements should be added to biogeneric legislation, to cover issues particularly relevant to biologics competition that Hatch-Waxman does not address.

- **Compulsory Listing of Process Patents:** Brand companies should be required to list in the Orange Book process patents, which are not required to be listed for small molecules in Hatch-Waxman. Process patents are more critical for biologic products than for small molecules and are more difficult to circumvent because, among other things, due to the immaturity of the industry there are fewer known processes to make biologics. Therefore, it is crucial for biogeneric legislation to contain a provision for

compulsory listing of process patents to promote patent certainty and thereby provide greater incentive to challenge biologic patents.

This patent listing requirement serves several functions. Among other things: (1) it helps facilitate generic competition by providing early resolution of patent infringement claims before generic launch; (2) it helps generic companies identify which patents apply to which products; and (3) it provides a mechanism for courts to take jurisdiction over patent infringement claims during the FDA approval process, long before the product receives FDA approval.

- **Compulsory Listing of Patent Applications:** Brand companies should also be required to list all pending patent applications relating to biologic drugs, without requiring patent certifications by biogeneric applicants. Patent applications, particularly those filed before the 2000 amendments to the Patent Act are hidden from public view and present a particular problem for biogenerics due to the longer prosecution periods for biologic patents. Requiring brand companies to list their pending patent applications will promote greater patent certainty and permit biogenerics to more accurately assess the risks of developing a biogeneric.

- **Compulsory Listing of Licensed Patents:** Brand companies should be required to list all licensed patents, even those that are not exclusively licensed. As discussed below, many of the broadest biopharmaceutical patents tend to be widely licensed by brand companies. Requiring brand companies to list all of the patents they have licensed on the reference listed drug, regardless of whether or not the licenses are exclusive, will help resolve infringement claims prior to generic launch as well as helping the generic company identify which patents apply to which products.

With these changes to the compulsory listing requirements, a biogeneric approval program similar in scope and provisions to Hatch-Waxman would be ideal.

Third, there is no reason to create additional data exclusivities for holders of biologic patents or NDAs. The current law provides for several incentives to create new biologic products, including patent term restorations under 35 U.S.C. §§ 154(b)(1)(B) and 156. Indeed, biologic patents are more likely to obtain patent term extensions, especially under § 156, due to the long and complex patent prosecutions. It is also worth remembering that biologic brand companies have reaped the benefit of these patent term extensions since the enactment of Hatch-Waxman, even though they have not been subjected to the generic competition provisions of Hatch-Waxman.

No new incentives beyond those under Hatch-Waxman are warranted. In fact, biologics would not be as likely to face generic competition as are manufacturers of small molecules, even with a biogeneric approval process like Hatch-Waxman, because biologic technology is far more complicated and expensive for generic companies to undertake. This additional expense and difficulty could operate as a de facto exclusivity for brand biologic

manufacturers. It bears noting that several panelists opposed to an exclusivity period for the first biogeneric applicant agreed that the additional expense and difficulty of developing a biogeneric would operate to limit biogeneric competition.

Moreover, contrary to the position taken by several panelists, biologic process patents are not narrow, are not necessarily weak and are not necessarily circumvented easily. Due to the immaturity of the biologic industry, biologic patents are more ubiquitous and, in practice, are frequently quite difficult to circumvent. There may be only a single known way to make the product.

In addition, sequence claims frequently do not cover the whole molecule. This is especially true in the case of larger molecules, such as monoclonal antibodies, where often the only sequence claimed is the complementarity determining region (CDR) of the antibody important for binding to the targeted antigen. As Naomi Pearce, IP Director and Counsel, Hospira indicated during the FTC's November 21, 2008 Roundtable (session 3 panel discussion): "For the large antibodies it is simply not correct to suggest that there is a full sequence – this CDR is approximately 12% of the light change of the molecule or 7-9% of the molecule. It is not correct to say that full sequence is being granted here."[1] We believe this summary to be accurate. By claiming only this small yet critical sequence of the antibody, patentees insure themselves of patent protection encompassing **any** antibody or other molecule including the claimed CDR sequence.

It is true that some small biopharmaceutical molecules, such as small proteins or peptides, may be protected by patents with claims directed to full sequences. That said, it is a rare occurrence when the only claim to a small biopharmaceutical molecule is a full sequence claim. For example, Amgen holds multiple patents covering its recombinant erythropoietin (EPO) product, including several with claims to sequences of EPO. A decision by the Federal Circuit Court of Appeals[2] upheld infringement findings on multiple patents against Hoechst Marion Roussell, Inc. on an EPO product, although the Court did limit the claims of one of those patents (US Patent No. 5,621,080) to cover only a 166 amino acid sequence of EPO (and not a 165 amino acid EPO as Amgen had argued), finding that Amgen had amended its claims during prosecution of the patent to limit their scope. And in a recent decision in United States District Court, District of Massachusetts[3], Amgen successful asserted other patents with sequence claims to a 165 amino acid sequence to permanently enjoin Roche from bringing its pegylated-EPO product into the marketplace. Although Roche's pegylated-EPO product was different in both size and performance, Amgen was able to secure a permanent injunction against the Roche product because the Roche product included an EPO sequence encompassed by one the Amgen patents.

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[1] Hospira Response, Page 28 of Session 3 Transcript.
[2] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006).
[3] *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. Oct. 2, 2008) (granting permanent injunction).

Process patents are not the only patents that biologic brand companies can obtain. There are a multitude of other types of patents that provide additional exclusivity protection for biologic products, including platform patents, which are extremely broad and tend to be overlapping, and method of treatment patents. And in the longer term, biologic patents are not likely to be limited to only sequences but will instead likely be much broader and targeted to cover alterations to the original products, similar to small molecule patents today.

Set forth below in Table 1 are just a few well-known examples of platform technology patents covering biopharmaceutical products. These patents are extremely broad and tend to overlap with one another, providing brand biopharmaceuticals with wide-ranging protection over their drug products. These patents are also widely licensed, which provides an additional reason to include compulsory listing requirements for licensed patents.

Table 1: Well-Known Examples of Biopharmaceutical Platform Technology Patents

Patent Number	**Patentee**	**Earliest Priority**	**Patent Expiry**	**Comments**
US 6331415 ("Cabilly II")	Genentech, Inc.	8 Apr. 1983	18 Dec. 2018	The invention relates to processes for producing an immunoglobulin or an immunologically functional immunoglobulin fragment containing at least the variable domains of the immunoglobulin heavy and light chains. This Patent is currently involved in a re-examination proceeding at the USPTO (control no. 90/007859). A final rejection has been issued and an appeal brief has been filed). The Patent is also the subject of litigation in the C.D. Cal. (Centocor v. Genentech, case no. 08-03573).
US 6455275	The Trustees of Columbia University in the City of New York	25 Feb. 1980	24 Sept. 2019	The invention relates to processes for inserting into eucaryotic cells a multiplicity of DNA molecules which includes genes coding for desired proteinaceous materials. This Patent is currently in a combined reissue/reexam proceeding (control no. 90/006953). The USPTO has issued a final rejection, and appeal and reply briefs have been filed.

Patent Number	Patentee	Earliest Priority	Patent Expiry	Comments
US 6407213 ("Carter")	Genentech, Inc.	14 Jun. 1991	18 Jun. 2019	The invention relates to various humanized antibodies and methods of making humanized antibodies. An application for patent term extension under 35 U.S.C. § 156 is currently pending for the '213 patent in connection with Lucentis. The requested term extension is 378 days.
US 5693761 ("Queen")	Protein Design Labs, Inc. (PDL)	28 Dec. 1988	2 Dec. 2014	The invention relates to novel methods for producing, and compositions of humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Licenses have been granted to the following companies/products: Genentech: bevacizumab (AVASTIN), efalizumab (RAPTIVA), omalizumab (XOLAIR), ranibizumab (LUCENTIS) and trastuzumab (HERCEPTIN); Roche: daclizumab (ZENAPAX); MedImmune: palivizumab (SYNAGIS); Wyeth: gemtuzumab ozogamicin (MYLOTARG); Biogen Idec: natalizumab (TYSABRI). Lintuzumab (ZAMYL).
US 6982321 ("Winter")	Medical Research Counsel	27 Mar. 1986	27 May 2020 (includes terminal disclaimer to US 6569430)	The invention related to an altered antibody produced by replacing the complementarity determining regions (CDRs) of a variable region of an immunoglobulin (Ig) with the CDRs from an Ig of different specificity, using recombinant DNA techniques.

In addition, arguments that biologic patents have a shorter patent life after launch of the brand biologic are misplaced. In fact, Dr. Kotlikoff examined these claims and discovered that the development for brand biologics is only about 7.4 months longer than for small molecules. And the additional cost of developing a biologic product is compensated by much higher prices and higher barriers to generic entry due to the additional cost to generic companies as well.

In sum, there is no reason to give biologics products extra data exclusivity protection that is not given to small molecule products. The Hatch-Waxman regime that works well for small molecules and, with minor modifications to the compulsory listing requirements, is likely to work equally as well for biologic products. For these reasons at least, we support sensible legislation modeled after Hatch-Waxman to provide a pathway to approval for biogeneric products.

* * *

Again, we thank the Commission for the opportunity to provide comments on these critical matters that should help to promote greater competition and much lower prices for pharmaceuticals. Should any questions arise, please do not hesitate to contact us at your convenience.

Very truly yours,

James F. Hurst, Esq.
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