

**Federal Trade Commission  
Public Request for Comments: Submission by Hospira, Inc.  
Emerging Health Care Competition and Consumer Issues  
September 30, 2008**

**Regulatory Exclusivities and Follow-On Biologic Drugs**

**1. What is the likely competitive effect of the market entry of a follow-on biologic competitor? Are there empirical models that predict the nature of this competition based on existing biologic drug product competition? How has competition developed between referenced and follow-on products in European markets? Would referenced product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?**

The likely competitive effect of the market entry of a biogeneric is a reduction in the price of the biologic. At this point, it is unclear how much these product prices will be reduced; however, increased competition will certainly result in lower prices. Given the high prices of biologics at present, any price erosion will have a positive effect on consumer and the federal government.

In terms of how competition has developed between referenced and follow-on proteins in European markets, Hospira can use its experience with a biosimilar erythropoietin (EPO) as an example. To date, two biosimilar EPO molecules have been approved under five different marketing authorizations. While the approvals have been for the entire European Union, Germany presents the best case to date as a country experiencing significant competition upon the entrance of biosimilars to the market. This is largely due to the fact that companies have to receive pricing and reimbursement approval in each individual country in the EU, which is a lengthy process. Therefore, the price erosion from a biosimilar erythropoietin in the majority of countries within the EU has yet to be realized.

In Germany, the biosimilar products are starting to make an impact, as IMS data shows that almost 16 percent of first generation EPO sales are attributed to biosimilars (on a dollar basis), and nine percent of total EPO sales (including the second generation products) are attributed to biosimilars. The best estimate is that the biosimilar EPOs appear to be priced approx 25 - 30 percent below the innovator's price prior to the entry of any biosimilar.

That being said, drug pricing in Europe is different than in the United States. While we can learn from their experience, it is important to recognize that they employ price controls that impact the potential competitive effect.

**2. What is the likely impact of a follow-on biologic product being designated “interchangeable” (i.e., receiving an approval that would permit pharmacists, without physician authorization, to fill a prescription for the referenced product with the follow-on product)? What are the prospects for the use of “authorized follow-on biologics” in these circumstances? Do the answers to these questions differ based on the type of biologic product involved?**

Upon receiving a designation of being “interchangeable,” the company marketing the biogeneric should be able to reduce its selling and administrative costs, which would result in greater price competition, benefiting the federal government and the consumer.

If the law allows the potential for an authorized biogeneric, it is likely the innovator company would take advantage of this opportunity, especially if the FDA establishes a process to obtain interchangeability. At this point, the impact of authorized biologics on competition is unclear; however, there could be a potential anti-competitive impact on the market. Hospira is concerned that authorized biologics could serve as a disincentive for some companies to invest in biogeneric development programs, which could reduce the level of competition in the marketplace.

**3. What competitive concerns are raised by joint research and development, supply, licensing, marketing, and distribution agreements between referenced biologic manufacturers and their follow-on biologic competitors? What would be the likely impact of a requirement that agreements between referenced drug product manufacturers and follow-on biologic applicants be filed with the FTC and the Department of Justice Antitrust Division?**

Congress could consider instituting a requirement to file relationships between referenced biologic manufacturers and biogeneric competitors with the FTC and DOJ, as required in the small molecule world by the Medicare Modernization Act of 2003. Beyond that, such relationships should be reviewed on a case-by-case basis, if necessary. Such relationships can be efficient, equitable, pro-competitive and positive for the consumer.

**4. How would the prospect of competition from follow-on biologic drugs influence research and development for new biologic drugs, improvements to existing biologic drugs, and the timing and rollout of new and/or improved biologic drugs? Does the market experience with non-biologic generic pharmaceutical drug products provide insights into these issues?**

In general, competition from biologics should provide an incentive for referenced biologic manufacturers to put more money and effort into innovation.

A recent paper by Dr. Laurence Kotlikoff entitled “Stimulating Innovation in the Biologics Industry: a Balanced Approach to Market Exclusivity” provides a sound rationale why increased competition actually drives more innovation. It also explains how the advent of generics of small molecule medicine was followed by an increase in research and development investment, the number of patents granted and new drug approvals over the past 20+ years. Dr. Kotlikoff further points out that evergreening is not addressed in any of the proposed bills, and that evergreening could allow referenced biologic manufacturers to make minor changes to an existing drug and “restart their monopoly protection clocks.” This type of behavior could lead to less true innovation.

**5. How does the method used by Medicare for reimbursement of biologic drug products affect pricing and competition of referenced biologic products? What factors are important for this effect and why? How would the Medicare reimbursement system likely affect**

**prices for both the referenced and follow-on biologic products? For example, does Medicare reimburse Part B drugs, including biological drugs, based on the Average Sales Price of all the biological drugs whose National Drug Codes (NDCs) reference the same Biologic License Application (BLA)? If so, how would a follow-on biologic drug that does not reference the BLA of the referenced drug affect the Medicare reimbursed price for referenced drug product? How will these and other Medicare reimbursement methodologies likely affect models of price competition after follow-on biologic drug entry?**

Competitive prices for reference biologics and biogenerics are market driven and not driven by Medicare reimbursement. As the market prices for these products are lowered, the Medicare reimbursement that is tied to the product's market price will be lowered also. Medicare will pay or reimburse less for biogenerics that are deemed interchangeable and substitutable with the reference product as small molecule generics are deemed by the FDA today. The greatest savings or price decreases are driven in the small molecule market place by competition between the "like" innovator and generic products. With increased competition, prices go down Medicare reimburses less and experiences greater savings. The key to obtaining the greatest savings under Medicare will be the ability to substitute biogenerics with innovator biologics and drive price reductions through competition. If a biogeneric does not reference the BLA of the reference drug, Medicare will need to follow the FDA's guidance in order to determine where to place the product for reimbursement purposes within the Medicare HCPCS coding system. Medicare may need to expand their HCPCS coding system to allow for "comparable" follow-on generic biologics versus traditional "substitutable" or "interchangeable" biogenerics.

**6. How are the patent portfolios claiming biologic drugs similar or dissimilar to the patent portfolios that claim small molecule (nonbiologic) drugs approved under the federal Food, Drug, and Cosmetic Act (FDCA)?**

Patent portfolios for biologic drugs are similar to portfolios for small molecule drugs in that they provide the same level of intellectual property protection: a valid patent will create a patent monopoly for 20 years plus the period of any patent term extension. Typical small molecule and biologic drug patent portfolios include compound patents, process patents, formulation patents, platform technology patents, and method of treatment patents.

However, patent portfolios for biologic drugs differ from portfolios for small molecule drugs in the following respects:

- (a) The immaturity of the global biopharmaceutical industry means that there are a significantly greater number of patents relating to a typical biologic drug than there are for a typical small molecule drug.
- (b) Because of the plethora of relevant "platform technologies" in the immature biopharmaceutical industry, this often results in a significantly greater number of interested patentees.

- (c) The immaturity of the US biopharmaceutical industry has resulted in greater uncertainty regarding the validity and scope of US patents regarding biologic drugs (as compared with patents regarding small molecule drugs) due to:
  - (i) the breadth of patent claims granted for inventions in complex technology clusters such as those in the biopharmaceutical fields; and
  - (ii) the relative lack of guidance from the courts on biotech-related patents as compared with the substantial jurisprudence available for small molecule drug-related patents.

If implemented for biologic drugs, a Hatch-Waxman-like system would help to facilitate competition as it would force patentees to identify the patents which apply to products.

- (d) Biopharmaceutical technologies are more complex than chemical technologies, and therefore patents regarding biologic drugs are more complex than patents regarding small molecule drugs.
- (e) Process patents are of significantly greater importance for biologic drugs products than for small molecules.

Due to the maturity of the pharmaceutical industry, process patents regarding small molecule drugs are almost always circumventable as there are routinely multiple ways to manufacture a particular chemical compound. However, this is not the case for biopharmaceutical process patents, which are difficult to circumvent. This means that process patents will be significantly more important in patent litigation regarding biologic drugs than small molecule drugs.

Hatch-Waxman does not permit innovators to “list” relevant process patents in the Orange Book. As discussed further below, Hospira supports the application of a Hatch-Waxman-like system to biologic drugs. However, due to the criticality of process patents for biologic drugs, the advantages of a Hatch-Waxman-like system will be compromised in the absence of a compulsory listing requirement for process patents. Hospira believes the competitive advantages of such a system (including facilitating competition by enabling pre-launch patent certainty) will be reduced or eliminated for many biologic drugs if process patents are not included in the compulsory listing requirements. Because of the differences in the criticality of process patents to small molecule drugs and biologic drugs, Hospira does not consider it necessary to require the compulsory listing of process patents for small molecules and believes it is appropriate to distinguish between small molecule drugs and biologic drugs in this way.

- (f) Biopharmaceutical patents are more likely than small-molecule related patents to have significant patent term extensions/restorations under 35 USC 154(b) because these patents often claim awkward and complex subject matter, resulting in continuations or long prosecutions at the USPTO.
- (g) There is a significantly greater proportion of “submarine” patents regarding biopharmaceutical products than small molecule products.

“Submarine” patents include:

- (i) patents issuing from applications filed before the 1995 GATT amendments to the Patent Act (ie filed before 8 June 1995), where the applications were not published after 18 months from the priority date; and
- (ii) patents issuing from applications filed after the 1995 GATT amendments to the Patent Act, but before the 2000 amendments to the Patent Act (ie filed after 8 June 1995 but before November 2000) which (in certain circumstances) will not be published after 18 months from the priority date.

Submarine patents in (i) above have a term of “17 years from grant” rather than “20 years from filing” (as is the case now, and as is the case for (ii) above). As a result, some submarine patents granted now will result in a patent monopoly for very old technology extending far beyond what would otherwise be granted. For example, a “submarine patent” granted 30 September 2008 resulting from an application filed 7 June 1995 would expire on 30 September 2025. However, a patent granted 30 September 2008 resulting from an application filed 8 June 1995 would expire on 8 June 2015.

Submarine patents are often the result of claiming awkward and often complex subject matter, resulting in long prosecutions at the USPTO arising from complex claims and appeals. Because the complex subject matter of biologic inventions often leads to long prosecution lengths for biologic patents, there are a greater proportion of submarine applications and patents regarding biologic drugs than small molecule drugs.

As submarine patents in (i) above are not required to be published until grant, and those in (ii) above will not be published until grant in certain circumstances, the existence of a submarine patent application may not be public knowledge unless and until a patent issues from that application. It is then impossible for biogeneric applicants to determine whether or not a submarine patent application exists unless and until the patent grants. It is common for submarine patents to grant years after the innovator launches the biologic drug in the US.

This has a significant impact on competition as:

- Innovator companies with submarine patents have less incentive to innovate due to the longer patent monopoly provided by such patents; and
- It is impossible for a biogeneric company to quantify the patent related risk relating to the launch of a biogeneric, which acts as a strong disincentive to launching a biogeneric.

In order to encourage competition for biogeneric drugs, which are more costly to develop than generic drugs, Hospira believes it is critical that compulsory patent listing requirements include the requirement for innovator companies to give notice of all pending “submarine” applications relating to biologic drugs. However, related Hatch-Waxman initiatives such as “paragraph IV” certifications and ANDA-like proceedings could not apply to submarine applications, as they are not yet granted, and therefore cannot be enforced.

**7. Are the regulatory exclusivities currently provided to pharmaceutical drug products in the FDCA appropriate for new biologic drugs and/or significant improvements to existing biologic products? Are they appropriate for specific types of biologics? Why or why not?**

Hospira believes that the Hatch-Waxman Act fairly addresses the issues of patent term restoration and data exclusivity for all pharmaceutical products, including biologics. The patent term restoration and data exclusivity provisions have provided adequate incentives for continued innovation in the pharmaceutical field, as is evident from the number of new drug products launched in the United States since enactment of Hatch-Waxman. There is no compelling argument or reason to believe that the same incentives will not adequately motivate future innovations in the biologic pharmaceutical field.

**8. What are the appropriate factors to consider when determining the optimal length of regulatory exclusivity periods for biologic drug products? Do these factors change based on the type of referenced product involved, the extent of competition facing the referenced product, or patent portfolios claiming the referenced product, and if so, how?**

Again, there is no basis for providing different periods of data exclusivity to drugs and biologics. Data exclusivity is awarded in order to protect the investment underlying the clinical data generated by the owner of the reference product. .

Factors to consider in assessing exclusivity include (i) time to develop a drug, (ii) cost to develop a drug and the commensurate returns generated, and (iii) impact on innovation, among other things. Dr. Laurence Kotlikoff, in his paper entitled “Stimulating Innovation in the Biologics Industry: a Balanced Approach to Market Exclusivity,” examines these factors and how biologics differ from traditional pharmaceuticals. In his paper he notes that, on average, the development timeline for biologics is only 7.4 months longer than that for traditional pharmaceuticals. He further notes that the cost to develop a biologic is expensive (\$1.24 billion), but cost alone should not be a determining factor. Rather one needs to look at cost relative to reward. On average, biologics are priced 22 times more than that of traditional pharmaceuticals. Lastly, Dr. Kotlikoff notes that increasing exclusivity actually would reduce innovation. As noted in the answer to question four, shortly after the approval of the Hatch Waxman bill, research and development spending for pharmaceutical companies increased, the number of patents increased and the number of drug approvals increased.

**9. How does the European Medicines Agency’s approach to regulatory exclusivities in its abbreviated regulatory approval pathway for follow-on biologics inform the U.S. approach?**

The European Medicines Agency (EMA) did not create new regulatory exclusivity provisions for biogenerics. When biogenerics were introduced in Europe, the EMA applied the same regulatory exclusivity provisions to both small molecules pharmaceuticals and biologics. In our view, the US should follow the EMA’s lead and adopt the same regulatory exclusivity provisions for both small molecule pharmaceuticals and biologics. There should be one consistent standard for all products.

**10. Is a marketing exclusivity period necessary to encourage companies to develop follow-on biologics and to seek their approval by the FDA? If so, why, and how should such an exclusivity period be structured?**

A short period of exclusivity for the first to market could provide an incentive to companies entering the biogenerics market; however, companies will not likely rely on winning exclusivity to invest in the products because the development time and investment for biogenerics is so great. A long exclusivity period would not make sense because it could act as a disincentive for some companies to make the investment for fear of not being the first to market.

**Patent Dispute Resolution Issues**

**1. Would it be important to have the litigation of any patent disputes proceed concurrently with the abbreviated FDA approval process for follow-on biologics? Why or why not? What has been learned from the experience under Hatch-Waxman about the incentives necessary to encourage early resolution of patent issues?**

Yes, it is very important that litigation of patent disputes proceed concurrently with the abbreviated FDA approval process for biogenerics. If this does not occur, the launch of the biogeneric is “at risk” of an injunction and damages. Due to the greater uncertainty surrounding the valid scope of patents and the lack of jurisprudence resulting from an immature biopharmaceutical industry as compared to a small molecule drug (as described above), this will operate as a significant disincentive to launch of a biogeneric and will thus operate as a disincentive to competition.

Hospira believes the application of a Hatch-Waxman-like system to biologic drugs would be an appropriate mechanism to encourage early resolution of patent issues for biologic drugs if (as noted above) the system included listing and certification requirements regarding process patents, and listing requirements regarding submarine patent applications.

**2. How long might the approval process for a follow-on biologic application take? What factors might influence this timing?**

The FDA approval process for a biogeneric should be similar to the proprietary small molecule approvals because most of the proposed legislation includes a user fee, which would provide the FDA with the resources necessary to review these applications. There are other factors to consider, however, including litigation and the associated “stay” period, which could prolong the application process. Additionally, if Congress mandates FDA to issue guidance documents prior to approving a product, the approval time for biogenerics could be considerably delayed.

**3. How might differences between patent portfolios for small molecule drugs and biologics affect patent litigation involving follow-on biologics? How long might patent litigation involving a follow-on biologic product take?**

Hospira is not aware of any differences between patent portfolios for small molecule drugs and biologics that might affect patent litigation involving biogenerics. As such, litigation times involving biologics and small molecules should be similar.

Hospira believes a 30 month stay on the regulatory approval of a biogeneric application would be an appropriate length of time to allow conclusion of biogeneric-related patent litigation if a Hatch-Waxman- like system is introduced for biologic drugs.

**4. When is it in the interest of a referenced biologic drug manufacturer to resolve patent issues prior to marketing by a follow-on applicant? When is it in the interest of a follow-on biologic applicant to resolve patent issues prior to marketing its follow-on biologic? When is it in the interest of either party to resolve patent issues following commercial marketing of the follow-on product?**

A referenced biologic manufacturer (as patentee/licensee) has no incentive to resolve patent issues prior to marketing by a biogeneric applicant. The referenced biologic manufacturer is motivated to delay the resolution of patent disputes and therefore prolong its monopoly in the marketplace. Generic competition erodes the referenced biologic manufacturer's market share and so it is motivated to delay any patent resolution.

It is always in the interest of the biogeneric applicant to resolve patent issues prior to marketing its biogeneric. By doing so the biogeneric applicant removes the risk of a possible injunction and removes the risk of both traditional and enhanced damages under 35 U.S.C. § 284.

Removing the risk of an injunction and damages facilitates greater certainty regarding the biogeneric applicant's launch strategies and enables competition in the market.

As discussed above, the application of a Hatch-Waxman-like system to biologic drugs would similarly facilitate competition in the biopharmaceutical industry.

**5. What are the legal impediments facing a follow-on biologic applicant that has not been sued for infringement to obtaining a declaratory judgment on patent infringement or invalidity issues prior to commercial marketing of its follow-on product?**

The scope of declaratory judgment jurisdiction in the context of patent litigation (for small molecule related patents and biologic drug related patents) is neither well-defined nor tested, especially in the absence of an overt threat of litigation by a third-party. Many legal uncertainties remain.

Hospira wishes to emphasize the importance of an effective and reliable mechanism for litigating unasserted brand patents in the biogeneric context. Biogeneric companies will have less incentive to expend significant resources to develop biogenics absent a procedural mechanism sufficient to ensure biogeneric companies can obtain patent certainty pre launch. At a minimum, this procedural mechanism should include an Orange Book-type process and declaratory judgment provisions similar to those in the current Hatch-Waxman provisions.

**6. Are regulatory exclusivities needed to encourage follow-on biologic applicants to challenge patents? Why or why not?**

As stated above, a short period of exclusivity for the first to market could provide an incentive to companies entering the biogenics market; however, companies will not likely rely on winning



exclusivity to invest in the products because the development time and investment for biogenerics is so great. A long exclusivity period would not make sense because it could act as a disincentive for some companies to make the investment for fear of not being the first to market.

**7. What opportunities will biologic drug manufacturers and follow-on applicants have to manipulate proposed new regulatory obligations (e.g., application notification obligations, declarations of patents claiming biologic drugs, etc.) and exclusivity periods surrounding a concurrent patent resolution process? What are the prospects for the improper use of citizen petitions to delay approval of follow-on biologic applications?**

The proposed regulations will delay the initiation of patent infringement actions by requiring the parties to undertake iterative communications for the purpose of determining which patents will be asserted in litigation. This iterative process will likely delay the start of litigation by more than six months. By delaying the initiation of patent infringement litigation, there is an increased likelihood that market entry will be delayed. Further, the iterative process amounts to a very slow game of chess. Hospira advocates the use of an Orange Book-like system for biogeneric applications.

Citizen's petitions (CPs) have proven to be a useful tool in delaying approval of generic applications in the small molecule context. Hospira believes that CPs are likely to be a frequently used tool for innovators seeking to delay approval of biogeneric products. In Hospira's view, genuine and supported safety concerns should be the only reason to delay biogeneric approval. In testimony before Congress in 2006, the FDA acknowledged that "a high percentage of the petitions" reviewed by the Office of Generic Drugs are denied. FDA explained that "very few of these petitions on generic drug matters have presented data or analysis that significantly altered FDA's policies." Between 2001 and 2005, the FDA issued 42 responses to citizen petition, denying 33 entirely, denying three in part, and granting six. See Statement of Gary Buehler, RPH, Director of the Office of Generic Drugs, before the Special Committee on Aging of the United States Senate (July 20, 2006). The FTC in 2000 submitted comments to the FDA regarding a proposed rule aimed at improving the citizen petition mechanism stating that, with regard to pharmaceutical companies filing citizen petitions (either through its own action or that of a proxy), "[t]he effect of such a petition could be to delay FDA approval of a rival drug application, even if the petition is not ultimately upheld." See <http://www.ftc.gov/opa/2000/03/fdacitpet.shtm>. Hospira shares the FTC's concerns, and encourages the FTC to monitor anti-competitive CPs and take action as necessary.

There are new regulations (section 914 of the FDAAA) directed to preventing the delays to generic approvals caused by citizens petitions. The FDA is prohibited from "delaying" the approval of an ANDA or a 505(b)(2) NDA unless the request is made in the form of a citizen petition and FDA determines that "a delay is necessary to protect the public health" (section 505(q)(1)(A)). While it is apparent these amendments might be of limited usefulness as there is mandatory timeline by which the FDA must determine that a delay is necessary, these provisions are a start to reducing the impact of purely strategic CP filing. At a minimum these new regulations should be extended to apply to any biogeneric application.

**8. How might referenced biologic product manufacturers and follow-on biologic applicants structure patent settlement agreements given the competitive dynamics arising from the marketing of follow-on biologic drugs? What incentives might exist for these companies to enter anticompetitive settlements? Should patent settlement agreements be filed with the antitrust agencies? What would be the likely effect of the filing requirement on settlements?**

Having a broad range of settlement options, is critical to resolving any litigation, but is particularly important in complex patent cases and few patent cases will be more complex than those involving brand and generic biologic pharmaceuticals. Litigation regarding biologic drugs consumes tremendous amounts of judicial resources. As discussed above, due to immaturity of biologics patent related jurisprudence, the complex and uncertain patent landscape for biologics drugs results in significant uncertainty in the marketplace, delaying competitive decisions for long periods of time as parties and the market await judicial determination of patent status.

In the case of patent litigation regarding biologics drugs, settlements may be, and frequently are, more efficient, equitable and pro-competitive than prolonged litigation.

Finally, the 2003 MMA amendments to Hatch-Waxman require participants in certain agreements to submit them to FTC and DOJ for review. Brand and generic companies thus know that settlement agreements will be subject to extensive antitrust review. Bringing agreements involving follow-on biologics under the same reporting requirements would provide FTC and DOJ with the opportunity to conduct similar reviews of these agreements, and ensure that parties to such agreements are circumspect about the anti-trust implications of their settlements.