

December 22, 2008

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

[Submitted at <http://secure.commentworks.com/ftc-healthcarecompetition>]

Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901
(Competition Issues Involving Follow-on Biologic Drugs)

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to submit supplemental comments to the Federal Trade Commission (FTC) regarding follow-on biologics (FOBs) competition issues. BIO submitted initial comments on September 30, 2008, and we were also very appreciative of the opportunity for two BIO staff members to participate in the November 21 Roundtable on Competition Issues Involving Follow-On Biologic Drugs. We are submitting these supplemental comments in response to comments and statements of other stakeholders, raised in written comments as well as at the November 21 meeting.

Specifically, BIO would like to emphasize:

- Any assumptions regarding the broad interchangeability of FOBs in the foreseeable future are not science-based;
- Interchangeability will not necessarily provide greater economic benefit from FOB market entry;
- The fledgling nature of the biotechnology industry makes it particularly susceptible to disincentives for investment;
- Because FOBs will not have to comply with rigorous “sameness” standards for traditional pharmaceutical generics, biologics patent portfolios will not provide the same level of certainty for innovators and investors as patents do for traditional pharmaceuticals against premature generic entry;



- A data exclusivity period of 14 years is necessary to maintain effective market protection for innovator biologics, and thus sufficient incentives for innovation; and
- Incentives for continued development of next-generation products are important for advancement of medical treatment and would not prevent FOB market entry.

These issues are discussed below.

Substitutability/Interchangeability

As we noted in our comments of September 30, 2008 (p. 4), it is BIO's position that patients and their physicians should decide the proper course of treatment, including which biologic to take. No two biologics are identical and some differences could have clinical implications that are not known at the time of approval. If a patient experiences an adverse event, it will be essential that the physician know specifically which product the patient received, to adequately provide care to that patient, as well as for the purpose of tracking adverse events that could affect other patients. Accordingly, we have urged Congress to ensure that patients are given only the biologic expressly prescribed by a physician. We note here that in October 2008 the American Medical Association (AMA) passed a resolution that is consistent with our position. The resolution commits AMA to "work with the US Food and Drug Administration and other scientific and clinical organizations to ensure that any legislation that establishes an approval pathway for follow-on biological products prohibits the automatic substitution of biosimilar medicines without the consent of the patient's treating physician" (AMA Resolution 918 (I-08)).

In our prior comments, we also cautioned that the term "interchangeability" is not defined by FDA and has no settled legal or regulatory meaning at this time. We noted that some use this word to describe products that are not "therapeutically equivalent" and that do not have the same or even similar active ingredients, but which are "interchangeable" in the sense that, under a physician's supervision, they could be used to treat the same disease or condition in the same patient. It has come to our attention, however, that some parties are using this ambiguity to claim that some biologics already approved under the Public Health Service Act are "interchangeable" without physician knowledge/consent. We find this statement extremely misleading, and are not aware of any biologics that have been designated as "interchangeable" to the extent that term is meant to imply substitutability without physician knowledge/consent.

In our September 30 comments, we also noted that the European Medicines Evaluation Agency (EMA) and certain member states of the European Union (EU) have recognized the fundamental differences between drugs and biologics with respect to substitutability. To supplement that statement, the table below provides more information regarding the positions of specific EU member states.

EU Countries Forbidding Substitution

Country	Ruling
Austria	Physicians obliged to prescribe by brand name
Czech Republic	Physicians obliged to prescribe by brand name
Denmark	Guidelines against substitution
Finland	No injectable drug may be substituted
France	Automatic substitution prohibited without consent of physician
Germany	No automatic substitution
Greece	Physicians obliged to prescribe by brand name
Hungary	No automatic substitution
Italy	No automatic substitution
The Netherlands	No automatic substitution
Norway	No automatic substitution
Slovakia	Official list stating which products cannot be substituted
Slovenia	No automatic substitution
Spain	No automatic substitution
Sweden	No automatic substitution
UK	No automatic substitution

Source: Hogan & Hartson, Morgan Stanley Research (as published in the Morgan Stanley Report "Follow-On Biologics: Expect a Slow Start", November 24, 2008, p. 2)

Further, BIO notes that officials in the United Kingdom have said, "When prescribing biological products, it is good practice to use the brand name. This will ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist."¹ In France, officials have said, "a systematic and uncontrolled substitution, based on the prescription of the international common denomination of the active substance, does not appear reasonable at this time," and "... physicians should be involved in decisions to substitute any BMP [biological medicinal product]."²

In our view, there is no realistic potential for scientifically-valid determinations of interchangeability at this time. Furthermore, even if interchangeability were possible, a finding by the Food and Drug Administration (FDA) of interchangeability does not necessarily imply that savings to consumers will be higher, as some participants in the Roundtable have argued. The degree of competition and potential cost savings arising from a follow-on biologics approval

¹ MHRA Drug Safety Update: Volume 1, Issue 7, February 2008: Available at <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2033917>.

² Pavlovic et al; Similar Biological Medicinal Products Containing Recombinant Human Growth Hormone: European Regulation; Hormone Research; 2008; 69; 14-21.

pathway is likely to be heavily dependent on numerous factors beyond the question of interchangeability, including number of market entrants, product quality, cost of production, price discounting, market penetration, potential market size for any given product, etc. Indeed, a finding of interchangeability may in fact lead to lower savings to consumers, depending on its impact on these other critical factors. BIO therefore believes it would be imprudent for the FTC to rely on erroneous scientific and economic assumptions – *i.e.*, that interchangeability is likely and would necessarily lead to greater cost savings – in crafting any public policy recommendations relating to a FOBs regime.

Patent Dispute Resolution

BIO notes that there appears to be a relatively high degree of consensus among participating stakeholders regarding the need for patent certainty at FOB launch. We would like to reemphasize that pre-approval patent resolution paired with adequate data exclusivity is even more essential in the biotech context than it was in the small molecule setting. Innovative biologics will face the increased business risk inherent in abbreviated FOB approval under a more liberal and more uncertain “similarity” standard, under which biologics patents could potentially be designed-around more easily than is the case for generic small molecule drugs today that are subject to a standard of sameness. In the absence of a pre-approval patent resolution pathway, a regulatory framework that routinely contemplates FOB launches before patent resolution would introduce yet additional uncertainty into the biologics business model because it would be impossible for innovators to predict, or even guess, which kind of remedy would be available to them even for patents that cannot be designed-around. This uncertainty will harm investment incentives in an industry that already is reeling from the financial and credit crises, and is already fraught with extremely high investment risk to investors. This uncertainty would also affect health care providers, payers and other market participants, and present an unacceptable risk of therapeutic disruption for patients and caregivers.

As became apparent during the Roundtable, a pre-approval patent resolution pathway presupposes innovator data exclusivity of sufficient length. The process should be timed so that it can be brought to conclusion prior to expiration of adequate innovator data exclusivity, *i.e.*, before the date on which the FOB product could receive marketing approval by the FDA. Accordingly, the appropriate time at which patent dispute resolution should commence should be set early enough during the innovator’s data exclusivity to allow for full district court litigation at least.³ This process should be initiated by a notification and information exchange process

³ BIO also notes the availability of *ex parte* and *inter partes* reexamination proceedings in the USPTO, under which FOB applicants could challenge the validity of problematic patents even earlier. Reexamination proceedings may not be suitable for every patent that poses a freedom-to-commercialize obstacle, but in situations where they can be effectively used they have been found to result in narrowing or cancellation of claims in many cases (see: Dennis Crouch, *Ex Parte Reexamination Statistics II*, available at <http://www.patentlyo.com/patent/2008/06/ex-parte-reexam.html>; and Andrew S. Baluch and Stephen B. Maebius, *The Surprising Efficacy of Inter Partes Reexaminations*, available at <http://www.patentlyo.com/patent/law/baluchmaebius.pdf>).

between applicants, reference product sponsors and patent owners that could be adapted from the confidential ANDA access provisions that have been implemented for small molecule generics under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. In the event of a final district court decision of validity and infringement, the statute should provide that FOB approval would not be made effective until patent expiration.

Fourteen Years of Data Exclusivity

Biotechnology companies must have some certainty that they can protect their investment in the development of new breakthrough therapies for a substantial period of time in order to secure the necessary resources from venture capital firms and other funding sources. Under the Hatch-Waxman regime, that protection comes largely from the patent system (including patent term restoration), due to the requirement that the generic product have the “same” active ingredient as the innovator. However, due to the very nature of a FOBs pathway, the patent system may not provide innovator biologics with as effective protection against follow-on manufacturers prematurely entering the market. As noted above, the uncertain “similarity” standard for approval of FOBs creates a greater potential for biologic patents to be designed around, particularly given some of the available case law involving the scope of biologic patents.

For example, Genentech was sued by Hormone Research Foundation over its recombinant human growth hormone product. The accused product differed by only two amino acids from the claimed product, but the U.S. Court of Appeals for the Federal Circuit (CAFC) nevertheless reversed the summary judgment of infringement because it construed the patent as not covering Genentech's growth hormone product. *Hormone Res. Found. v. Genentech*, 904 F.2d 1558 (Fed. Cir. 1990). Notably, in that case the court rejected the argument by the patent owner that the claims should be construed to also cover sequences “similar” to the claimed one, holding that Genentech's product would have to be “identical,” not merely “similar,” in order for the accused product to infringe.

Similarly, in *Amgen v. Hoechst Marion Roussel*, 314 F.3d 1313 (Fed. Cir. 2003), Amgen had claimed a mature erythropoietin amino acid sequence of 166 amino acids – TKT’s accused product had 165. The court, applying a narrow claim construction, found that Amgen’s claim was not literally infringed. Amgen then attempted to mount a case of infringement under the doctrine of equivalents – something it could not successfully do since that doctrine had, in the interim, been severely constrained by the Supreme Court’s *Festo* decision (see the subsequent CAFC opinion after remand and another appeal: 457 F.3d 1293).

In *Genzyme v. TKT*, 346 F.3d 1094 (Fed. Cir. 2003), Genzyme sued TKT for infringement of its patents claiming cells with “chromosomally integrated” alpha-galactosidase genes that are stably over-expressed by controlling regulatory sequences. TKT, the accused infringer, did not introduce an exogenous alpha-galactosidase gene in its cells, but introduced an exogenous promoter to drive over-expression of the cells’ endogenous gene. Genzyme argued that

“chromosomally integrated” means just that: “on the chromosome,” and it should not matter whether the overexpressed alpha galctosidase gene is the cell’s own or one that was introduced. The court adopted a more narrow construction and held that TKT’s cells were not covered by the patent, and that literal infringement had not been shown.

Such past experience with biotechnology patent litigation indicates that litigation under a FOBs regime may be more uncertain than in the ANDA context, because it will, to a greater degree, involve complicated litigation over both literal infringement and infringement under the doctrine of equivalents. Because claim construction issues are so much more prevalent in biotechnology patent litigation, biotechnology innovators face an increased risk that accused products can be extremely close to both the narrowly-construed claim and the reference product and still not be covered by the patent. This patent uncertainty, combined with the inherent uncertainty of a “similarity”-based FOBs regime, could severely impact biotechnology investment.

In order to provide sufficient certainty and thus continued incentives for biomedical innovation, any statutory pathway for FOBs therefore must include a substantial period of data exclusivity. And for biologics to receive the same length of effective market protection as small molecule drugs receive under the Hatch-Waxman Act, the period of data exclusivity in any FOBs framework must be 14 years following marketing approval.

There are several data points that support the need for 14 years. In 1984, Congress enacted patent term restoration provisions to provide pharmaceuticals with up to 14 years of patent protection following marketing approval. This time period was selected so that "research intensive companies will have the necessary incentive to increase their research and development activities." H.R. Rep. No. 98-857, at 41 (1984). As a result, the average period of time for marketing a drug product with patent protection now is 11.5 years, and new drugs are, on average, marketed in the U.S. for 13.5 years before the entry of generic competition. These data points demonstrate that, while 14 years is a maximum period for patent term restoration, the Hatch-Waxman system has come remarkably close on average to achieving that desired degree of protection for small molecule products. Accordingly, any FOBs pathway should at least guarantee that same degree of effective market protection for biologics, and for the reasons discussed above, such protection is most effectively provided through data exclusivity. Anything less could skew investment away from biologics research and development, which is at the cutting-edge of health care innovation in therapeutics areas such as cancer, HIV/AIDS, Alzheimer’s, Parkinson’s, diabetes, and many other life-threatening diseases.

Further, a forthcoming paper by Bennett, Golec and Vernon shows that the economic breakeven point for biologics research and development is at least 17 years,^[1] consistent with other analyses referenced by BIO in our earlier comments. Some have argued that, because of the likelihood that FOB entry in the future will have less economic impact on innovators than generic entry

^[1] Bennett, Alan, Joseph Golec, and John Vernon, 2008, Exploration of Potential Economics of Follow-on Biologics and Implications for Data Exclusivity Periods for Innovators, University of North Carolina draft working paper.

does today, the length of data exclusivity for biologic innovators can be reduced accordingly. However, the return-on-investment analyses noted in our comments do not assume *any* FOB entry. As Professor Grabowski stated at the FTC hearing, "...when we look at seven- and ten-year exclusivity periods with the CBO assumptions [on FOB entry], we never get convergence [of breakeven return on investment] for 50 years." These facts reinforce our belief that an insufficient data exclusivity period will create significant uncertainty among biotech investors as to whether they will be able to recoup their substantial investments within a reasonable period of time, thus harming biotech innovation across the board. BIO also notes that any assessment of the sufficiency of a "time for recoupment" period will be performed during the initial phases of investment, approximately 12 years prior to ultimate FDA approval. It therefore is critical that a FOBs regime be crafted in a way that provides investors the ability to predict this period with reasonable certainty.

The need for a substantial period of data exclusivity as part of the establishment of an abbreviated pathway for FOBs cannot be overstated. Without the assurance that an innovator biologic can be protected for a sufficient period of time against other entrants relying on the innovator's substantial research and development efforts, investment and thus innovation in biologics will suffer. The negative effects will be felt not only by those seeking to develop new and important treatments, but by the patient communities that seek to benefit from innovative therapies to address currently unmet clinical needs.

Next Generation Innovation

BIO would like to highlight the fact that data protection for a next generation product will in no way affect the ability of a FOB to enter the market based on the original innovative product. The success of a next generation product will depend on its benefits for patients and its price when compared to the follow-on and other marketed products. If the next generation product's benefit is minor in comparison to existing products, then it is unlikely – particularly in today's price-sensitive payer market – that granting data exclusivity to the next generation product will impact the marketplace in any meaningful way. However, without any separate data exclusivity for next generation products, major advances will be stymied.

It should also be noted that, if companies could easily forestall generic competition in the small molecule market by making minor improvements to existing products, such practices would be widespread. However, in 2007, generics accounted for 67.3 percent of the total prescriptions dispensed nationally, suggesting that such activity is either not occurring or is not successful.⁴

Further, some extension of data exclusivity for the original innovator product is necessary to effectively incentivize the development of new indications for or other improvements to existing products – developments that are particularly valuable from a public health standpoint in the field of biologics generally and with respect to therapeutic areas such as cancer in particular.

⁴ See URL: http://www.amcp.org/data/jmcp/JMCPMaga_April08_318-321.pdf.

The current Hatch-Waxman model of providing additional exclusivity only with respect to the new indication itself is not sufficient because, once the FOB for the original innovative product is approved, health care practitioners may decide to use the FOB to treat the new indication regardless of whether the FOB was approved for that indication. Development of a product for a new indication is a significant undertaking – it can take an innovator company four to five years to conduct clinical trials necessary for FDA approval. Without substantial data exclusivity on the original product, it would be difficult for companies to obtain the resources to develop such treatments, resulting in an incalculable public health loss.

In sum, BIO again appreciates the opportunity to further present our positions regarding follow-on biologics competition. We look forward to continued discussion with the FTC on this issue and to working with Congress to create an approval pathway for FOBs that recognizes the scientific and intellectual property differences between drugs and biologics and include appropriate incentives for the continued development of much-needed therapies.

Sincerely,

John Taylor
Executive Vice President, Health