

Wyeth Pharmaceuticals

500 Arcola Road
Collegeville, PA 19426

Matthew Eyles

Vice President, Public Policy
484 865 5132 tel
484 865 6420 fax

**BY ELECTRONIC DELIVERY**

<http://secure.commentworks.com/ftc-healthcarecompetition>

September 30, 2008

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

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

Dear Federal Trade Commission:

Wyeth Pharmaceuticals welcomes the opportunity to comment on the Federal Trade Commission (FTC) proposal on Emerging Health Care Competition and Consumer Issues. Wyeth Pharmaceuticals, a division of Wyeth, is one of the world's largest research driven pharmaceutical and health care products companies with leading products in the areas of women's health care, infectious disease, gastrointestinal health, central nervous system, inflammation, transplantation, hemophilia, oncology, vaccines and nutritional products.

Wyeth appreciates FTC's interest in the topic of biosimilars or "follow-on biologics" and the competitive issues that could arise upon the market availability of these types of products. As the fourth largest biotechnology manufacturer in the world, Wyeth shares FTC's interest in this topic and has been actively engaged in the global debate on appropriate regulatory approval mechanisms.

Wyeth's Policy Position on Biosimilars¹

Wyeth believes that there is no single template for regulatory approval that will be applicable to all biosimilars due to the complexities associated with developing and manufacturing biologics. Biosimilars—like all prescription products—should be required to provide adequate supporting data to demonstrate their safety and

¹ As a point of clarification, Wyeth believes the term "biosimilars" is the most appropriate to describe these types of products. Accordingly, that is the term used in this section delineating our policy position. For the purpose of our responses to the specific questions raised in the FTC proposal, however, we will utilize the term "follow-on biologics" to be consistent with the terminology in the proposal.



efficacy. The approval of biosimilars should include two distinct evaluations. The first is whether the product is safe and effective; the second is whether the biosimilar and innovator product may be deemed interchangeable.

Biosimilars should not ordinarily be understood as interchangeable with approved reference products, absent data to support interchangeability. In addition, unless chemically identical, fully comparable and safely interchangeable with the innovator product, biosimilars should have a unique name that reflects their unique manufacturing processes and origins. This unique name is necessary to ensure against inappropriate or inadvertent interchange as well as to promote long-term pharmacovigilance and adverse event monitoring.

Finally, any biosimilar approval mechanism must include adequate intellectual property protections—including appropriate data exclusivity periods—to promote innovation and encourage new product development.

Response to the FTC Proposal

We offer the following in response to the questions raised in the FTC proposal:

Competition Issues Involving Follow-on Biologic Drugs

A. Regulatory Exclusivities and Follow-on Biologic Drug Competition

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?*

Follow-on biologics cannot be rated for interchangeability in the same way as chemical generic compounds. Most traditional chemical molecules (also known as “small molecule” pharmaceuticals) can be exactly replicated. This allows drug products that incorporate the molecules to be determined “bioequivalent” – if the products meet applicable data requirements – and therefore freely interchanged. In contrast, it is not possible to make an exact copy of a biological product due to its derivation from cell culture or whole living organisms and the complex manufacturing processes involved. As such, there is bound to be a degree of variability in any attempt to copy a biologic. Therefore, reaching a finding of bioequivalence as between two biologic products – even if such a finding were theoretically possible –



typically poses far more complex scientific issues than in the small-molecule world. In addition, from a clinical perspective, seemingly minor variations in characteristics as between two biological products can have unpredictable consequences for safety and efficacy in patient use.

Consequently, follow-on biologics should not automatically be deemed interchangeable with approved innovator products. Rather, to demonstrate interchangeability, applicants should be required to provide additional clinical data clearly establishing the safety of interchangeable use of the innovator and biosimilar, including immunological safety, as applicable.

The current EMEA guidelines do not specifically speak to interchangeability but instead leave determinations of interchange up to Member States. To date, legislation has passed in France (February 2007) and Spain (September 2008) prohibiting automatic substitution of a follow-on biologic for an innovator reference product.

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?***

Under Medicare Part B, drugs and biologics are reimbursed according to the Healthcare Common Procedure Coding System (HCPCS). Under Medicare Part D, drugs are reimbursed at the individual National Drug Code (NDC) level. The Centers for Medicare & Medicaid Services (CMS) will need to determine whether biosimilars will be considered single-source or multi-source products. If they are determined to be multi-source, the HCPCS code (J-code level) could encompass multiple NDC codes.

Medicare reimburses biologics that are “incident to” physician’s services in the office setting and the hospital outpatient department (HOPD) setting under Part B. Manufacturers of drugs and biologics must complete an application



process in order to obtain a unique HCPCS code. If an application is approved, CMS issues a unique HCPCS code for the product under its generic name. Then, CMS calculates the appropriate reimbursement level by collecting manufacturer-submitted average sales price (ASP) data and increasing the corresponding ASP by the applicable percentage (i.e., ASP+6% in the physician's office; in 2008, ASP+5% in the HOPD; and in 2009, ASP+4% in the HOPD).

Given the lack of an established approval process for biosimilars (and therefore the lack of a concomitant reimbursement policy), the various positions on interchangeability and degrees of similitude between biosimilars and reference products in pending congressional proposals, and uncertainty on naming issues for biosimilars products, it is unclear how biosimilars might be reimbursed. The relationship between reference product coding and reimbursement and that of a biosimilar will depend heavily on how these issues are resolved in any final biosimilars regulatory approval process.

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 claiming biologic drugs and those containing small molecules may contain the same types of patents. However, Wyeth expects those portfolios to differ in at least three ways. First, Wyeth expects patents claiming methods of making biologics may have a more prominent role in biologics portfolios. Second, Wyeth expects that those portfolios may lack patents broadly claiming the active biologic ingredient. Finally, Wyeth expects biologic portfolios may contain more patents owned by third parties, such as patents covering platform technologies.

Accordingly, if a regulatory approval pathway is enacted for follow-on biologics, innovators may receive even less protection from their patents than traditional small molecule innovators receive. This is particularly true if legislation does not require that follow-on biologics be identical to the innovator product.

The cornerstone for approval of a generic drug product is the requirement that it be the "same as" the reference drug. A generic drug approved under section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §301 et al.) is likely to infringe the reference drug's product patent because the generic



drug's active ingredient is—by statutory necessity—the same as the reference product's active ingredient.

The sameness standard for traditional generic product approval under an Abbreviated New Drug Application (ANDA), although grounded in public health considerations, therefore has the added effect of reinforcing the protection offered by innovator patents. A regulatory approval process for follow-on biologics based only on similarity, rather than sameness, would introduce greater uncertainty about whether a particular innovator product patent can be enforced against a follow-on biologic.

- 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?***

Wyeth believes that data exclusivity associated with a follow-on biologics pathway should be at least 14 years from the date of initial approval of an innovator product with additional exclusivity available for post-approval indications.

Patents and data exclusivity are both incentives for investment in innovation. They work in a complementary fashion. Patents reward an invention by providing the innovator with the right to prevent anyone else from making, using or selling the patented invention for a defined period of time. Data exclusivity recognizes the large-scale investment required to develop safety and effectiveness data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and effectiveness of its product. Data exclusivity does not prevent an applicant from submitting an application and obtaining approval based solely on its own data. Moreover, neither patents nor data exclusivity bar other innovators with competing, non-infringing drugs from the market.

As the Hatch-Waxman compromise for small molecules reflects, patent protection is necessary but not sufficient in itself to provide adequate incentives for medical innovation. Some patent life is necessarily lost during the time consumed by the extensive development and FDA approval process that is required to bring a new medicine to market, and patent term restoration provides only partial compensation for this lost time. Further, in the case of biologics, a product patent may provide insufficient protection if a follow-on biologic applicant can circumvent the patent under a similarity standard (rather than equivalence) for follow-on biologic approval. Moreover, patents nearly



always have a measure of uncertainty, but investments in the testing and clinical trials needed to obtain FDA approval must be made long before an innovator knows whether a patent may someday be successfully challenged.

Data exclusivity provides a measure of certainty, allowing investments in clinical trials to be supported. The uncertainty of patent protection, which emphasizes the need for data exclusivity, is evident in the research of Grabowski and Kyle. Their research found that the number of patent lawsuits associated with Paragraph IV filings has grown in recent years, and these legal challenges are occurring much earlier in drug lifecycles.² The authors conclude these trends are shortening the average time that innovators have to attempt to recoup their research and development investment.³

According to Grabowski, “[m]ost of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an ANDA filing with a paragraph IV certification.”⁴ Furthermore, these challenges and the accompanying “uncertainty adversely impacts biopharmaceutical research and development resulting in firms abandoning research and development projects on future drug candidates with uncertain patent prospects. Early patent challenges also can have a chilling effect on the development of new indications and formulations given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval.”⁵

To address the concerns about patent challenges and uncertainty, Grabowski has determined that the appropriate period of data exclusivity for biologics should be 12.9 to 16.2 years.⁶ These figures are based on the estimated period of time it takes a portfolio of biologics marketed by a mature company to earn back the average cost of research and development needed to bring a new biologic to market.

² Grabowski, HG and Kyle, M, “Generic Competition and Market Exclusivity Periods in Pharmaceuticals,” *Managerial and Decision Economics* 491-502 (28:2007).

³ *Ibid.*

⁴ *Ibid.*

⁵ *Ibid.*

⁶ Grabowski, HG, “Data Exclusivity for New Biological Entities,” Duke University Department of Economics working paper (June 2007), available at <http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf>.

Wyeth

Wyeth believes this research supports a period of at least 14 years of data exclusivity for biologics. To provide an incentive for continued research leading to new indications post-approval and after patents have expired, additional exclusivity should be available for post-approval indications, in light of the central importance of post-approval research to achieving medical progress and the investment needed to support the clinical trials required to obtain an FDA-approved new indication.

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?*

Biologics differ from small molecules in many ways; one way that impacts the regulatory protection timelines is the significant difference in manufacturing and supply chain processes. Manufacturing a commercial biological product can take six months to one year, and the challenges in the manufacturing environment of issues such as sterility, change control, and technological requirements, are extreme. Likewise, inventory management is especially challenging and requires precise forecasting and intense supply chain oversight. Due to these factors, it is not uncommon for a biologic product to obtain FDA approval, yet not actually be commercially available for another six to nine months thereby shrinking the benefit afforded by patent protection and data exclusivity.

The time necessary to recoup the research and development investment and the management of manufacturing and supply chain issues are factors that necessarily apply to – and are unique for – each biologic product. This is due to the unique nature of each product. Products vary in size and complexity, which impacts manufacturing challenges. Market competition can be fierce, requiring additional tightly defined, costly studies to demonstrate product differentiation and cost-benefit analysis to payers and patients. Patent portfolios can be extremely complex, which can limit the affected parties' commercial benefit, thus driving down incentives to invest in innovation.

Studies have recently determined the cost of bringing a new drug to market to be \$1.2 billion.⁷ Both patent protection and data exclusivity are important

⁷ DiMasi, JA and Grabowski, HG, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 469-79 (June 2007).

Wyeth

tools in encouraging this significant level of investment in biologic drug product innovation. As stated above, Wyeth agrees with the Grabowski calculations regarding the appropriate period of data exclusivity, and supports a 14-year exclusivity period for biologics to adequately account for the time it takes a product to earn back the average cost of research and development needed to bring it to market.⁸

There are two additional situations that warrant additional exclusivity –new, post-approval, indications and second-generation biologics. New indications can include, (among other things), an expansion of approved uses, treatment of different conditions or patient populations, or demonstration of improved results when the product is used in combination with another medicine. Biologics are unique in that one product can often be found to have a variety of treatment uses, a situation notable in inflammation products and oncologics.

Boston Consulting Group estimates that it takes three to six years to achieve FDA approval of a new indication.⁹ During this time, costly studies are conducted even though a significant risk remains that the new indication will not be approved. Such research must have an opportunity to earn a return in order to be viable. As a result, a significant period of additional data exclusivity should be available for new indications in order to encourage innovators to pursue new indications that could improve patient outcomes.

Second-generation biologics require new, full Biologic License Applications (BLAs) for approval, and should therefore receive the same data exclusivity period as other new innovator biologics. Second-generation biologics have new active substances with different molecular structures, physical properties, and clinical features from the first-generation biologic. As a result, these products can provide substantial therapeutic benefits and lead to improved patient outcomes. Because the approval of these products is based on substantial research data, generated through the same types of costly studies involved in new product approvals, second-generation biologics should be considered new molecules and receive the same data exclusivity protections as new innovator products.

⁸ Grabowski, HG, “Data Exclusivity for New Biological Entities,” Duke University Department of economics working paper (June 2007), *available at* <http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf>.

⁹ Boston Consulting Group, “Continued Development of Approved Biological Drugs: A Quantitative Study of Additional Indications Approved Postlaunch in the United States” (2007).

Wyeth

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?

See Wyeth's response to Question 7.

B. 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?

Wyeth believes that a patent litigation procedure could be drafted in a variety of ways. Any such procedure, however, needs to create a mechanism in the biologics licensing statute administered by FDA (*i.e.*, title 42) to:

- Allow the follow-on biologic applicant and patent holders to have sufficient opportunity—before marketing of the follow-on biologic—to identify relevant patents that are potentially infringed by an application. This should include a mechanism to provide patent holders with confidential access to the application and a detailed explanation of the follow-on biologic's manufacturing processes;
- Support prompt resolution of patent disputes through adjudication prior to a follow-on biologic's entry to the market and to enable patent holders to receive notification when a follow-on biologic applicant intends to launch its product and seek injunctive relief;
- Encourage resolution of patent disputes before approval of the follow-on biologic, upon expiration of the innovator product's data exclusivity period;
- Keep follow-on biologics that infringe a patent off the market by preventing final FDA approval until patent expiry; and
- Enforce these requirements.

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

Biologics are structurally more complex than small molecules. Consequently, each biologic and its associated manufacturing process is unique and cannot be exactly duplicated by another manufacturer. Each BLA for a follow-on biologic will generally need to contain complete manufacturing information, including



data to establish comparability to the reference product, plus full reports of clinical studies to demonstrate clinical safety and efficacy. Consequently, the review time for follow-on biologics can be expected to approximate that typically associated with original BLAs for new biological products.

The current Prescription Drug User Fee (PDUFA) performance goal for FDA's review of an original standard BLA is ten months. However, the total review time ultimately depends upon a variety of factors including but not limited to the complexity of the data submitted in the application, whether any important scientific issues are identified during the course of review that may require additional data or analyses, and the duration of time required for the applicant to respond to FDA's inquiries.

The approval time for a follow-on biologic will depend on similar factors. Most notably, these will likely include the completeness of the application, the complexity of the reference biologic, the adequacy of the data submitted to demonstrate the quality, safety and efficacy of the product, and the level of comparability to the innovator or reference product.

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?*

As stated above, the patent portfolios claiming biologic drugs and those containing small molecules may contain the same types of patents. However, Wyeth expects those portfolios to differ in at least three ways. First, we expect patents claiming methods of making biologics may have a more prominent role in biologics portfolios. Second, we expect that those portfolios may lack patents broadly claiming the active biologic ingredient. Third, Wyeth expects that biologic portfolios may contain more patents licensed from third-parties. Accordingly, once a regulatory approval pathway has been enacted for follow-on biologics, innovators of biologics products may receive even less protection from their patents than traditional small molecule innovators do. This is particularly true if legislation does not require that follow-on biologics be identical to the innovator product.

The cornerstone for approval of a generic drug product is the requirement that it be the "same as" the reference drug. A generic drug approved under section 505(j) is likely to infringe the reference drug's product patent because the generic drug's active ingredient is—by statutory necessity—the same as the reference product's active ingredient. As we discussed in our response to



Question A(6) above, this sameness standard has the added effect of reinforcing the protection offered by innovator patents. A regulatory approval process for follow-on biologics that did not share this standard would necessarily introduce greater uncertainty about patent enforcement.

Wyeth believes that numerous factors affect the length of litigation, including the number of patents in suit, the complexity of the issues, the cooperation of the parties, and the caseload of the particular court. Accordingly, Wyeth expects the length of litigation to vary by case. However, overall, Wyeth believes that the length of litigation is likely to increase primarily because of the increased complexity of the factual and legal issues relating to follow-on biologics.

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?*

As stated above, Wyeth believes it is in the interest of referenced biologic drug manufacturers to obtain resolution of patent disputes before approval of the follow-on biologic upon expiration of the innovator product's data exclusivity period. Moreover, Wyeth believes it is necessary to provide for prompt resolution of patent disputes through adjudication prior to a follow-on biologic's entry on the market, including by enabling patent holders to be notified when a follow-on biologic applicant intends to launch its product and seek injunctive relief.

Wyeth also believes that, in some cases, it may be in the interest of follow-on biologic applicants to resolve patent issues following commercial marketing of the follow-on product. This may hold particularly true in cases in which the follow-on a biologic applicant believes market entry will result in a settlement acting to resolve any outstanding patent issues.

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?*

Wyeth believes the primary impediment for a follow-on biologic applicant to obtain a declaratory judgment on patent infringement or invalidity issues prior



to commercial marketing is the Constitutional requirement that there be an actual case or controversy, as most recently analyzed by the Supreme Court of the United States in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007).

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

For purposes of this question, Wyeth understands the term “regulatory exclusivity” to be akin to “marketing exclusivity,” such as the 180-day exclusivity period currently available for generic manufacturers of small molecule products.

As discussed above, Wyeth believes that data exclusivity recognizes the large-scale investment required to develop the safety and effectiveness data needed to support an application for FDA approval, and accordingly bars another company from relying on the innovator’s data for a period of time to demonstrate the safety and effectiveness of its product. Thus, the data exclusivity afforded innovator companies represents a reward for taking on the tremendous risk associated with the development, approval, and manufacturing of biologics.

Wyeth believes that follow-on biologic applicants also take on some risk, albeit substantially less risk than innovator companies. Accordingly, Wyeth believes that, consistent with its view on data exclusivity, follow-on biologic applicants should also be eligible for regulatory exclusivity period.

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?*

Absent detailed information on a proposed patent litigation system, this question is difficult to answer. However, as discussed in Question B(1) above, Wyeth believes that manipulation of regulatory obligations can be minimized if the follow-on biologic applicant and patent holders have sufficient opportunity—before marketing of follow-on biologic—to identify relevant patents that are potentially infringed by the application. Again, we believe this should include a mechanism to provide patent holders with

Wyeth

confidential access to the application and a detailed explanation of the follow-on biologic's manufacturing processes.

With regard to citizen petitions, Wyeth believes these remain an essential vehicle to allow the public to raise issues with FDA, and that they permit a valuable public dialogue about such issues.

Conclusion

Again, Wyeth appreciates the opportunity to comment on the important issues raised in the FTC's Emerging Health Care Competition and Consumer Issues notice. We look forward to engaging with the FTC on the elements of a meaningful and appropriate regulatory approval mechanism for biosimilars/follow-on biologics. If you have any questions about Wyeth's comments, please do not hesitate to contact me.

Sincerely,

?

Matthew D. Eyles
Vice President, Public Policy
Wyeth Pharmaceuticals