Emerging Health Care Competition and Consumer Issues—Comment, Project No. P083901

Comments submitted by the Generic Pharmaceutical Association

Regulatory Exclusivities and Follow-On Biologic Drug Competition

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 a biogeneric entering the market is the reduction in price, saving consumers and taxpayers billions of dollars each year. Hatch/Waxman has provided consumers with significant savings upwards of 80 percent of the brand product. In addition, past history has shown that when more generics enter the market, prices fall even further.

GPhA is not aware of any studies analyzing the competition that has developed in the EU. Regarding reference product manufacturers reducing cost: that is a question that the brand industry itself will have to answer. However, we have rarely seen price reductions of brand products under Hatch-Waxman, hence there is no reason to believe that brand biopharmaceutical firms will decrease prices when biogenerics are available in the marketplace.

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?

To achieve maximum savings from lower-cost biogenerics, there must be robust competition in the biologics market, which results only if legislation enacts a workable regulatory pathway that provides for interchangeability. Interchangeable biogenerics would give pharmacists and doctors the choice of switching from a brand to a more affordable generic equivalent, thus providing lower-cost reimbursement options to health plans, the government and other third-party payers. If the U.S. adopts nothing more than an EU type "biosimilar" system, the promise of maximum savings from biogeneric competition would never be achieved.

Further, legislation that allows for interchangeable biogenerics is essential to providing the incentives technology innovators assert they need to invest and develop new and advanced characterization and process control technologies. If legislation prevents FDA from making interchangeable determinations, scientific innovation from technology companies will be held back because the incentive to innovate will not be there. Given the need for affordable, safe and effective biopharmaceuticals in the marketplace, and the need to maintain state-of-the-art science and technology to determine, at least for some products, their interchangeability, it is very important that FDA be given authority to use its expertise to make critical judgments to determine that two products are interchangeable.

Interchangeability determinations dramatically reduce the need for firms to engage in comprehensive marketing efforts, thereby reducing the cost of the product. Additionally, smaller firms will be encouraged to compete since interchangeability will provide purchasers with confidence that the products are the same as the reference product without the need for special marketing programs, thus allowing them to compete on price and service.

The entry of "authorized biogenerics" is a question for the brand industry. Nevertheless, past history in the chemical drug world has shown that brand companies typically put out an authorized generic

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?

Joint R&D agreements certainly occur in the pharmaceutical industry. They do not raise anticompetitive concerns in and of themselves, and often times are vital to the development of new pharmaceuticals. Thus it would be wrong to view them with suspicion. Nevertheless, Congress certainly could consider extending the MMA's agreement regarding reporting requirements, which currently apply to certain agreements involving applications submitted under Hatch-Waxman, to the generic biologics arena.

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?

There would be no generic product without a brand product, so it is in the best interest of generic companies that brand companies continue their innovation of new drugs. Likewise, it is in the best interest of patients, taxpayers, healthcare providers and the government that lower-cost generic versions of medicines be allowed to come to market expeditiously.

Boston University professor Laurence Kotlikoff, in his September 2008 study "Stimulating Innovation in the Biologics Industry," showed that Hatch-Waxman positively influenced research and development: "Hatch-Waxman's success did not come at the price of innovation. On the contrary, the legislation appears to have accelerated innovation. Figure 1 shows that research and development in pharmaceuticals, measured relative to sales, increased dramatically in the years after 1984. R & D is now running between 16 percent and 18 percent of sales, on an annual basis, compared with 8-10 percent of sales prior of Hatch-Waxman."

Not only did R& D increase with competition from generic competitors, but patents granted increased dramatically after Hatch-Waxman as did FDA approvals of new molecular entities (as Kotlikoff shows in Figures 2 and 3, pages 10-13). GPhA believes that competition from follow-on biologic drugs will spur innovation in much the same way as chemical drugs under Hatch-Waxman—if the incentives and reasonable exclusivity are achieved.

Kotlikoff states definitely in his executive summary: "Numerous papers in the economics literature on invention and monopoly protection stress that competition, not protection, is the true source of innovation and that overextending monopoly protection can be counterproductive. It may do little or nothing to incentivize new discovery, and may simply delay when the next discovery comes on board. Thus, rights to exclusive marketing periods can lead to less, not more, innovation over time."

Former Congressman Jim Greenwood, now the head of the brand biologic trade association BIO, acknowledged this recently when he said competition from generic companies "will stimulate more innovation." Former FDA Deputy Commissioner for Medical and Scientific Affairs Scott Gottlieb said legislation to expose biologics to competition would unleash innovation and "accelerate development of improved products, not just lower cost." Similarly, Congressman Pallone correctly noted that "[w]hen Hatch-Waxman was enacted in '84, its detractors claimed that it would stifle innovation, yet the number of new technologies developed in the last 20 years, particularly in biologics, has been staggering."

Further, the Congressional Budget Office's 1998 report "How Increased Competition from Generic Drugs Has Affected Prices" detailed another key lesson learned from the implementation of Hatch-Waxman: Generic competition "has played an important role in holding down national spending on prescription drugs from what it would otherwise have been." Considering only sales through pharmacies, the CBO estimated that by substituting generic for brand drugs, purchasers saved roughly $8 billion to $10 billion in 1994 (at retail prices). These savings have increased substantially over the past decade as generic utilization has climbed from approximately 43% in 1996 to 67% in 2007. [see http://www.cbo.gov/doc.cfm?index=655&type=0&sequence=1]

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?

As GPhA understands it, the statutory scheme as it exists today does not give providers the same incentive to use generic biologics as it does to use generic small molecule drugs. Consequently, in order for taxpayers to achieve the same type of savings that they experience from the introduction of generic small molecule drugs, Medicare reimbursement of biologic drug products likely will need to be modified.

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)?

Some innovators claim that patents are not enough to guarantee protection of biotech drugs because, it has been suggested, biologic patents primarily claim a process rather than a chemical entity. Innovators suggest that exclusivity is needed in addition to patents to ensure proper protection for brand biologics. That is not true. Biologic products typically have more patents protecting them than chemical drugs -- and each of these patents offer 20 years of protection to the claims they cover, regardless of the length of any exclusivity period granted. In addition, biologics are eligible for a patent term restoration of up to five years under Hatch-Waxman. As a result, valid and enforceable biotech patents offer good and sufficient intellectual property protection.

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?

In regard to a model for biologics, Hatch-Waxman has been extremely successful for the innovator industry, as well as the generic industry. It strikes a reasonable balance between market incentives and competition which provides affordable access. Hatch-Waxman provides protection beyond that afforded to any other industry and has achieved its goal of innovation and access. GPhA believes that five-year market exclusivity, along with intellectual property and the patent restoration provisions included in the Hatch-Waxman amendments, provides a reasonable balance between innovation and access and should be used for biogenerics. Hatch-Waxman has provided the U.S. with the most robust pharmaceutical industry in the world.

There are a number of lessons learned from Hatch-Waxman. Loopholes in the original law allowed brand companies to block generic competition through creative patent listings. Many of these loopholes were corrected in the 2003 Food and Drug Administration Medicare Prescription Drug, Improvement, and Modernization Act. Here, too, careful consideration must be given to exclusivity of any biogeneric legislation to assure that patent issues do not prohibit FDA approval. Patent considerations should be addressed without involvement of FDA ministerial responsibilities.

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?

To date, there have been no objective assessments supporting the need for an exclusivity period different from what is provided in Hatch-Waxman. To the contrary, Dr. Kotlikoff shows that in fact Hatch-Waxman is likely the best model for an approval pathway for generic biologics will spur innovation and allow competition in the marketplace. Even accepting the assumptions in the 2007 DiMasi-Grabowski study – which the generic believes are questionable – there is just a minimal increase in the average development and approval time for biologics over chemical drugs (97.7 months vs. 90.3 months). Thus we do not believe that biologics should receive anything above and beyond that offered by Hatch-Waxman in terms of new exclusivity incentives.

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?

Exclusivity periods should be based on the entirety of a particular regulatory and patent system. When comparing the U.S. and EU systems, it becomes readily apparent that the exclusivity periods provided in the EU are not a legitimate model for guiding the U.S. For instance, price controls are prevalent in the EU, while the U.S. does not impose price controls. Further, the EU members have different patent systems, not only different from the U.S., but different from each other. On balance, the EU does not provide the same protection as the U.S. system.

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?

Hatch-Waxman's generic exclusivity provisions are the cornerstone of that statutory scheme. It is the only provision that provides the incentive needed for generic companies to undertake the considerable risk that comes with navigating intellectual property for the brand product and patent. Biogeneric companies will be very reluctant to invest resources if there is no possibility for recouping the costs that come with patent challenges. A defined exclusivity scheme is one mechanism to incentivize generic firms to take the risks associated with a biogeneric development program.

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?

Patent uncertainty acts as a drag on generic product investment and market introduction. Consequently, it is imperative that a follow-on biologics bill contain an effective patent dispute resolution mechanism, one that not only provides for the clear and timely resolution of patent disputes, but also prevents frivolous suits from delaying competition in the marketplace. Such a process is best achieved via a voluntary system initiated by the generic company. Allowing the brand company to sue on any patent prior to generic launch necessarily would delay the generic's ability to obtain certainty with regard to certain patents, and in the process, would significantly delay generic marketing. This is one lesson learned from Hatch-Waxman, which allows brand companies to immediately sue on a small subset of patents. The delays would be even longer if brand companies were allowed to immediately sue on any and all patents in its portfolio.

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

Several of the legislative proposals for follow-on biologic applications include the assessment of a user fee. User fees provide substantial resources for FDA review activities including the addition of experts in biotechnology and related scientific disciplines that will be responsible for the review of follow-on biologic applications. Currently, the review timeline for approval of new innovative drugs and biologicals is approximately one year. These reviews include safety and efficacy assessments of new and often very complex entities that have no marketing history in the U.S. In most cases, the FDA review teams, supported by user fees, review and approve these applications within twelve months. When follow-on biologic applications are submitted to FDA, the Agency and clinicians will have extensive experience with the innovator product and/or product class and the scientific knowledge of these products will be far advanced compared to knowledge base when the innovator product was first approved. Therefore, based on FDA expertise, it is expected that applications for follow-on biologics will be reviewed and acted upon quite promptly. If Congress mandates guidances prior to FDA acceptance, and such guidances require a public input period, this would significantly delay generic competition. The FDA should allow applicants to present the best science available to evaluate the approvability of the file.

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?

GPhA is not aware of any differences between patent portfolios for small molecule drugs and biologics that might affect patent litigation involving follow-on biologics. Brand companies obtain many patents protecting small molecule drugs and biologics alike. Indeed, it is not at all uncommon to see a branded product (whether small molecule or biologic) with a dozen or more related patents, and for these patents to have been procured over time in order to give the brand company years and years of patent protection.

How long a particular case takes will depend upon a variety of factors. The most important factor in how long brand/generic biologic patent cases will take likely will be the patent dispute resolution mechanism that Congress enacts as part of a follow-on biologic approval pathway. A system like that proposed in H.R. 1038 would allow for expeditious patent dispute resolution and thus expedited generic marketing, while still respecting legitimate patent rights. This is true because, among other things, it permits only those patent disputes that would delay generic marketing to be litigated concurrently with FDA review of the generic application. Any other patent disputes would be litigated post-launch. On the other hand, a system like the one in H.R. 5629 would be wholly unworkable and lead to significant delays in generic marketing, which likely is one of the reasons that BIO supports that bill. This is so because, among other things, the bill would allow brands and other third parties to litigate virtually any patent concurrently with FDA review. By allowing brands to bury the generic company in patents pre-launch necessarily will delay generic market entry.

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 noted above, patent uncertainty acts as a drag on generic product investment and marketing. Thus, follow-on biologics legislation should provide a mechanism for timely resolution of patent disputes, in addition to prohibiting frivolous suits from delaying generic competition. Again, this is best achieved via a voluntary process that is initiated by the generic company, such as the one proposed in H.R. 1038. Allowing the brand company (let alone additional third parties) to sue on any patent prior to generic launch would tie the generic up in patent litigation for years and years, which is what H.R. 5629 proposes. As noted above, such a system would significantly delay the generic's ability to obtain certainty with regard to patents that could impact generic product launch. Finally, as a matter of fairness, there should be a limitation on remedies available to the patentee with respect to any patent where the owner does not fulfill its obligations under the statutory scheme.

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?

GPhA recognizes that recent developments in declaratory judgment (DJ) case law increase the likelihood of DJ subject matter jurisdiction under certain circumstances. Because it is critical that generic companies have an effective and reliable mechanism for litigating all relevant patents, GPhA encourages Congress to consider enacting declaratory judgment provisions for follow-on biologic companies that will withstand constitutional scrutiny.

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

Hatch-Waxman provides the first company to challenge the brand's patents with a generic exclusivity period precisely because Congress knew that mounting such challenges are risky and costly. But Congress also knew that such challenges were necessary if consumers were to have increased access to affordable generic medicines more quickly. The same will be true for follow-on biologics. Brand biologics makers will seek to enforce their intellectual property just as aggressively as traditional brand makers. It thus will be critical that generic companies have some incentive to shoulder the burdens, risks and expenses that come with patent cases, particularly at the inception of follow-on biologics.

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?

Congress has not enacted follow-on legislation yet and thus GPhA cannot comment on how such statutory provisions possibly could be abused to delay follow-on biologics approvals. Nevertheless, in looking at the pending bills, it seems clear that a follow-on biologics bill containing unnecessary barriers to follow-on biologic application submission and/or approval certainly could (and likely would) be abused in order to delay follow-on market entry. For example, provisions that would require a mandatory guidance or rule-making process prior to application submission or approval would provide an easy opportunity for those seeking to delay follow-on approvals to delay the process. The same is true of provisions that would provide brand exclusivity on products that do nothing but modify already existing biological products. If brand companies receive exclusivity, particularly a long period of exclusivity, for modifications of existing biologics, brand companies will be able to manipulate the process such that consumers likely will receive little benefit from the introduction of follow-on biologic products (and thus generic companies will have little incentive to develop such products in the first place). Brand exclusivity for modified existing biological products will allow brands to constantly shift the market from one brand product to the next version of the same brand product, just as the generic company is about to enter the market. This is, in fact, what traditional drug makers routinely attempt to do when going from an immediate release product to an extended release product. By shifting the market from one product to the next, consumers do not see the savings they should when generics hit the market, nor do they get the benefit a truly new and innovative brand product.

GPhA thus urges Congress to avoid unduly long brand exclusivity periods, particularly for modifications to existing biological products – just as Congress did when enacting Hatch-Waxman. In addition, limiting the ability for citizen petitions to improperly delay applications should be a part of any follow-on legislation.

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?

GPhA plainly has no information with respect to whether patent cases that have not even been brought yet will be resolved by settlement. Nevertheless, since the vast majority of all litigation brought ends through some type of dispute resolution mechanism, it seems reasonable to assume that some brand/generic biologic patent litigation cases will conclude with a settlement of some sort. And of course, 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 pharmaceuticals. There are limitations on how long exclusivity may be maintained by the first applicant in HR 1038 that GPhA believes would allow the public timely access to these products while still providing a reward for challenging patents for early entry.

Further, while FTC has made its opinion of brand/generic pharmaceutical settlements in Hatch-Waxman litigation well known, the fact is that such settlements routinely contain significant pro-consumer benefits, such as guaranteed pre-patent expiration generic market entry. GPhA is not aware of any incentive for brand and generic companies to enter into "anticompetitive" settlements agreements in biologic patent cases.

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 reported 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.