Emerging Health Care Competition and Consumer Issues
Teva Pharmaceuticals Response to the Federal Trade Commission

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 competitive effect of biogenerics entering the market are increased affordability of and access to much needed treatments, as well as important savings for payors and taxpayers. Twenty-five years after Congress passed Hatch-Waxman, generic penetration is upwards of 65 percent, demonstrating increased access to medicines for patients. However, generics only account for close to 12 percent in drug spending, which translates into significant savings—in some cases as much as 80 percent off the brand product price.

Teva is not aware of any studies analyzing the competitive effects of biosimilars in the European Union. Whether reference product manufacturers reduce cost is a question that the brand industry itself will have to answer. We have rarely seen price reductions of brand products under Hatch-Waxman, and have no reason to believe that brand 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?

If legislation enables a reasonable regulatory pathway that provides for interchangeability, maximum savings will be achieved. Interchangeable biogenerics would make the choice of switching from a brand to a more affordable generic equivalent as simple as possible, thus providing lower-cost reimbursement options to health plans, the government and other third-party payers. Without interchangeability, maximal savings from biogeneric competition would not be realized.

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.

In the chemical drug world, brand companies typically put out an authorized generic when they view it as profitable. We foresee the strong possibility of a similar landscape in the biogeneric world.

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?

Teva believes that joint research and development, supply, and other such agreements between brand and generic biologic companies do not raise competitive concerns in and of themselves. Moreover such agreements often provide a vital mechanism for bringing affordable pharmaceuticals to market, and we envision a similar role for such agreements in the biologics marketplace. If Congress requires that such agreements should be filed at the FTC and the Department of Justice, then the current agreement reporting requirements under MMA may provide a useful template.

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 nonbiologic generic pharmaceutical drug products provide insights into these issues?

As history has demonstrated, competition drives innovation, it does not hinder it. Teva sees no reason why this will not also be the case with biogeneric competition, as it was with chemical compound competition in the late 1980s and 1990s. Boston University professor Dr. 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). Teva Pharmaceuticals 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 in the legislation.

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." Scott Gottlieb, former FDA Deputy Commissioner for Medical and Scientific Affairs, said legislation to expose biologics to competition would unleash innovation and "accelerate development of improved products, not just lower cost." Congressman Pallone correctly noted,

"When 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?

Teva does not believe that the statutory scheme as it exists within Medicare Part B today give providers the same incentives to use biogeneric drugs. In order for taxpayers to achieve the savings that they should obtain from generic competition, Medicare reimbursement of these products will certainly need to be modified to ensure that the system is not inadvertently encouraged to utilize brand over other 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)?

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. Moreover, many biotech products are protected by a larger number of patents than chemical products.

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?

Hatch-Waxman has been extremely successful for the innovator industry, as well as the

generic industry and would be a good model for biologics. 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 through competition and access to more affordable medicines. Teva believes that five-year market exclusivity, along with the patent restoration provisions included in the Hatch-Waxman amendments, provides a reasonable balance between innovation and access and should be considered for biogenerics.

To our knowledge, there have been no appropriate assessments supporting the need for an exclusivity period different from what is provided in Hatch-Waxman. Dr. Kotlikoff's study shows that in fact Hatch-Waxman is likely the best model for an approval pathway for generic biologics that will spur innovation and allow competition in the marketplace because there are no meaningful differences between the pharmaceutical industry and the biotech industry to justify deviating from the Hatch-Waxman model. For example, one example is that despite the large cost of developing a biologic, Kotlikoff found that one key factor when determining exclusivity is invention cost relative to invention reward rather than just invention cost:

> *There is no question that bringing a new biologic medication to market is exceptionally expensive – an estimated $1.24 billion. But cost per se is not economically relevant. What matters is cost relative to reward…Compared with pharmaceuticals, biologics are more costly to produce. But their reward is also considerably higher. Indeed, compared to chemical medications, biologic medications appear to have a lower ratio of invention cost to invention reward. Moreover, there is no presumption in the economics literature on optimal monopoly protection that products entailing higher cost relative to reward should be provided longer periods of exclusivity. (Pages 8-9)*

In addition to examining cost relative to reward, Kotlikoff argues that risk and non-diversifiable risk must be considered. He shows that there are no justifiable reasons why a biologics pathway should be treated differently than for chemical drugs because not only is the biotech industry not riskier than the pharmaceutical industry, but the opposite is true.

> *Only one in five of all drugs tested clinically make it to market, with the success rate possibly lower in biologics. But modern finance teaches us that collections of individual investments, each of which is highly risky, can, thanks to the law of averages (law of large numbers), be quite safe. If only one in 20 experimental drugs makes it to market, but you experiment with 1,000 such drugs, you can be pretty sure that close to 50 will be successful...When it comes to non-diversifiable risk, the biotech industry is riskier than most, but not by much. Consequently, the cost of equity capital in biotech is only 18 percent higher than the average across other industries. Moreover, a quarter of U.S. industries are riskier than biotech, but none of these garner longer monopoly protection. The appendix lists 25 industries with higher costs of equity capital than biotech. The semiconductor industry is the most risky, with a cost of capital of 89 percent above the average. The pharmaceutical industry, interestingly enough, is much riskier than biotech. Its cost is 35 percent above average. (9)*

In addition, previous studies (2007 DiMasi-Grabowski) – which we believe may be flawed – note that 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).

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?

In addition to the points made above regarding no substantive difference between biologic and drug cost and risk sufficient to justify prolonged exclusivity, Teva believes some of the appropriate factors to determine the optimal length of regulatory exclusivity would be a proper balance to incentivize innovation and competition, a caution of brand evergreening, and a knowledge of what the past 25 years under Hatch-Waxman has taught us:

Dr. Kotlikoff argues that the proper balance to incentivize innovation is indeed the Hatch-Waxman model, and going beyond those years of exclusivity would actually harm innovation:

> *[P]roviding greater incentive to innovate leads to less, not more, innovation over time. (16)*
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> *Policies that lengthen the time between innovations may do little to stimulate more innovation; instead, they may simply reduce the pace of innovation (the number of discoveries per unit of time) on which the economy's growth so critically depends. (4)*
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> *Prolonged monopoly protection raises additional concerns. It distorts consumer choice by maintaining artificially high prices of those goods and services that are being protected. (5)*
>
> *Evergreening will multiply the economic costs of expanding monopoly protection via exclusivity arrangements. Brand companies can, and routinely do, make relatively minor changes to their existing products in order to restart their monopoly-protection clocks. These changes include changing the medication strength…changing the form of medication (e.g., switching from a pill to capsule), modifying the method of delivery…expanding indications…pegylation…and glycosolation (adding sugar molecules to the medication)… Minor modifications of new proteins should receive either no monopoly protection or very limited protection.*

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. The exclusivity periods provided in the EU are not a legitimate model for guiding the U.S. since, for example, 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.

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 an important part of that statutory scheme. It provides the incentive for generic companies to undertake the risk that comes with challenging the

intellectual property of the brand product. Most companies contemplating biogenerics will be reluctant to invest the significant resources required to determine interchangeability 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 on the risks associated with an interchangeable 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 inhibits generic product investment and market introduction. It is therefore important that a follow-on biologics bill contain an effective patent dispute resolution mechanism that provides for the clear and timely resolution of patent disputes, as well as prevents frivolous suits from delaying competition in the marketplace. Teva believes such a process is best achieved with a voluntary system initiated by the generic company. Allowing the brand company to sue on any patent prior to generic launch would delay the generic company's ability to obtain certainty with regard to certain patents, and in the process, would significantly delay generic marketing.

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

Various legislative proposals for abbreviated biologic license applications include the user fee assessment. 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. The review timeline for approval of new innovative drugs and biologicals is now 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. Given FDA experience with biologics, it is expected that applications for follow-on biologics will be reviewed and acted upon in a similar timeframe. If Congress mandates guidances prior to FDA acceptance, and such guidances require a public comment 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?

Teva is not aware of any differences between patent portfolios for small molecule drugs and biologics that might affect patent litigation involving follow-on biologics other that the increased number of patents for biologics.

How long litigation takes will depend upon various factors, the most important of which is the mechanism that Congress enacts as part of a follow-on biologic approval. The system proposed in

H.R. 1038 would allow for expeditious patent dispute resolution and thus expedited competitor marketing, while still respecting legitimate patent rights. This is because it permits only those patent disputes that would delay generic marketing to be litigated concurrently with FDA review of the generic application. Other patent disputes would be litigatable post-launch. The system like the one in H.R. 5629 would be unworkable and lead to significant delays in generic marketing because the bill would allow brands and other third parties to litigate virtually any patent concurrently with FDA review. Allowing brands to bury the generic company in patents prior to 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?

Patent uncertainty is problematic for both innovator and competitor so the timely resolution of potential disputes should benefit all parties. Patent uncertainty inhibits product investment and marketing. Biogeneric drug legislation should provide a mechanism for timely resolution of patent disputes, in addition to prohibiting frivolous suits from delaying competition. This in our view is best achieved through a voluntary process that is initiated by the generic company, such as the one proposed in H.R. 1038.

Allowing the innovator company and additional third parties to sue on any patent prior to competitor launch would engage both parties in patent litigation for years and years. Unfortunately H.R. 5629 proposes such a system which would significantly delay the competitor company's ability to obtain certainty with regard to patents that could impact product launch. Also, 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?

Recent declaratory judgment (DJ) case law increases 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, we encourage 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?

Brand biologics patentees will seek to enforce their intellectual property just as aggressively as those in Hatch-Waxman. It will therefore 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?

In looking at the pending legislation, it seems clear that a follow-on biologics bill containing unnecessary barriers to follow-on biologic application submission and/or approval likely would be abused in order to delay follow-on market entry. As an 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.

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. 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 of a truly new and innovative brand product.

Therefore, Congress should avoid enacting unduly long brand exclusivity periods—just as Congress did when enacting Hatch-Waxman—particularly for modifications to existing biological products.

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?

Teva believes it is a reasonable possibility that some brand/generic biologic patent litigation cases will conclude with a settlement of some sort in a generic biologics marketplace. Settlements in the chemical compound world routinely contain significant pro-consumer benefits, such as guaranteed pre-patent expiration and generic market entry. Teva is not aware of any incentive for brand and generic companies to enter into "anticompetitive" settlement 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 are aware that reported agreements will be subject to extensive antitrust review. Should Congress bring agreements involving follow-on biologics under the same reporting requirements, FTC and DOJ will have the opportunity to conduct similar reviews of these agreements.