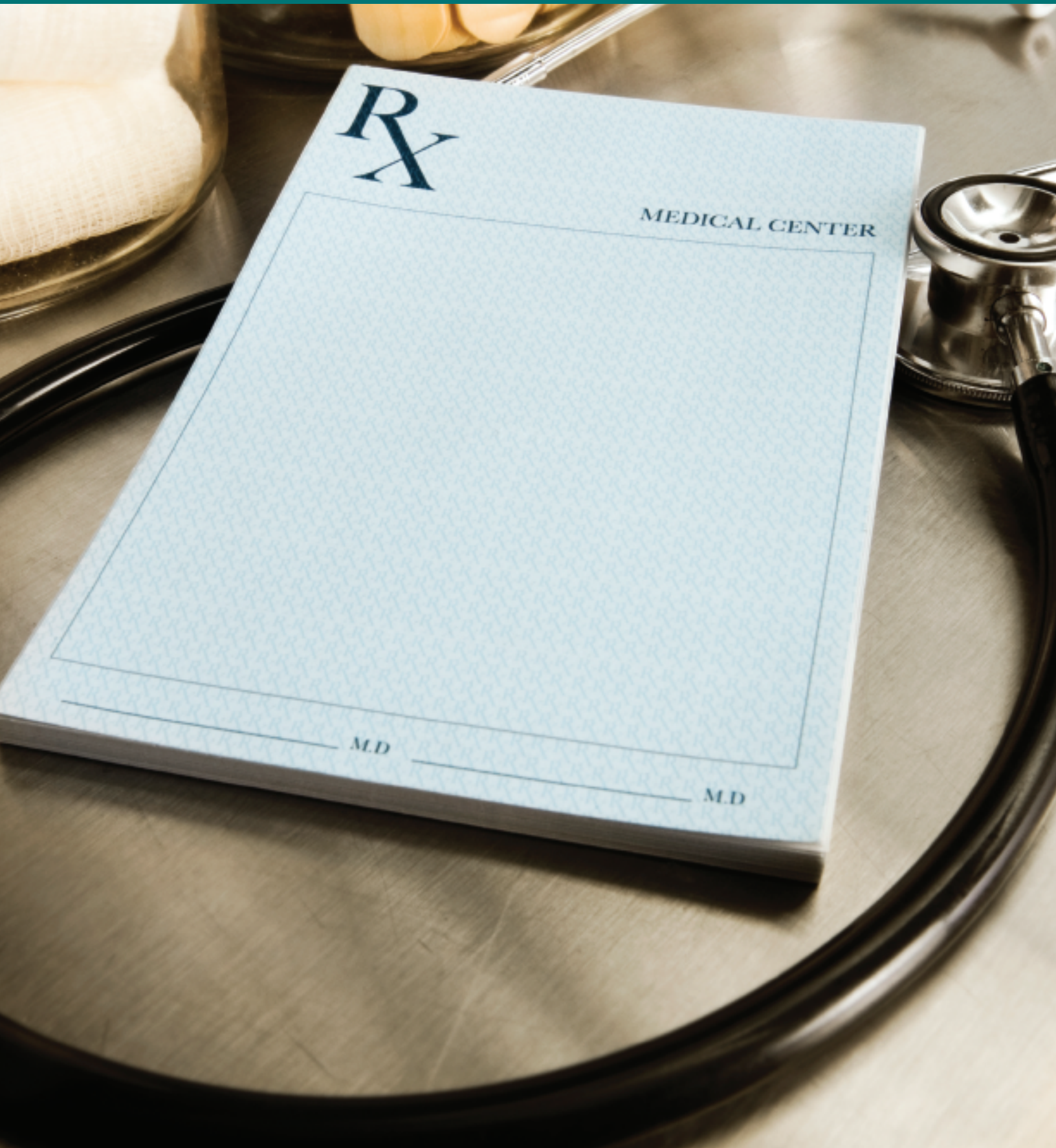




# Emerging Health Care Issues: Follow-on Biologic Drug Competition

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## EXECUTIVE SUMMARY

Over the past three decades, the lure of patent protection, coupled with the ability to price at market rates, has spurred pioneer drug manufacturers to develop new therapeutic drugs known as biologics. These innovations have improved medical treatments, reduced suffering, and saved the lives of many Americans. Biologic drugs are protein-based and derived from living matter or manufactured in living cells using recombinant DNA biotechnologies. The therapeutic proteins that form the basis of these biologic drugs are far more complex and much larger than the chemically synthesized, small molecules that form the basis of most pharmaceutical products.

Biologic drug innovations, however, are expensive. As examples, annual treatment for breast cancer with the biologic drug Herceptin can cost \$48,000 and the annual treatment for rheumatoid arthritis with Remicade can cost approximately \$20,000. Indeed, in 2007, Americans spent \$286.5 billion for prescription drugs, \$40.3 billion of which was for biologic drugs.<sup>1</sup>

Questions have arisen whether the price of biologics might be reduced by competition if there were a statutory process to encourage “follow-on biologics” (“FOBs”) to enter and compete with pioneer biologics once a pioneer drug’s patents have expired. The obvious model for such a statute is the Hatch-Waxman Act, which Congress enacted in 1984 to allow the Food and Drug Administration (“FDA”) to approve the sale of generic versions of branded drugs, among other things.<sup>2</sup> The Hatch-Waxman Act does not apply to biologics, which the FDA approves pursuant to the Public Health Safety (“PHS”) Act. Rather, Hatch-Waxman applies only to drugs regulated under the Federal Food Drug and Cosmetic Act (“FD&C Act”); these drugs are generally chemically synthesized, small-molecule products, not biologics.

Under Hatch-Waxman, competition from generic drugs has substantially reduced prescription drug prices and overall prescription drug expenditures, increased access to therapeutic drugs for more Americans, and hastened the pace of innovation.<sup>3</sup> In recent years, however, several court decisions have permitted “pay-for-delay settlements” that have reduced the procompetitive aspects of the Hatch-Waxman Act. The Commission supports legislation to prohibit these types of settlements in which the branded manufacturer pays the would-be generic

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<sup>1</sup> These sales figures are based on wholesale prices reported in the IMS Top Line Industry Data. Press Release, IMS Health, IMS Health Reports U.S. Prescription Sales Jump 3.8 Percent in 2007, to \$286.5 Billion (March 12, 2008), available at <http://www.imshealth.com> (follow “Press Room” hyperlink; then follow “IMS Health Care Reports News Release” hyperlink).

<sup>2</sup> See The Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 301 *et seq.* (2009), as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act” or “Hatch-Waxman”) and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, 21 U.S.C.A. § 355(j) (2009) and 35 U.S.C.A. § 271(e) (2009) [United States Code Annotated].

<sup>3</sup> See generally Jennifer S. Haas, et al., *Potential Savings from Substituting Generic Drugs for Brand-Name Drugs: Medical Expenditure Panel Survey, 1997-2000*, 142 ANNALS INTERNAL MED. 891 (June 2005); Wendy H. Schacht and John R. Thomas, Congressional Research Service (CRS), Library of Congress, *Report for Congress, Follow-On Biologics: Intellectual Property and Innovation Issues*, at 4 & 18, 110th Cong. (Jan. 17, 2008), available at [http://www.biosimilars.com/CRS\\_FOBs.pdf](http://www.biosimilars.com/CRS_FOBs.pdf).

entrant to abandon its patent challenge and delay entering the market with a lower cost, generic product.<sup>4</sup>

Hatch-Waxman does not require generic applicants to duplicate the clinical testing of drugs already proven safe and effective. Duplication of safety and efficacy information is costly, an inefficient use of scarce resources, and, as the FDA has explained, raises ethical concerns associated with unnecessary human testing.

To be approved under Hatch-Waxman, the applicant must show that its generic drug product is “bioequivalent” to (basically, the same as) the branded drug product. A bioequivalence showing is much less expensive than the clinical testing required for a branded drug product. Because the generic drug is “bioequivalent” to the branded drug, it can be safely substituted for the branded drug and expected to be as effective as the branded drug. To take advantage of generic competition, states have laws that allow pharmacists automatically to substitute a generic for a branded drug, unless a doctor has indicated otherwise.

The scientific differences between biologic and small-molecule drug products, however, complicate efforts to devise an approval process for FOB drugs based on bioequivalence. Biologic products are more complex and immunogenic than small-molecule drugs.<sup>5</sup> Current technology does not yet allow for the creation of an exact replica of a pioneer biologic drug product, according to the FDA. In addition, technology is not yet robust enough to determine whether an FOB product is “interchangeable” with the pioneer product such that a patient would be able to switch between the two products without the risk of an adverse effect. In light of these complexities, current legislative proposals permit FDA approval of an FOB drug that is sufficiently *similar* to, but not an exact replica of, the pioneer biologic product.<sup>6</sup> A showing of similarity is likely to save FOB manufacturers some clinical testing expenses but would require substantially more expense than a showing of bioequivalence for small-molecule generic drugs.

Whether competition between a pioneer biologic and an FOB is likely to be similar to competition between a branded and a generic drug is crucial to determining whether legislation to foster FOB competition should follow the same model as the Hatch-Waxman Act. Basic questions include whether the same issues that prompted provisions of the Hatch-Waxman Act that restrict entry by generic competitors are likely to be present in the context of FOB competition. To answer these questions, the Commission studied how competition between

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<sup>4</sup> See *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs: Hearing Before the H. Subcomm. on Commerce, Trade, and Consumer Protection, Comm. on Energy and Commerce*, 111th Cong. (2009) (Prepared Statement of the Federal Trade Commission), available at <http://www.ftc.gov/os/2009/03/P859910payfordelay.pdf>.

<sup>5</sup> Immunogenicity raises safety and effectiveness concerns because of a biologic drug’s ability to stimulate an immune response. See Letter from Frank M. Torti, Principal Deputy Comm’r and Chief Scientist, FDA, to Frank Pallone, Jr., Chmn., H. Subcomm. on Health, (Sept. 18, 2008) at 1, available at [http://energycommerce.house.gov/Press\\_110/fdabiosimilarrespons20080918.pdf](http://energycommerce.house.gov/Press_110/fdabiosimilarrespons20080918.pdf).

<sup>6</sup> See H.R. 1427, 111th Cong. § 3(a) (2009); H.R. 1548, 111th Cong. § 101 (2009).

pioneer biologics and FOBs is likely to develop to determine whether similar entry restrictions would benefit consumers.

The Commission brings substantial expertise to examining likely models of competition and likely competitive effects from particular regulatory schemes.<sup>7</sup> To assist in its study of the issues, the Commission solicited two rounds of public comments, conducted a public roundtable discussion on November 21, 2008, and accepted additional analysis and comments through May 2009. This report analyzes and synthesizes the Roundtable discussion, the comments received, and relevant economic literature to assess these issues. The Commission's findings and recommendations follow.

## **1. Competition Between a Biologic Drug and an FOB is Much More Likely to Resemble Brand-to-Brand Competition than the Dynamics of Brand-Generic Competition under Hatch-Waxman.**

Pioneer manufacturers, potential FOB manufacturers, and payors were virtually unanimous in their predictions that competition from FOB drug entry is likely to resemble brand-to-brand competition, rather than brand-to-generic drug competition. Experience to date for two markets with both pioneer biologic and FOB competitors (in Europe and the U.S.) confirms that, unlike generic drug entry, FOB entry has not resulted in steep price discounting, or rapid acquisition of market share, by FOB manufacturers.<sup>8</sup> This finding is true for a number of reasons:

- **The substantial costs to obtain FDA approval, plus the substantial fixed costs to develop manufacturing capacity, will likely limit the number of competitors that undertake entry with FOB products.** FOB products are likely to take eight to ten years to develop, and their development will likely cost between \$100 and \$200 million. These amounts differ substantially from the product development costs for small-molecule generic drugs, which typically take three to five years to develop and cost between \$1 and \$5 million.
- **Given these high entry costs, FOB entrants are likely to be large companies with substantial resources, and it is likely that only two to three FOB entrants will seek**

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<sup>7</sup> The Commission has reviewed pharmaceutical and biotechnology mergers for over 30 years, and has conducted numerous investigations and enforcement actions involving the conduct of branded and generic small-molecule drug manufacturers arising in the context of the Hatch-Waxman Act. See <http://www.ftc.gov/be/0608rxupdate.pdf>. The Commission also conducted a detailed empirical study of the experience during the 1993-2001 under the Hatch-Waxman Act's procedures designed to facilitate entry of generic drugs. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002). Since 2004, FTC staff has reviewed every drug company patent settlement filed under Hatch-Waxman, and issued annual reports on the types of patent settlements being undertaken. The reports are available at <http://www.ftc.gov/be/healthcare/drug/index.htm>.

<sup>8</sup> Historically, some biologic protein products have been regulated as drugs under the FD&C Act, including insulin, and human growth hormones. The FDA has approved six follow-on protein products under the FD&C Act. See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States Hearing Before H. Subcomm. on Health and the H. Comm. on Energy and Commerce*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Medical Officer, FDA), available at [http://energycommerce.house.gov/cmte\\_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf](http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf).

**approval to compete with a particular pioneer biologic drug.** Current pioneer biologic drug manufacturers are likely to become FOB competitors in those markets in which they do not currently compete. Moreover, high entry costs are likely to limit FOB drug entry to markets with sales in excess of \$250 million per year. The small number of likely FOB entrants contrasts significantly with the 10 or more generic entrants seen in many markets for small-molecule drugs.

- **The lack of automatic substitution between an FOB product and a pioneer biologic drug will slow the rate at which an FOB product can acquire market share and thereby increase its revenues.** In small-molecule drug markets, automatic substitution erodes a branded manufacturers' market share quickly once the first generic product enters the market. This situation is unlikely to occur in FOB markets. Unlike small-molecule generic drugs, FOB products will not be designated as "therapeutically equivalent" with the pioneer biologic drug product. The lack of therapeutic equivalence means that, like pioneer manufacturers, FOB manufacturers will have to market their products and negotiate individual contracts with purchasers.
- **An FOB drug also may have difficulty gaining market share due to concerns about safety and efficacy differences between a pioneer biologic drug and the competing FOB.** Physicians and their patients who have been taking a pioneer biologic drug may be reluctant to switch to an FOB due to a risk that the patients will react differently to the FOB than to the pioneer drug. Concerns such as these may limit FOB market opportunities to newly diagnosed patients.
- **The specialty pharmaceutical characteristics of FOBs also are likely to constrain the ability of an FOB entrant to obtain market share.** Specialty drugs, including biologic drugs, are commonly used to treat patients with severe, chronic diseases and sometimes fatal conditions. These drugs, which are primarily injected or infused, are combined with ancillary medical services and products that require specialty training for proper handling and administration. Because most biologic products are delivered to patients in clinics, hospitals, doctor's offices, or other medically supervised settings, shifting to another biologic product is typically more costly because it requires restocking of inventory and retraining of nurses and healthcare providers.
- **Biologic drugs currently are not reimbursed pursuant to strategies that payors often use to incentivize the use of lower-priced drugs; this, too, may limit market share acquisition by FOBs.** Biologic drug products are typically delivered to patients by healthcare providers as part of medical treatments (*e.g.*, dialysis treatments or oncology treatments) and reimbursed by health insurers as part of patients' medical benefits rather than pharmacy benefits. Consequently, traditional payor strategies to incentivize utilization of lower-priced drugs, including the use of co-pays and tiered formularies, are unlikely to apply to drive up the market share of FOBs. FOB pricing and market shares also are likely to be affected by the reimbursement methodologies used by Centers for Medicare and Medicaid Services ("CMS") for infused and injected drugs, which may not effectively drive share to lower-priced drugs.

- **As a result of these factors, FOB competition against a pioneer biologic drug is likely to develop as follows:** FOB entry is likely in biologic drug markets of greater than \$250 million. Only two or three FOB manufacturers are likely to attempt entry for a given pioneer drug product. These FOB entrants are unlikely to introduce their FOB products at price discounts any larger than between 10 and 30 percent of the pioneer products' price. Although not as steep a discount as small-molecule generic drugs, a 10 to 30 percent discount on a \$48,000 drug product represents substantial consumer savings. Pioneer manufacturers are expected to respond and offer competitive discounts to maintain market share. This price competition is likely to lead to an expanded market and greater consumer access. Nonetheless, the lack of automatic substitution will slow significant market share acquisition by FOB products. As a result, pioneer manufacturers are likely to retain 70 to 90 percent of their market share and, therefore, will likely continue to reap substantial profits years after entry by FOB drugs.

## **2. Existing Incentives that Support Brand-to-Brand Competition Among Biologic Drugs – Patent Protection and Market-Based Pricing – Are Likely to be Sufficient to Support FOB Competition and Biologic Innovation.**

A legislative process for an abbreviated FDA approval of an FOB is likely to be an efficient way to bring FOBs to market because of the time and cost savings it provides. Given that FOB competition with a pioneer biologic drug is likely to resemble brand-to-brand competition among biologics, the question arises whether provisions that delay FOB entry and restrict competition are necessary to benefit consumers. No economic arguments suggest that such provisions are necessary to foster pioneer drug innovation or entry of interchangeable FOBs.

Brand-to-brand competition among biologics has developed without any special legislative incentives, but rather through reliance on the patent system and market-based pricing. Patent protection enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights.<sup>9</sup> Market-based pricing allows biologic drug firms to charge prices that reflect the value of the drugs to consumers and thus assists firms not only in recouping their substantial investments in biologic drugs, but also in receiving accurate market signals about the value of developing particular biologic drugs.

Market experience shows that pioneer pharmaceutical and biologic products already compete against other branded pharmaceutical and biologic entrants, and this competition benefits consumers. Currently, pioneer or first-in-class branded products engage in a race with other branded competitors to bring products to market.<sup>10</sup> It is likely that FOB competition similarly will develop without any special legislative incentives.

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<sup>9</sup> F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, 3d Ed. 621 (1990).

<sup>10</sup> See Joseph DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 *PHARMACOECONOMICS* Supp 2:1-14, 10 (2004). Although this study examined pharmaceutical products primarily, it included several biologic drugs as well.

Indeed, any decision to adopt special legislative incentives that restrict competition may harm consumers. The Commission is mindful that the benefits of suppressing rivalry by either pioneer or FOB manufacturers are realized by a comparatively small number of firms who fully understand the importance of restricting competition. By contrast, the costs of restricting competition tend to be spread broadly across a large number of consumers, each of whom suffers a comparatively modest penalty compared to the relatively substantial gain realized by incumbent producers.<sup>11</sup> The phenomenon of highly focused benefits and broadly distributed costs gives firms a greater incentive to organize political resources to restrict competition.

**a. A Twelve- to Fourteen-Year Exclusivity Period is Unnecessary to Promote Innovation by Pioneer Biologic Drug Manufacturers.**

As explained earlier, pioneer biologic drug manufacturers are very likely to continue to earn substantial revenues even after the entry of FOBs. FOBs are unlikely to introduce their products at price discounts beyond 10 to 30 percent. Moreover, FOBs are likely to have difficulty rapidly growing their market shares as compared to generic small-molecule drug products. Indeed, projections are that branded biologic drugs are likely to maintain their first-mover advantages by retaining 70 to 90 percent of their market share years after FOB entry.

In addition, there is very little data to suggest that biologic drugs under development are likely to be unpatentable. Pioneer biologic drugs are covered by more and varied patents, including manufacturing and technology platform patents, than small-molecule branded products. Moreover, there is no evidence that patents claiming a biologic drug product have been designed around more frequently than those claiming small-molecule products.

Pioneer biologic manufacturers nevertheless have suggested that Congress institute a period of 12 to 14 years of branded exclusivity that would begin once a pioneer biologic was approved by the FDA.<sup>12</sup> During this period, the FDA would be prohibited from approving an FOB product that would compete with the pioneer biologic drug. This branded exclusivity would be in addition to, and would run concurrent with, a biologic drug's existing patent protection. The economic model put forth by pioneer drug manufacturers to justify this period is

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<sup>11</sup> See Organization for Economic Co-operation and Development, *Challenges Obstacles Faced by Competition Authorities in Achieving Greater Economic Development Through the Promotion of Competition, Contribution from the United States* (Feb. 5, 2004), available at <http://www.scribd.com/doc/1170395/US-Federal-Trade-Commission-2004Challenges20Obstacles20aced20by20Competition>.

<sup>12</sup> This report uses the term “branded exclusivity” rather than “data exclusivity” because current legislative proposals permit an FOB applicant to rely on FDA’s finding or conclusion that an approved pioneer drug is safe and effective. This reliance does not involve disclosure to the FOB applicant, or to the public, of the data in the pioneer manufacturers’ application. See Letter from Director Steven K. Glason, Center for Evaluation and Research (“CDER”), FDA to Petitioners (May 30, 2006) at 6, available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>. The term “data exclusivity” suggests a use of the information that is inconsistent with FDA’s longstanding interpretation of its approval process.



based on the average time required to recoup the investment to develop and commercialize a typical biologic drug (referred to as the “Nature model”).<sup>13</sup>

Congress has implemented exclusivity provisions in the past to encourage the development of new and innovative drug products when the drug molecule is in the public domain, and therefore not patentable. The Hatch-Waxman Act provides a five-year exclusivity period to incentivize the development of new chemical entities and it provides a three-year exclusivity period for new clinical investigations of small-molecule drugs. In other instances, Congress has implemented an exclusivity period when market-based pricing has not provided sufficient incentive to develop drug products for children or small patient populations.

Central to each of these exclusivities is a public policy trade-off: a restriction on competition is provided in return for the development of a *new* drug product or *new* use of an existing product. A 12- to 14-year exclusivity period departs sharply from this basic trade-off, because it does not spur the creation of a *new* biologic drug or indication. The drug has already been incentivized through patent protection and market-based pricing.

The potential harm posed by such a period is that firms will direct scarce R&D dollars toward developing low-risk clinical and safety data for drug products with proven mechanisms of action rather than toward new inventions to address unmet medical needs. Thus, a new 12- to 14-year exclusivity period imperils the efficiency benefits of a FOB approval process in the first place, and it risks over-investment in well-tilled areas.

The Nature model as currently structured contains numerous methodological and conceptual weaknesses that render its results too imprecise and non-robust to inform discussions about the ideal length of any branded exclusivity period. A model that balances the benefits of FOB competition (*i.e.*, lower prices and an increased pace and scope of innovation) with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model’s approach.

Moreover, to the extent that there are new biologic molecules that cannot obtain patent protection, an exclusivity period may be warranted. Because there is no evidence about the lack of patentability of new biologic products, nor that market forces have been insufficient to incentivize their development, the Commission has not recommended a specific length for an exclusivity period.

**b. Special Procedures to Resolve Patent Issues Between Pioneer and FOB Drug Manufacturers Prior to FDA Approval Are Unnecessary and They Could Undermine Patent Incentives and Harm Consumers.**

Once a pioneer biologic drug manufacturer receives FDA approval and is about to market its product, it faces the risk of patent infringement litigation. FOB manufacturers are likely to face the same risk. If they believe the patent situation justifies their decisions to launch prior to

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<sup>13</sup> Henry C. Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 (June 2008).

resolution of any patent infringement litigation, they will enter once they have received FDA approval. If not, they will wait for the patents to expire and then launch their product. Special procedures, providing an early start to resolving patent disputes between pioneer and FOB manufacturers prior to FDA FOB approval, are not necessary to encourage FOB entry that otherwise would not have occurred.

Hatch-Waxman's special procedures for small-molecule drugs provide for an early start of patent litigation. Hatch-Waxman procedures have been the subject of extensive litigation, unintended consequences, and delayed generic entry. These procedures were designed in 1984 to address the issue of "judgment proof" generic defendants. In small-molecule drug competition, the profits of the alleged infringer (the generic entrant) are substantially less than the loss of profits by the branded product manufacturer, because of the substantial price differences between branded and generic products. Consequently, especially at the beginning of the generic industry in 1984, concerns existed that generic entrants in small-molecule drug markets might be unable to satisfy a potential treble damage award for infringing the branded manufacturer's patents.

FOB entrants will not be similarly judgment proof. FOB drug manufacturers are likely to be many of the same companies that have pioneered biologic drugs; thus, they will have the expertise and resources necessary to assess whether to launch their product before any patent infringement litigation is resolved, just as they do with a launch of a pioneer branded drug. Moreover, FOB manufacturers are highly unlikely to offer steep discounts that could jeopardize their ability to pay patent damages.

Special procedures are unlikely to be successful in providing patent certainty to the parties, because pioneer biologic drugs are covered by more and varied patents than small-molecule drugs. A special pre-approval patent resolution process is unlikely to succeed in raising and resolving all pertinent patent issues prior to FDA approval. Patents claiming the pioneer product may issue after a pre-approval process has begun and/or after FDA approval. The FOB manufacturer's application and product also may change during the approval process such that starting patent litigation prior to FDA approval would not ensure earlier resolution. Moreover, without a mechanism to enforce the rules of a pre-approval resolution process, there is no guarantee that litigation started prior to FDA approval will end earlier. In essence, early start does not guarantee early resolution.

Special procedures also could undermine the innovation incentives that patent protection affords pioneer biologic manufacturers. Although special procedures govern patent litigation between branded and generic competitors over small-molecule drug products, these procedures are the exception, not the norm.

Finally, based on the experience under Hatch-Waxman, a pre-approval patent resolution process also is likely to lead to consumer harm, including the facilitation of anticompetitive conduct that defeats the purpose of starting the patent litigation early. In the Hatch-Waxman context, branded manufacturers have used the pre-approval patent regulations to delay generic entry. In addition, generic and branded competitors have entered into "pay-for-delay" patent settlements that delay entry, not encourage it. It is likely that a pre-approval patent resolution

process in the FOB context could facilitate collusive agreements and/or provide the pioneer biologic drug manufacturer with competitively sensitive information about a significant potential competitor to which it otherwise would not have access.

**c. FOB Drug Manufacturers Are Unlikely to Need Additional Incentives to Develop Interchangeable FOB Products.**

The question arises whether an FOB manufacturer needs an incentive beyond market-based pricing to develop an interchangeable FOB drug, such as a limit on when subsequent interchangeable FOB drug entry can occur. This limitation would allow the first interchangeable FOB manufacturer to recoup its development expenses. Because the market dynamics of FOB entry are likely to resemble competition among branded biologic drugs, provisions modeled after the Hatch-Waxman Act's 180-day marketing exclusivity are unlikely to be necessary and, indeed, could harm consumers.

The Hatch-Waxman Act provides a 180-day marketing exclusivity period to the first generic drug applicant that seeks FDA approval prior to the expiration of patents relating to the branded drug product. No other generic manufacturer may obtain FDA approval to market its product until the first generic has sold its product for 180 days or has forfeited its exclusivity period.

The 180-day exclusivity period incentivizes generic manufacturers to challenge the patents claiming a pioneer small-molecule drug product. A court finding of patent invalidity benefits not only the challenger, but also subsequent generic applicants whose entry is no longer blocked by the patent. Thus, the 180-day marketing exclusivity period prevents immediate free-riding by subsequent generic applicants on a favorable outcome that results from a generic applicant's patent challenge. As subsequent generic firms enter, generic prices can drop to 80 percent off the branded price, depending upon the number of entrants.<sup>14</sup> The exclusivity period is supposed to permit the first generic entrant to recoup its patent litigation costs before the substantial price drop caused by multiple generic entrants.

The competitive dynamics that justified the 180-day exclusivity period for small-molecule generic drugs are unlikely to be present here, because the entry of a subsequent interchangeable FOB is unlikely to cause a substantial price drop due to the high costs of developing and manufacturing and FOB. The first interchangeable FOB to enter will continue to earn sufficient profits even after entry of subsequent interchangeable products. Thus, market opportunities are likely to be sufficient to incentive development of interchangeable FOBs.

Not only do market dynamics counsel against an FOB exclusivity period, but the anticompetitive delay in entry evidenced in small-molecule generic drug markets is likely to

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<sup>14</sup> See David Reiffen & Michael Ward, "Branded Generics" As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 *MANAGERIAL AND DECISION ECONOMICS*, 251-265, 264 (2005), available at [http://ftc.gov/be/healthcare/wp/12\\_Reiffen\\_BrandedGenericsAsAStrategy.pdf](http://ftc.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf).

repeat if an exclusivity provision for interchangeable FOBs is implemented.<sup>15</sup> The current 180-day exclusivity period exacerbates the problem of “pay-for-delay” settlement that prevents generic entry.<sup>16</sup>

Awarding an FOB exclusivity period on a “first-to-approve” rather than a “first-to-file” basis does not lessen the potential harm. These anticompetitive consequences are likely to result if the period can be extended, the period does not run immediately upon its award, or if a firm has the ability to delay triggering the running of the period through, for example, a patent settlement, acquisition, merger, or agreement.

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<sup>15</sup> See FDA, Center for Drug Evaluation and Research, 180-Day Generic Drug Exclusivity (2001), available at [http://www.fda.gov/cder/about/smallbiz/generic\\_exclusivity.htm#COURT](http://www.fda.gov/cder/about/smallbiz/generic_exclusivity.htm#COURT) (“This 180-day exclusivity provision has been the subject of considerable litigation and administrative review in recent years...”).

<sup>16</sup> See *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs: Hearing Before the H. Subcomm. on Commerce, Trade, and Consumer Protection, Comm. on Energy and Commerce, 111th Cong.* (2009) (Prepared Statement of the Federal Trade Commission), available at <http://www.ftc.gov/os/2009/03/P859910payfordelay.pdf>.

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**APPENDIX A**

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## INTRODUCTION

The Commission initiated this inquiry because decisions of regulatory bodies such as the Food and Drug Administration substantially shape business rivalry.<sup>1</sup> This inquiry is very mindful of how innovation in the biotechnology industry is highly dependent on patent protection.<sup>2</sup>

Biotechnology innovation is costly and unpredictable, requiring significant amounts of investment to test and commercialize new drug products. By preventing rival firms from free riding on discoveries, patents allow firms to recoup the substantial capital investments made to discover, test, and obtain regulatory approval of new drug products. Patents also are necessary to attract the capital to fund high-risk investment in the biotechnology industry.<sup>3</sup> Thus, this report approaches this problem by examining the likely competitive effects of a new regulatory scheme in the highly risky, costly and time-consuming process of bringing new biologic drugs to the market.

Chapter 1 of this report examines the likely market impact of FOB entry and contrasts it to the market impact of small-molecule generic drugs. The Commission is mindful that the likely competitive effects of FOB entry are based on the available knowledge of existing external market conditions. For example, the likely competitive effects of FOB competition could change if technology breakthroughs occur, biosimilar safety issues arise, health insurance coverage expands, or payor and reimbursement strategies change, among others. In sophisticated industries such as biotechnology, external conditions can and do change and often alter expectations of profit-maximizing firms.<sup>4</sup> This industry, however, has shown significant ability to adapt and thrive under new market conditions.<sup>5</sup> The Commission expects the robust and dynamic market conditions of the biologic drug industry to continue with the entry of FOB drug products.

Chapter 2 examines whether in addition to patent protection and market-based pricing, pioneer biologic drug products need a branded exclusivity period to promote innovation in biologic drug markets. Chapter 3 examines whether special procedures are necessary to resolve

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<sup>1</sup> The Commission outlined its preliminary views on the likely effects of an abbreviated regulatory approval pathway for biologic drug products in May 2008. See Letter of the Federal Trade Commission to the Honorable Frank Pallone, Jr., Chairman, Subcommittee on Health, Committee on Energy and Commerce, House of Representatives (May 2, 2008), available at: [http://energycommerce.house.gov/Press\\_110/110-ltr.050208.respto040308.FTC.pdf](http://energycommerce.house.gov/Press_110/110-ltr.050208.respto040308.FTC.pdf).

<sup>2</sup> It is beyond the scope of this report to determine whether a 20-year patent life is the optimal period to incentivize innovation in this and other industries that rely on patent protection.

<sup>3</sup> See FEDERAL TRADE COMM'N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (2003), Ch. 3 at 1, available at <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>.

<sup>4</sup> See Charles E. Phelps, *Managing the Market: Regulation and Technical Change in Health Care*, HEALTH ECONOMICS, at 498-546 (3<sup>rd</sup> ed. 2003).

<sup>5</sup> See Iain M. Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFFAIRS 1:10-22, 14 (2004).

potential patent disputes between pioneer and FOB manufacturers prior to FDA approval of an FOB drug product. Chapter 4 examines whether market profits are insufficient to incentivize the development of interchangeable FOB products.

The FTC appreciates the 29 comment filers and 30 panelists who contributed time, effort, and thoughtful analysis to these issues before, during, and after the public roundtable discussion. We also are grateful for the intellectual property and economic experts proffered by the biotechnology and pharmaceutical manufacturers.

# CHAPTER 1 BACKGROUND AND LIKELY MARKET IMPACT OF FOLLOW-ON BIOLOGIC COMPETITION

## I. BACKGROUND

Innovations in biotechnology have improved medical treatments, reduced suffering, and saved the lives of millions of Americans. The lure of patent protection, coupled with the ability to price at market rates, has spurred pioneer drug manufacturers to develop new therapeutic drugs known as biologics.<sup>1</sup> The Food and Drug Administration (“FDA”) approves biologic drugs under the Public Health Safety Act (“PHS Act”).

These innovations, however, are expensive. As examples, annual treatment for breast cancer with the biologic drug Herceptin can cost \$48,000 and the annual treatment for rheumatoid arthritis with Remicade can cost approximately \$20,000. Indeed, in 2007, Americans spent \$286.5 billion for prescription drugs, \$40.3 billion of which was for biologic drugs.<sup>2</sup>

In 1984, Congress enacted the Hatch-Waxman Act to allow the FDA to approve the sale of generic or follow-on versions of off-patent branded drugs.<sup>3</sup> This process applies to drugs regulated only under the Federal Food Drug and Cosmetic Act (“FD&C Act”), which are generally chemically-synthesized, small-molecule products. It does not apply to drugs approved under the PHS Act.

Under Hatch-Waxman, generic applicants are not required to duplicate the clinical testing of drugs already proven safe and effective. Rather, to be approved, the applicant must show that its generic drug product is the same as the branded drug product. A bioequivalence showing is much less expensive than the clinical testing required for a pioneer branded drug product and thus, is an efficient way to leverage scarce research and development (“R&D”) funds to target innovative drug development.

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<sup>1</sup> Biologic drugs are derived from living matter or manufactured in living cells using recombinant DNA biotechnologies. See FDA Center for Biologic Drug Evaluation and Research (CBER), *Frequently Asked Questions About Therapeutic Biologic Drug Products*, available at <http://www.fda.gov/cder/biologics/qa.htm>.

<sup>2</sup> These sales figures are based on wholesale prices reported in the IMS Top Line Industry Data. Press Release, IMS Health, IMS Health Reports U.S. Prescription Sales Jump 3.8 Percent in 2007, to \$286.5 Billion (March 12, 2008), available at <http://www.imshealth.com> (follow “Press Room” hyperlink; then follow “IMS Health Care Reports News Release” hyperlink); see also CONG. BUDGET OFFICE (“CBO”) 110TH Cong., BUDGET OPTIONS VOL.1: HEALTH CARE at 126-28 (2008), available at <http://cbo.gov/ftpdocs/99xx/doc9925/12-18-HealthOptions.pdf> [hereinafter, “BUDGET OPTIONS”].

<sup>3</sup> See The Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 301, *et seq.* (2009), as amended by The Drug Price Competition and Patent Term Restoration Act of 1984 [hereinafter, the “Hatch-Waxman Act” or “Hatch-Waxman”] and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, 21 U.S.C.A. § 355(j) (2009) and 35 U.S.C.A. § 271(e) (2009). See Appendix B for a description of the new and abbreviated drug approval processes.

Competition provided by the generic drug industry has reduced prescription drug prices, increased access for more Americans, and hastened the pace of innovation.<sup>4</sup>

There is no similar approval process for biologic drugs.<sup>5</sup> Rather, once a biologic drug product's patents expire, the follow-on applicant must duplicate the clinical testing of the pioneer biologic drug. This duplication of safety and efficacy information is costly, an inefficient use of scarce resources, and, as the FDA has explained, raises ethical concerns associated with unnecessary human testing.

The desire to avoid these consequences by creating an approval process for follow-on biologic ("FOB") drugs takes on urgency in light of the significant number of biologic drugs that go off-patent within the next several years. Figure 1-1 shows the 27 top selling biologic drug products, many of which go off patent by 2015.<sup>6</sup> The drugs listed comprise approximately 87 percent of the total global value of the biologics industry of \$112 billion.

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<sup>4</sup> See generally Jennifer S. Haas *et al.*, *Potential Savings from Substituting Generic Drugs for Brand-Name Drugs: Medical Expenditure Panel Survey, 1997-2000*, 142 ANNALS INTERNAL MED. 891 (June 2005); Wendy H. Schacht & John R. Thomas, Congressional Research Service (CRS), Library of Congress, *Report for Congress, Follow-On Biologics: Intellectual Property and Innovation Issues*, at 4 & 18, 110th Cong. (Jan. 17, 2008), available at [http://www.biosimilars.com/CRS\\_FOBs.pdf](http://www.biosimilars.com/CRS_FOBs.pdf).

<sup>5</sup> See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States Hearing Before H. Subcomm. on Health and the H. Comm. on Energy and Commerce*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Medical Officer, FDA), available at [http://energycommerce.house.gov/cmte\\_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf](http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Woodcock-testimony.pdf) [hereinafter, "Woodcock Statement"]. Historically, some biologic protein products have been regulated as drugs under the FD&C Act. The FDA has approved six follow-on protein products under the FD&C Act, including Hylenex (hyaluronidase recombinant human), Hydase (hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatropin [rDNA origin]). *Id.*

<sup>6</sup> See Bernstein Research Comment (9/29/08) at 2; Biotechnology Industry Organization ("BIO"), Health Overview, available at <http://www.bio.org/healthcare> (last accessed June 8, 2009); CBO, BUDGET OPTIONS at 126; Hospira (Wilkie Farr) Comment (12/22/08) at 5 and Attachment 1. Patent expiration information was obtained from SEC form 10-K filings. FDA maintains a searchable catalog of approved drug products including drug approval history. See, Drugs@FDA, available at <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA>.

**Figure 1-1: Top-Selling Biologic Products (estimates of peak sales in billions)**

Drug	2008 Sales	Year Approved	Drug	2008 Sales	Year Approved	Drug	2008 Sales	Year Approved
Avastin	\$9.2	2004	Novolog	\$3.7	2000	Rebif	\$1.7	2002
Enbrel	\$8.0	1998	Erbitux	\$3.6	2004	Cerezyme	\$1.5	1994
Remicade	\$7.9	1998	Aranesp	\$3.2	2001	Tysabri	\$1.4	2004
Humira	\$7.3	2002	Recombinate	\$2.9	1998	NovoSeven	\$1.4	1999
Rituxan	\$7.3	1997	Lucentis	\$2.7	2006	Synagis	\$1.3	1998
Herceptin	\$5.7	1998	Avonex	\$2.6	1996	Neupogen	\$1.3	1991
Lantus	\$5.1	2000	Novolin	\$2.5	1991	Betaseron	\$1.2	1993
Epogen/ Procrit	\$5.1	1989	Humalog	\$2.2	1996	Humulin	\$1.1	1992
Neulasta	\$4.2	2002	PEGASYS	\$2.0	2002	Kogenate FS	\$1.1	1993

The scientific differences between biologic and small-molecule drug products, however, complicate efforts to devise an approval process for FOB drugs. Biologic products are more complex and immunogenic than small-molecule drugs.<sup>7</sup> Current technology does not yet allow for the creation of an exact replica of a pioneer biologic drug product, according to the FDA.<sup>8</sup> In addition, technology is not yet robust enough to determine whether an FOB product is “interchangeable” with the pioneer product such that a patient would be able to switch between the two products without an adverse effect.

In light of these complexities, current legislative proposals permit FDA approval of an FOB drug that is sufficiently *similar* to, but not an exact replica of, the referenced branded biologic product.<sup>9</sup> A showing of similarity is likely to save clinical testing expenses but would require substantially more expense than a showing of bioequivalence for small-molecule generic drugs. Unlike small-molecule drugs, FOB products would not be designated as “therapeutically equivalent” with the referenced product. The lack of therapeutic equivalence means that a pharmacist may not substitute prescriptions for a pioneer product to an FOB product without physician consent. As technology and scientific understanding develops, however, the approval process could provide a means by which an FOB applicant could show that its product is interchangeable with the pioneer product.

<sup>7</sup> Immunogenicity raises safety concerns because of a biologic drug’s ability to stimulate an immune response. An immune response to a therapeutic protein can range from development of detectable but not clinically significant antibodies to an immune response with significant impact on safety or effectiveness, including the potential to decrease or block the clinical effect of the therapeutic protein. See Letter from Frank M. Torti, Principal Deputy Comm’r and Chief Scientist, FDA, to Frank Pallone, Jr., Chmn., H. Subcomm. on Health, (Sept. 18, 2008) at 1, available at [http://energycommerce.house.gov/Press\\_110/fdabiosimilarrespons20080918.pdf](http://energycommerce.house.gov/Press_110/fdabiosimilarrespons20080918.pdf).

<sup>8</sup> *Id.* at 4; Woodcock Statement at 1 (“[T]he idea of *sameness*, as the term is used in the generic drug approval process under the [FD&C] Act and applied to small-molecules, will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products under the [PHS] Act.”).

<sup>9</sup> See H.R. 1427, 111th Cong. § 3(a) (2009); H.R. 1548, 111th Cong. § 101 (2009).

In the current legislative debate, questions have arise over whether the same issues that prompted provisions of the Hatch-Waxman Act that restrict entry by generic competitors are likely to be present in the context of FOB competition. To answer these questions, the Commission initiated a public inquiry, including a public workshop and a series of public comments, to examine how FOB competition is likely to develop to determine whether similar entry restrictions would benefit consumers.<sup>10</sup>

This chapter describes the regulatory background necessary to understand how an FOB approval process could be used by FOB manufacturers. It then describes the likely market impact of FOB entry and contrasts it to the market impact of small-molecule generic drugs. This analysis sets the stage for the discussion in Chapters 2 through 4 of specific issues regarding how to foster FOB competition to benefit consumers.

## **II. THE NEW DRUG AND GENERIC APPROVAL PROCESSES**

### **A. New Drug Approval Processes Under the FD&C Act and the PHS Act**

To obtain FDA approval of a new small-molecule drug under the FD&C Act or a biologic product under the PHS Act, the manufacturer must prove that the product is safe and effective. Manufacturers must submit the following information to the FDA for approval:

- (a) pre-clinical analytical tests, pre-clinical studies and formulation studies;
- (b) an Investigational New Drug Application (“IND”) to initiate human clinical testing;
- (c) adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for its intended use;
- (d) approval and validation of commercial scale manufacturing facilities used in production of the product;
- (e) drug manufacture and analytical methods; and
- (f) proposed product packaging and labeling.<sup>11</sup>

The pre-clinical phase of any new drug development typically identifies compounds (either small-molecule or protein-based) that target a particular disease or are therapeutically beneficial. Once a lead compound is isolated, the manufacturer conducts pre-clinical safety trials, as well as trials in predictive animal models to determine if the compound works as expected. This pre-clinical phase typically takes one to five years.<sup>12</sup>

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<sup>10</sup> See Notice of Public Workshops and Roundtables and Opportunity for Comment, Emerging Health Care Competition and Consumer Issues, 73 Fed. Reg. 51479-51482 (Sept. 3, 2008), available at <http://www.ftc.gov/bc/workshops/hcbio/index.shtml>.

<sup>11</sup> See 42 U.S.C.A. § 262; 21 U.S.C.A. § 321, *et seq.* (2009).

<sup>12</sup> See, e.g., Ernst R. Berndt *et al.*, *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA* (Nat’l Bureau of Econ. Research, Working Paper No. W11425, 2005).

After pre-clinical tests are completed, a drug sponsor submits these results in an IND to the FDA before human clinical trials may commence.<sup>13</sup>

Clinical trials typically consist of three phases. In Phase I, a small group of patients is given the drug to determine if the drug is safe in humans. In Phase II, a small sample of the intended patient population is given doses of the drug to provide a preliminary assessment of the efficacy of the drug for a specific clinical indication, find dose tolerance, and find the optimal dose range. Phase III studies are initiated if Phase I and Phase II studies indicate the drug is safe and has some efficacy in the targeted patient population. Phase III studies are designed to gather sufficient data in a broad target population in order to establish safety and efficacy for a particular indication.

The time to conduct these trials varies based on factors such as indication, availability of reliable ways to measure efficacy, size of patient populations in the clinical trials, ease of patient accrual, as well as a host of other factors. Despite these variances, Phase I takes approximately one year, Phase II (including dose ranging studies) takes approximately two years, and Phase III takes approximately three years.<sup>14</sup>

## **B. Generic Drug Approval Under the FD&C Act**

Rather than requiring a generic manufacturer to repeat the costly and time-consuming new drug approval process, the Hatch-Waxman Act permits generic drug applicants to file an Abbreviated New Drug Application (“ANDA”). The object of the ANDA process is to demonstrate that the generic drug product has the same active ingredient, route of administration, dosage form, strength, and proposed labeling as the branded drug. The ANDA also must contain sufficient information to demonstrate that the generic drug is “bioequivalent” to the relevant branded product.<sup>15</sup> As a result of providing this information, the generic applicant may rely on the FDA’s previous findings of safety and effectiveness for the branded drug, and the applicant, therefore, does not have to perform its own clinical studies. This reliance allows generic applicants to save substantial time and development costs.<sup>16</sup> The FDA will deem a generic drug product therapeutically equivalent to the branded product. This designation allows the generic drug to be automatically substituted by a pharmacist for the branded product.

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<sup>13</sup> 42 U.S.C.A. § 262; 21 U.S.C.A. § 321, *et seq.*; 21 C.F.R. 601.2; 21 C.F.R. 312 (2009).

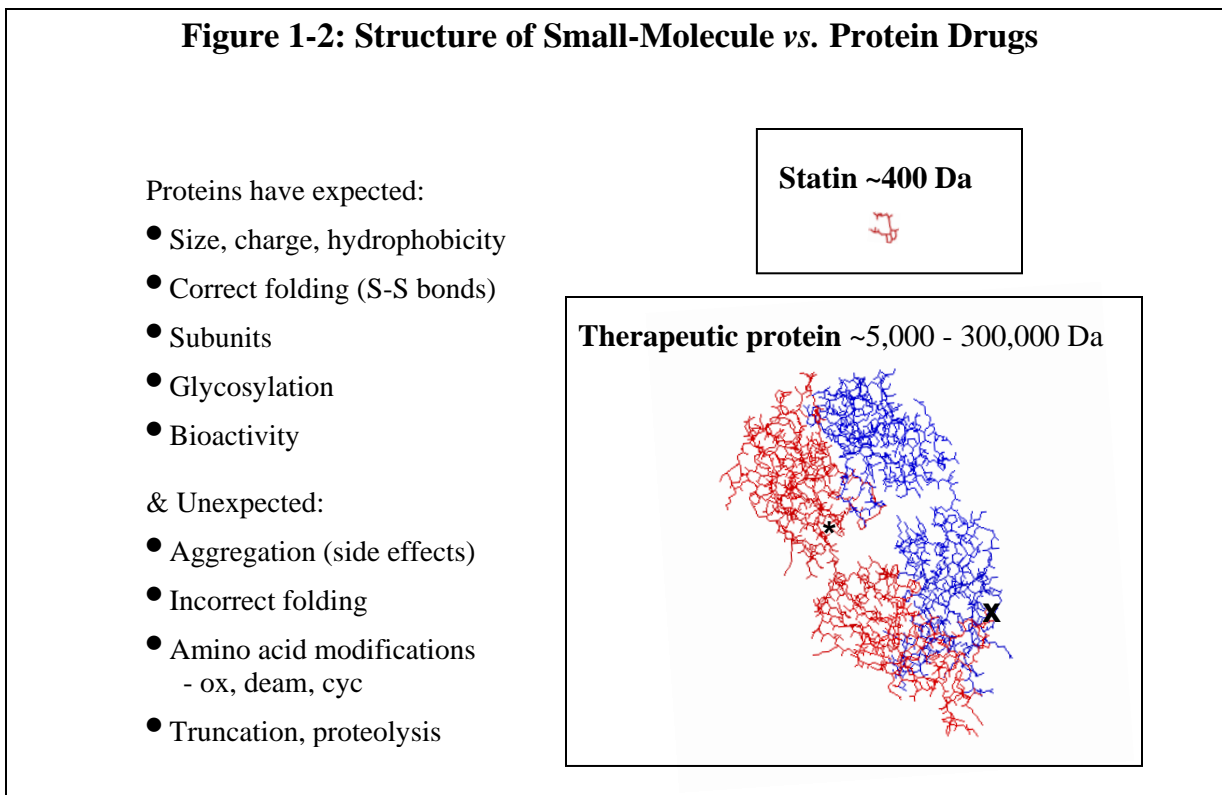
<sup>14</sup> See Henry Grabowski *et al.*, The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Public Health Service Act Follow-on Biologics: Key Issues and Assumptions, White Paper (July 1, 2007) at 8, 25, 27-28, 33 (unpublished paper on file with Analysis Group, Inc.), available at [http://www.analysisgroup.com/analysisgroup/News\\_Study-Effects-Federal-Spending-Follow-On-Biologics-Legislation.aspx](http://www.analysisgroup.com/analysisgroup/News_Study-Effects-Federal-Spending-Follow-On-Biologics-Legislation.aspx) [hereinafter “White Paper”].

<sup>15</sup> 21 U.S.C.A. § 355(j)(2)(A)(iv)(2009). Bioequivalence means that the rate and extent of absorption of the generic drug is not significantly different from the rate and extent of absorption of the reference listed drug when administered at the same dosage.

<sup>16</sup> CBO, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*, at ix (1998), available at <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> [hereinafter, “*Increased Competition from Generic Drugs*”].

### C. Issues in Translating the Generic Drug Approval Process to Biologic Drugs Under the PHS Act

The scientific differences between biologic and small-molecule drugs complicate efforts to devise an approval process for FOB drugs based on bioequivalence.<sup>17</sup> Figure 1-2 shows the size differences between a typical small-molecule drug and a biologic protein and lists some of the complexities surrounding protein drugs. These differences include a ten to hundred-fold difference in size. A small-molecule drug, such as a statin (*e.g.*, Lipitor, Mevacor), is small (only 400 Daltons) and simple in contrast to a biologic drug. A biologic drug is significantly larger (5,000-300,000 Daltons) and has a complex structure with three-dimensional folding which performs complex binding, unlike small-molecules. Any deviation in a biologic protein's structure can result in aggregation, incorrect folding and structural anomalies (*e.g.*, truncation, proteolysis and amino acid modifications) that can have unexpected effects on efficacy and safety.<sup>18</sup>



Source: Behrman Presentation at 6

<sup>17</sup> Testimony of Rachel Berhman, Associate Comm'r for Clinical Programs, Director of the Office of Critical Path Programs, FDA, at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues (Nov. 21, 2008) at 10-20, available at <http://www.ftc.gov/bc/workshops/hcbio/transcripts/081121biologic-transcript.pdf> [hereinafter transcript cites are referenced as [last name] at [page]]; Woodcock Statement at 8-9.

<sup>18</sup> Behrman at 10-20; Rachel Behrman, *Follow-on Biologics: A Brief Overview at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues* (Nov. 21, 2008) at 6 [hereinafter "Behrman Presentation"].



Current limitations in analytical methods make it difficult to characterize and compare large molecules to determine their level of sameness. Manufacturing a consistent biologic drug product presents additional difficulties.<sup>19</sup> In light of these challenges, it is unlikely that FOB manufacturers could only use analytic methods to show that their FOB products have the same active ingredient as the pioneer biologic product, as generic small-molecule drug applicants do pursuant to the Hatch-Waxman Act.<sup>20</sup>

In light of these complexities, current legislative proposals permit FDA approval of an FOB drug that is sufficiently *similar to*, but not an exact replica of, the pioneer product.<sup>21</sup> A showing of similarity is likely to save clinical testing expenses but would require substantially more expense than a showing of bioequivalence for small-molecule generic drugs. The amount of savings, however, may vary depending upon the complexity of the pioneer product to ensure that the FOB product is safe, pure and potent.<sup>22</sup> Although abbreviated compared to a full development program, FOB applicants are likely to perform Phase I and Phase III studies, but with fewer patients. FOB manufacturers also must seek approval and validation of their commercial-scale manufacturing facilities at or before initiation of clinical trials.<sup>23</sup> For each additional indication for which they seek labeling, FOB manufacturers are likely to be required to perform Phase I – Phase III clinical testing.<sup>24</sup>

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<sup>19</sup> See Woodcock Statement at 8 (“Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.”); Behrman Presentation at 6; Behrman at 13-20.

<sup>20</sup> See Behrman at 12-13 (“[P]roteins [biologics] . . . are chains of amino acids . . . they can range from very simple to extremely complex, and when they're very complex, they are folded; they have things stuck on them; they can unfold again; and then they can aggregate.”); see also Norman at 153 (“[T]he chemical [small-molecule] compound itself is something that always looks like chicken wire, so it's got a methyl on one end and maybe an ethyl on the other, but it's going to look like methyl ethyl chicken wire, and every follow-on generic or branded firm] that makes that molecule . . . is going to make methyl ethyl.”).

<sup>21</sup> See S. 1695, 110th Cong. (2008); H.R. 1427, 111th Cong. (2009).

<sup>22</sup> See Woodcock Statement at 11 (“When the mechanism of action is well understood and there is a significant amount of clinical experience with a product, it may be easier to make a scientific assessment of the ability to rely on conclusions about safety and efficacy from a prior application.”).

<sup>23</sup> For a description of the FDA clinical requirements required to approve the first biosimilar product in the U.S. see Letter from Director Steven K. Glason, Center for Evaluation and Research (“CDER”), FDA to Petitioners (May 30, 2006) at 7, 25 (Novartis’ application for Omnitrope included “CMC[chemistry, manufacturing and control], nonclinical pharmacology and toxicology, human pharmacokinetic and pharmacodynamic, and clinical safety and effectiveness data,” including 3 Phase III trials), available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> [hereinafter “FDA’s Second Response to Omnitrope CPs”]; see Grabowski, *White Paper* at 25-26 (“Obtaining approvable [FOB] manufacturing capacity may take 3 to 7 years.”).

<sup>24</sup> See Henry Grabowski *et al.*, *Entry and Competition in Generic Biologics*, 28 MANAGERIAL AND DECISION ECONOMICS 439-51 (development time for FOB estimated at 5-8 years, 3 years for preclinical

Unlike small-molecule drugs, FOB products would not be designated as “therapeutically equivalent” with the referenced product. The lack of therapeutic equivalence means that a pharmacist may not substitute prescriptions for a pioneer product to an FOB product without physician consent. The approval process could provide, however, a means by which an FOB applicant could show that its product is interchangeable with the pioneer product as technology and scientific understanding develops.<sup>25</sup>

It also is likely that FOB manufacturers could become innovators. For example, they may develop “biobetter” FOB drugs that improve upon the safety and effectiveness of the pioneer product. In other instances, FOB firms could develop improved manufacturing processes and analytics, resulting in safer biologics manufactured by both pioneer and FOB manufacturers, and/or more efficient manufacturing and testing methodologies, resulting in lower-priced biologic drugs.<sup>26</sup> One commenter suggested that the “incentive for enhanced and innovative biologics manufacturing capacity is an oft-forgotten but critically-important aspect of innovation, particularly in the context of biologics, and it is one that can enable a direct reduction in the cost of goods and an increased durability of supply.”<sup>27</sup>

### **III. PHARMACEUTICAL PRICING, MARKET DYNAMICS AND THE LIKELY COMPETITIVE IMPACT OF FOLLOW-ON BIOLOGICS**

Pioneer manufacturers, potential FOB manufacturers, and payors explained that it is likely that an FOB approval process under the PHS Act will result in the approval of biosimilar products, not interchangeable ones. This section describes the likely market

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work, 2-4 years for clinical trials and 1 year for FDA approval); Grabowski, *White Paper* at 25-26 (“FOB development and trials will likely take 3 to 5 years, and obtaining FDA approval another one and a half to two years.”); *see also id.* at 5, 27-30.

<sup>25</sup> The term “interchangeable” is not currently defined in the PHS Act. Many panelists and commenters suggested that interchangeability was unlikely to be possible in the near term. *See* Buckley at 47 (“In Europe, to date 14 countries have ruled that these products are not interchangeable”); *see id.* at 51; Phillips at 103. Participants noted that the European Union (“EU”) member states (including France, Germany, United Kingdom, Italy and Spain) have all rejected the practice of substitution of a biologic by the pharmacist without the physician’s consent. Amgen Comment (9/30/08) at 2-3, 6; Novartis Comment (9/29/08) at 2, 16-17; Brugger at 38-39.

<sup>26</sup> *See* Behrman at 78; *see also* Momenta Comment (12/22/2008) at 3 (new analytic tools developed by Momenta to characterize proteins may provide significant “value and cost savings to the innovator drug development process . . . to enhance the quality of their products by more precisely controlling variability of a number of attributes in the final drug product . . . and reduce the need for very costly, potentially unnecessary clinical trials.”).

<sup>27</sup> Novartis Comment (9/29/08) at 3-4; Brugger at 54 (“We’ve developed an innovative analytical approach to these complex molecules, both in better understanding the [biologic] product, but also a deeper understanding of the manufacturing process.”); *see also id.* at 55, 79; Momenta Comment (9/30/08) at 2.

effects of biosimilar product entry and contrasts it to the market effects of entry by small-molecule generic drugs.

### A. Pharmaceutical Pricing and the Effect of Generic Drug Entry

In the United States, a pioneer manufacturer of either small-molecule or biologic drugs is free to charge a monopoly price for its product to the extent the market conditions permit or it is perceived to offer greater health benefits compared to existing drugs or medical treatments.<sup>28</sup> Patent-protected drug products also may be able to prevent the manufacturer from facing competition, thus enabling the manufacturer to charge a monopoly price.

Manufacturers of small-molecule and biologic drugs market their products through a variety of channels including a specialty detail sales force, free samples or prescription coupons, medical education and conferences, peer review journal publications, direct-to-consumer advertising, and formulary access. Formulary access is controlled either by private prescription benefit managers (“PBMs”) for reimbursement by health insurance companies or managers for coverage by various public payors (*e.g.*, Department of Veterans Affairs, Medicare, state Medicaid programs).<sup>29</sup>

Approval of a breakthrough or pioneer drug product is increasingly followed by entry of a subsequent branded product(s).<sup>30</sup> The head start that the breakthrough product has had over subsequent branded products has decreased over the past three decades from 8.2 years during the 1970s to 2.25 years in the 1990s.<sup>31</sup>

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<sup>28</sup> See FEDERAL TRADE COMM’N, PHARMACY BENEFITS MANAGERS: OWNERSHIP OF MAIL ORDER PHARMACIES, (August 2005) [hereinafter “FTC PBM REPORT”] at 63, available at <http://www.ftc.gov/reports/pharmbenefit05/050906pharmbenefitrpt.pdf>.

<sup>29</sup> Generally, each PBM negotiates with branded drug manufacturers for discounts or market share payments that are based on the branded drug’s preferred status on the PBM’s drug formulary or on the branded drug’s market share among the PBM’s members. Branded drug manufacturers make these payments to encourage the PBM to dispense their branded drugs rather than competing branded products within a therapeutic class. Drug formularies are used primarily for drugs dispensed in a retail pharmacy environment. See FTC PBM REPORT, Ch. 1 at 4, 6.

<sup>30</sup> Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 PHARMACOECONOMICS Supp 2:1-14 (2004) (The study included several biologic drugs). In the 1990s all of the breakthrough products had branded competitors in clinical development at or before their approval; *id.* at 10.

<sup>31</sup> *Id.*; F.M. Scherer, *Markets and Uncertainty in Pharmaceutical Development* 13 (FACULTY RESEARCH WORKING PAPERS SER., HARV. UNIV., JOHN F. KENNEDY SCHOOL OF GOV’T, 2007), available at [http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/\\$File/rwp\\_07\\_039\\_scherer.pdf](http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/$File/rwp_07_039_scherer.pdf).

When the FDA approves a branded competitor, price competition ensues, market size expands, and market share shifts among the competitors.<sup>32</sup> Brand-to-brand competition results in negotiated price discounts in the range of 18 to 27 percent off the pioneer's product price.<sup>33</sup> Brand-to-brand competition also expands the market (in units and dollars) for a therapeutic class of drugs by increasing awareness of conditions and treatments from increased detailing, advertising, and marketing, as firms compete to influence physician prescribing behavior in favor of their brands.<sup>34</sup> Price competition among branded firms therefore increases access for patients.

For drugs approved under the FD&C Act, generic entry occurs when patent protection ends<sup>35</sup> (either at patent expiration or by a court finding of non-infringement or invalidity). The number of generic entrants after patent expiration is largely a function of fixed entry costs compared to the market opportunity.<sup>36</sup> The first generic entrant generally offers a price that is 25 percent lower than the branded drug's price. The price discount can rise to 80 percent with multiple generic entrants.<sup>37</sup>

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<sup>32</sup> See FEDERAL TRADE COMM'N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (2003), Ch. 2 at 11 [hereinafter "FTC PATENT REPORT"], available at <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>; FTC/DOJ HEALTH CARE REPORT, Ch. 6 at 3-9.

<sup>33</sup> Although the competing branded product's list price, including Average Wholesale Price ("AWP") or Wholesale Acquisition Cost ("WAC"), is typically at parity, the firms compete by offering price discounts to the largest, most sophisticated, and price sensitive customers, such as PBMs. These discounts are confidential. See IMPROVING HEALTH CARE: A DOSE OF COMPETITION: A REPORT BY THE FEDERAL TRADE COMM'N AND THE DEP'T OF JUSTICE (July 2004), Ch. 7, at 11-17, available at <http://www.ftc.gov/reports/healthcare/040723healthcarerept.pdf> [hereinafter "FTC/DOJ HEALTH CARE REPORT"]; see also DiMasi and Paquette, *The Economics of Follow-on Drug Research and Development*, at 12 (average discount offered by subsequent branded rivals were 26% off price leader and 14% off the class average); CBO, *Increased Competition from Generic Drugs*, at 24-25.

<sup>34</sup> See FTC/DOJ HEALTH CARE REPORT, Ch. 6-7; FTC PATENT REPORT, Ch. 2, at 11.

<sup>35</sup> In general, if the patent application was filed after June 7, 1995, the patent expires 20 years from the date on which the application was filed. 35 U.S.C.A. § 154(a)(2)-(3) (2009). If the application was filed by June 7, 1995 and issued after June 7, 1978, the term is the later of 17 years from issuance or 20 years from filing. 35 U.S.C.A. § 154(c). If the application was filed by June 7, 1995 and issued before June 8, 1978, the expiration date was 17 years from issuance, i.e., 1995 or earlier.

<sup>36</sup> Generally, the number of generic entrants increases with the market size. In one study of the 40 oral small-molecule drugs with patent expiry between 1992 to 1998, an average of 12 generic firms entered when the market size before patent expiry was over \$250 million. In comparison, when market size was less than \$250 million, only 5 generic firms entered. Grabowski, *Entry and Competition*, at 440, 444-46; see also David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 REVIEW OF ECONOMICS AND STATISTICS, 37-49, 38 (2005) ("more firms enter, and enter more quickly, in markets with greater expected rents"), available at <http://www.ftc.gov/be/econwork.htm>.

<sup>37</sup> See Reiffen, *Generic Drug Industry Dynamics*; see also CBO, *Increased Competition from Generic Drugs*, at 28; Grabowski, *Entry and Competition*, at 444, 446 (economic analysis concludes that 1 generic entrant results in discounts of 10%, 5 generic firms 37%, 5 entrants 40%, 10 entrants 60%, and 95% after 20 entrants); Grabowski, *White Paper* at 42-44, 52-53; OTA, *Pharmaceutical R&D*, at 297; Roy Levy, *THE PHARMACEUTICAL INDUSTRY: A DISCUSSION OF COMPETITIVE AND ANTITRUST ISSUES IN AN ENVIRONMENT OF CHANGE* (1999) at 73-76, 197 [hereinafter "LEVY REPORT"], available at <http://www.ftc.gov/os/2006/07/P052103BarrierstoGenericEntryTestimonySenate07202006.pdf>.

Marketplace experiences have documented the rapid erosion of a branded drug's sales once the first generic product is introduced.<sup>38</sup> The rapid decline of the branded product's market share is largely a function of state substitution laws and price sensitive customers' use of drug formularies.<sup>39</sup> State substitution laws allow a pharmacist to dispense a generic drug when presented with a prescription for its branded equivalent, unless the physician or consumer directs otherwise. In addition, PBMs and retail pharmacies have substantial incentive to dispense generic drugs because the margins on generic drugs are greater than they are for branded products, resulting in greater profits for PBMs and retail pharmacies.<sup>40</sup> These two factors enable the generic entrant to erode a majority of the market share of the branded product within the first year.<sup>41</sup> When additional generic firms enter, they compete against incumbent generic firms for market share, not the branded manufacturer, because the first generic firm has already obtained most of the branded manufacturer's sales.

## **B. Likely Market Effects of Biosimilar Entry**

Competition from FOB drug entry is likely to resemble brand-to-brand competition rather than generic drug competition.<sup>42</sup> Experience to date for two products

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<sup>38</sup> See Grabowski at 42 (generic erosion 90%), Heldman at 26-28 (generic erosion 80%); see also Golding at 49, Buckley at 52; Grabowski, *Entry and Competition*, at 444 (brands lose 67% of market share within a year); CBO, *Increased Competition from Generic Drugs* at 29-31; David Reiffen & Michael Ward, "Branded Generics" As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 *MANAGERIAL AND DECISION ECONOMICS*, 251-65 (2005), available at [http://ftc.gov/be/healthcare/wp/12\\_Reiffen\\_BrandedGenericsAsAStrategy.pdf](http://ftc.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf); Henry Grabowski & John Vernon, *Longer Patents for Increased Generic Competition in the U.S.: The Hatch-Waxman Act After One Decade*, 10 *PHARMACOECONOMICS* supp. 2:110-23 (1996) (brands lost 50% of prescriptions within a year); U.S. Cong., Office of Technology Assessment ("OTA"), *Pharmaceutical R&D: Costs, Risks and Rewards*, OTA-H-522 (1993), at Table F-3, p. 297, available at <http://www.princeton.edu/~ota> (Princeton University hosts the OTA legacy site, follow "OTA publications" hyperlink and use search engine there to find article by title) [hereinafter "*Pharmaceutical R&D*"].

<sup>39</sup> See CBO, *Research and Development in the Pharmaceutical Industry* at 48 (2006), available at <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>; CBO, *Increased Competition from Generic Drugs*, at 27-30; Grabowski, *Entry and Competition*, at 444-45.

<sup>40</sup> See FTC PBM REPORT at x, 12, 74-75.

<sup>41</sup> See Reiffen & Ward, *Branded Generics*; Grabowski & Vernon, *Longer Patents for Increased Generic Competition*; Grabowski, *Entry and Competition*, at 444.

<sup>42</sup> See Duke University Comment (12/23/08) at Table 3; BIO Comment (9/30/08) at 2; Grabowski *White Paper* at 2, 4-6, 8-9, 40-41, 48; see also Paul Heldman *et al.*, Citigroup Research, Citigroup Global Markets, *A Global "Generic Biologics" Guidebook* at 5 (November 6, 2006)[hereinafter "Citigroup 2006 FOB Guidebook"]; *Safe and Affordable Generic Biotech Drugs: The Need for a Generic Pathway: Hearing before the H. Oversight and Gov't Reform Comm.*, 110th Cong. 1-14 (2007) (statement of Henry Grabowski, Duke University), available at <http://oversight.house.gov/documents/20070416132526.pdf>; Grabowski, *Entry and Competition*, at 448-49 (after extensive economic modeling, the authors conclude that and FOB prices relatively close in price to branded biologics); CBO Cost Estimate (S.1695), *Biologics Price Competition and Innovation Act of 2007 S. 1695, As Ordered Reported by the S. Comm. on Health*,

with both branded and FOB competitors (in Europe and the U.S.) shows that four factors have dampened substantial price discounting by, and rapid share shifting to, FOB manufacturers as compared to the effects of generic drug entry. As a result, branded manufacturers are likely to continue to reap profits after FOB entry.

## 1. Fewer FOB Competitors Due to High Barriers to Entry

Fewer FOB competitors are expected due to the technological barriers and the high cost of entry.<sup>43</sup> FOB products are likely to take eight to 10 years to develop and to cost between \$100 and \$200 million.<sup>44</sup> Higher development costs for FOB products, compared to small-molecule generic drugs, include those associated with manufacturing, clinical trials, and post-marketing surveillance.<sup>45</sup> By contrast, small-molecule generic drugs product development costs range from approximately \$1 to \$5 million.

Follow-on biologic manufacturers will likely have to build, equip and qualify their own manufacturing facilities, which is likely to cost \$250 to \$1 billion.<sup>46</sup>

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*Education, Labor, and Pensions on June 27, 2007 (June 25, 2008), available at <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf> [hereinafter “S. 1695 Report”].*

<sup>43</sup> See CBO S. 1695 Report at 6 (“CBO expects that certain drugs could face competition from several firms by 2018, although we believe it would be more typical for an innovator biologic to face competition from between one and three competitors.”); Grabowski, *Entry and Competition*, at 446-47 (because of bioreactor capacity constraints and high fixed costs for *de novo* biologic manufacturing facilities, the number of FOB entrants is likely to be smaller than that predicted for generic small-molecule markets for the foreseeable future); see also Buckley at 53 (“The number of entrants will certainly be fewer. . . There are technological know-how [barriers] . . . the price of clinical trials . . . the length of the approval process, the likelihood of a successful application . . . and you start to see that the number of players that can submit a successful application is just much smaller.”); Amgen Comment (9/30/08) at 5; Ahlstrom at 44-45; Grabowski at 42; Heldman at 25; Lane at 46. The technological barriers to entry vary on the complexity of the biological product. Several FOB manufacturers are predicted to be able to obtain FDA approval for biosimilar versions of first generation recombinant proteins. However, as the biological products become more scientifically complex, as in the case of many of the monoclonal antibodies, the technological barriers to entry are so significant that few predict FOB in the next decade.

<sup>44</sup> See Sumanth Kambhammettu, Senior Research Analyst, Frost & Sullivan, *The European Biosimilars Market: Trends and Key Success Factors*, (Oct. 27, 2008) (“average cost of bringing a biosimilar to market is around \$100-\$200 million”), <http://www.obbec.com/specialreports/20-biopharmaceuticals/2152-the-european-biosimilars-market-trends-and-key-success-factors>; CBO S. 1695 Report at 6; Duke University Comment (12/23/08) at Table 3; BIO Comment (9/30/08) at 2; Grabowski *White Paper* at 2, 4-6, 8-9, 40-41, 48; Grabowski, *Entry and Competition*, at 442; Citigroup 2006 FOB Guidebook at 5; see also Ahlstrom at 53; Lane at 40, 46; Zuckerman Comment (12/22/08) at 12.

<sup>45</sup> See BIO Comment (9/30/08) at fn. 2, 1, 9, 17, 20; Grabowski, *White Paper*; CBO S. 1695 Report at 4-7; GPhA Comment (9/30/08) at 3 (citing CBO, *Increased Competition from Generic Drugs*).

<sup>46</sup> See Novartis Comment (9/29/08) at 7; Wyeth Comment (12/18/08) at 6 (“[T]he cost of manufacturing facilities is staggering, and this large investment must be made long before a product is approved by the regulatory agencies.”); Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 (June 2008) [hereinafter “NATURE”]; *Patent Reform Act of 2007: Hearing on H.R. 1908 Before the H. Subcomm. on Courts, the Internet, and Intellectual Property of the H. Comm. on Judiciary*, 110th Cong. 65 (2007) (statement of

Additionally, biologic manufacturing is costly, difficult and often requires acquiring or duplicating proprietary cell lines that are protected by both patents and trade secrets. These barriers further reduce the number of likely successful FOB entrants.

In addition to the development and manufacturing costs, FOB competitors are likely to engage in marketing and sales support for their FOB products.<sup>47</sup> These high costs are likely to limit FOB drug entry to markets with sales in excess of \$250 million per year.<sup>48</sup>

In light of these high entry costs, FOB entrants are likely to be large companies with substantial resources. Current biologic drug manufacturers are likely to become FOB competitors in those markets in which they do not currently compete. Potential FOB entrants could include well-established biotechnology, and hybrid biopharmaceutical firms such as: Abbott, AstraZeneca (acquisition of MedImmune and CAT), Baxter (acquisition of Knoll), Biogen/IDEC, Eli Lilly (acquisition of Imclone), Johnson & Johnson (acquisition of Centocor), Pfizer (recent announced acquisition agreement with Wyeth), Roche (acquisition of a majority interest in Genentech), Novo Nordisk, and Sanofi-Aventis.<sup>49</sup>

FOB firms in Europe who have an interest in developing FOB products for the U.S. market include: Novartis (including its generics division Sandoz), Teva, Hospira (partnering with German generics firm Stada), and Momenta (partnering with Novartis). Additionally, commenters recognized branded pharmaceutical firms such as Merck, Boehringer Ingelheim, and Wyeth.<sup>50</sup>

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Kevin Sharer, Amgen, Inc. ("Amgen" CEO), *available at* <http://judiciary.house.gov/hearings/April2007/Sharer070426.pdf>. ("It takes approximately 5 years and \$1 billion to build a factory to produce biotech medicines."). FOB manufacturers will likely have to develop their own in-house manufacturing because the worldwide capacity constraints puts greater leverage in the hands of contract manufacturers to seek maximum profits by maintaining their relationships with branded firms and the highest revenue producing branded products. Grabowski, *Entry and Competition*, at 442.

<sup>47</sup> See Lane at 35-36; Urlep at 34.

<sup>48</sup> Janet Woodcock *et al.*, *The FDA's Assessment of Follow-On Protein Products: a Historical Perspective*, 6 NATURE REVIEWS DRUG DISCOVERY 437-42 (June 2007); Grabowski, *Entry and Competition*, at 446 (only 3 entrants predicted in markets where the branded biologic has sales over \$1 Billion).

<sup>49</sup> See Natasha Singer, *Bristol-Myers's Reliance on Three Drugs Casts Doubt on Strategy*, N.Y. TIMES, Jan. 27, 2009, at B3 (listing recent biopharmaceutical acquisitions); Andrew Jack, *Sanofi-Aventis Ready to Join Pfizer on the Acquisition Trail*, FINANCIAL TIMES, February 2, 2009 at 13 ("[T]he latest is a spurt of consolidation in the pharmaceuticals sector"); Andrew Pollack, *Wyeth Deal May Slow Pfizer Biotech Acquisitions*, N.Y. TIMES, JAN. 26, 2009, at B4; ("Schering-Plough's considerable biologics expertise will complement Merck's novel proprietary biologics platform"), *available at* [http://www.merck.com/newsroom/press\\_releases/corporate/2009\\_0309.html](http://www.merck.com/newsroom/press_releases/corporate/2009_0309.html).

<sup>50</sup> See CVS Caremark Comment (12/22/08) at 3; Momenta Comment (12/22/2008) at 4; Andrew Jack, *AstraZeneca Chief Calls the Shots*, FINANCIAL TIMES, December 23, 2008 at 18 ("The move is the third instance in recent weeks of a large pharmaceutical company [AstraZeneca] that has been traditionally focused on developing innovative medicines to express a desire to shift to generic [biologic] medicines."); Susan Todd, *Merck Launches Biologic Division Drugmaker to Invest \$1.5 B into Venture*, NEWARK STAR

## 2. Lack of Interchangeability

The lack of interchangeability and automatic FOB substitution are likely to dampen how quickly an FOB manufacturer acquires market share compared to generic drug entry.<sup>51</sup> In small-molecule drug markets, automatic substitution erodes a branded manufacturers' market share quickly once the first generic product enters the market. As more generic products enter, they compete for market share among themselves, as the branded manufacturer already has lost its market share to the first generic entrant. This situation is unlikely to occur in FOB markets as FOB manufacturers will be required to market their products and negotiate individual contracts with purchasers in competition with the branded manufacturer's product.<sup>52</sup> FOB market share is likely to depend on: order of entry into the market; clinical trial results; size of detailing sales force; direct-to-consumer advertising; and access to formularies, which include price discounts to the most sophisticated, price-sensitive customers.<sup>53</sup>

FOB market penetration also is likely to be hampered by lingering or institutionalized uncertainty about interchangeability and safety differences between pioneer and FOB products.<sup>54</sup> This uncertainty may be heightened if the FOB product does not share the same name as the pioneer biologic product.<sup>55</sup> Physicians and their

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LEDGER, December 10, 2008 at 61 ("We anticipate that [Merck] will take a leadership position in follow-on biologics."). Merck BioVentures is developing an FOB equivalent to Amgen's Aranesp which Merck expects to launch in 2012 to be followed by five more FOBs of several best-selling biologic drugs due to lose patent protection by 2017. On November 24, 2008, Eli Lilly and Company acquired the biologic company Imclone, the biologic manufacturer of Erbitux (with global sales of \$3.6 billion) for \$6.5 billion beating out Bristol-Myers Squibb. Press Release, Eli Lilly & Co., Lilly to Acquire Imclone Systems in \$6.5 Billion Transaction, (October 6, 2008), *available at* <http://newsroom.lilly.com/releasedetail.cfm?ReleaseID+338523>. In June 2007, AstraZeneca completed its \$15 billion acquisition of MedImmune. AstraZeneca, Annual Report and Form 20-F Information, at 83-84 (2007); Bernstein Research Comment (9/29/08) at 2.

<sup>51</sup> See, e.g., CCPM Comment (9/30/08) at 3 ("In the absence of a designation as interchangeable, it likely will take longer for the [biosimilar] to garner significant market share and brand manufacturers will have less incentive to compete based on price."); see also CVS Caremark Comment (12/22/08) at 4.

<sup>52</sup> See, e.g., Hospira (Wilkie Farr) Comment (12/22/08) at 5 ("Without an "interchangeable designation, biosimilar companies would be compelled to invest significant sums to market and promote biosimilars, thus driving up the cost to the consumer. Reference companies also would have less incentive to compete on price. Reference drug companies would be more likely to try to out-market the biosimilar companies, further driving up the costs of *both* the reference drug and market entry by the biosimilar.").

<sup>53</sup> See *supra* notes 35-40 and accompanying text regarding negotiated price discounts for different purchasers.

<sup>54</sup> See Amgen Comment (9/30/08) at 2-3; BIO Comment (12/22/08); Ahlstrom at 43.

<sup>55</sup> Generally, the FDA approves the use of the same name for a generic small-molecule as the reference branded drug because both products share the same the active ingredient. In contrast, an FOB drug manufactured by a different process than the reference branded biologic drug may share the same mechanism of action, may share the same efficacy and side effects, and may even be considered or approved as interchangeable with the reference branded biologic drug but may still not be given the same name as the brand. See Horton at 98; BIO Comment (9/30/08) at 4; PCMA Comment (9/26/2008) at 5;



patients who have been safely taking a pioneer biologic drug product may be reluctant to switch to an FOB product because of the risk that the patient will react differently to the new drug.<sup>56</sup> These concerns may limit the FOB market opportunities to newly diagnosed patients or patients who had not improved by using the pioneer biologic drug. These concerns may dissipate as providers become more experienced with FOBs.<sup>57</sup>

### **3. Specialty Pharmaceutical Characteristics**

The specialty pharmaceutical characteristics of FOB drugs also are likely to constrain market share acquisition.<sup>58</sup> Specialty drugs, including biologic drugs, are commonly used to treat patients with severe, chronic diseases and sometimes fatal conditions. These drugs, which are primarily injected or infused, are combined with ancillary medical services and products which require specialty training for proper handling and administration.<sup>59</sup> Because most biologic products are delivered to patients in clinics, hospitals, and doctor's offices, or other medically-supervised settings, shifting to another biologic product is typically more costly because it requires restocking inventory and retraining nurses and healthcare providers.<sup>60</sup>

### **4. Fewer Payor Strategies to Incentivize Rapid Uptake of FOBs**

Biologic drug products are typically delivered to patients by healthcare providers as part of medical treatments (*e.g.*, dialysis treatments or oncology treatments) and reimbursed by health insurers as part of patients' medical benefits rather than the pharmacy benefits. This situation contrasts with small-molecule drug products which are dispensed by pharmacists to the patients and reimbursed by the insurance providers as

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FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (Sept 1, 2006) ("The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small-molecule drugs."), *available at* <http://www.fda.gov/cder/news/biosimilars.htm>.

<sup>56</sup> CVS Caremark Comment (12/22/08) at 4 ("Given the uncertainty surrounding the equivalence of innovator and follow-on biologics, PBM, payors and physicians are more likely to be focused on clinical information and dialogue about the prudence of switching to a particular follow-on biologic or innovator drug. This ad hoc, non-uniform approach will ultimately drive the adoption of follow-on biologics, but at a pace than seen with generic small-molecule drugs.").

<sup>57</sup> *Id.*

<sup>58</sup> CBO S. 1695 Report; Ahlstrom at 43.

<sup>59</sup> Golding at 64-65; CVS Caremark Comment (12/22/08) at 1. Specialty pharmaceuticals often are distributed in separate channels to preserve the viability and safe administration of the products.

<sup>60</sup> Golding at 64-65.

part of the patients' pharmacy benefit.<sup>61</sup>

Traditional payor strategies used to manage pharmacy benefits that incentivize rapid shifting of patients from branded drugs to lower-priced generic drugs – for example, by requiring higher co-pays from patients for drugs off the formulary – are likely to be of limited use for biologic drugs. Consequently, payors will have fewer strategies to incentivize the rapid uptake of lower-priced FOBs, especially biosimilars.<sup>62</sup> In addition, the reimbursement methodologies used by Centers for Medicare and Medicaid Services (“CMS”) for biologic drugs are likely to be important factors affecting the market impact of FOBs and pricing of FOBs.<sup>63</sup>

Because of these four characteristics, payors, branded manufacturers, and FOB manufacturers forecasted that pioneer manufacturers are likely to maintain market share for several years even after FOB entry. They predicted that market share acquisition by FOBs would be modest, lagging substantially behind the sometimes blistering competitive pace established by generic small-molecule entrants.<sup>64</sup> Several commenters

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<sup>61</sup> For example, costs for senior citizens for biologic drugs are generally reimbursed under Medicare Part B, rather than Part D. See CBO BUDGET OPTIONS at 106, 126-27; AARP Comment (12/22/08) at 1; CVS Caremark Comment (12/22/08) at 7.

<sup>62</sup> Alhstrom at 43-45 (noting that insurance plans and PBMs immediately cover generic drugs and immediately implement tools to switch their patients from the brand to the generic small-molecule drug which results in the 80-90% share shift to generics a market dynamic that she does not predict will be duplicated in the biologic-FOB market experience any time in the near future.”); Buckley at 47 (“It’s going to be the decision of the physician and the patient as to whether or not a drug will be substituted for a therapy that they may already be on or a therapy that they may be considering taking.”); see also Golding at 49.

<sup>63</sup> Mylan Comment (1/5/09) at 5-6. In contrast to the authority CMS has to incentivize the use of generic small-molecule products, currently, there is no express statutory authority for the CMS to reimburse FOBs in such a way as to incentivize utilization of the lowest priced biologic product. CVS Caremark Comment (12/22/08) at 7; Miller at 213-14. The Congressional Budget Office has indicated that a change to the Medicare Part B reimbursement methodologies would be needed to maximize savings from FOB products. See generally CBO BUDGET OPTIONS; CVS Caremark Comment (12/22/08) at 7; Heldman at 29-31 (“The current formula under Medicare provides a financial incentive for physicians and hospitals, when using the drugs in an outpatient setting to use the higher cost drugs...because Medicare reimburses at the average sales plus a 6 percent markup. In addition, current law requires Medicare [to give] a follow-on biologic that the FDA doesn’t deem interchangeable . . . a separate billing code....”); Amgen, Inc. v. F. Hoffmann-La Roche Ltd., 2008 U.S. Dist. LEXIS 77343 at \*169-73 (D. Mass. Oct. 2, 2008) (noting that the court could not conclude that entry by Roche’s branded EPO biologic drug, Mircera, would reduce Medicare Part B reimbursement for EPO drugs).

<sup>64</sup> CVS Caremark Comment (12/22/08) at 4; Buckley at 52-53; Bernstein Research Comment (9/29/08) at 1-2; BIO Comment (9/30/08) at fn. 2.; Amgen Comment (9/30/08) at 5 (“The combination of these factors will make it very unlikely that biosimilar products will bring about the price differential that generic products do.”); Momenta Comment (9/30/08) at 3 (“The likely competitive effect of a follow-on biologic entering the market is the gradual reduction in prices of the biologic.”); Hospira Comment (9/30/08) at 1 (“The best estimate is that the biosimilar EPOs [in the EU] appear to be priced approx 25 - 30 percent below the innovator’s price prior to the entry of any biosimilar.”); CCPM Comment (9/30/08) at 2 (“According to the March, 2008, edition of the Red Book, Omnitrope's price is a 34% discount from the original product.”); Grabowski, *White Paper* at 6 (“The extent of entry will likely be much lower for FOBs

concluded that uptake of FOBs will likely be “slower and less extensive than for many small-molecule drugs.”<sup>65</sup> They estimated that the uptake for FOBs will range between 10 percent and 30 percent.<sup>66</sup> They also noted that the market share uptake of FOBs will be correlated to the price which in turn is affected by the sums needed to generate clinical trial data required by the FDA to obtain approval.<sup>67</sup>

Panelists noted that as the market gained positive experience with FOBs, market uptake of FOBs could increase.<sup>68</sup> Conversely, they also predicted that if the market had negative experiences with FOBs from safety or efficacy issues (immunogenicity, heparin like contamination or problems akin to the generic drug scandals of the 1980’s), then FOB uptake could also be significantly dampened.<sup>69</sup>

### C. Market Experience with Biosimilar Entry

Market experience with both pioneer and FOB competitors confirms that FOB competition is likely to resemble branded competition rather than generic competition as seen for small-molecule drug products. The European Union adopted an approval process for follow-on biologics in 2004.<sup>70</sup> To date, the European Medicines Agency has approved biosimilars for three products: (1) EPO (erythropoietin stimulating agent or “ESA”) to treat anemia; (2) human growth hormone (“HGH”) to treat children with small stature, and other conditions associated with deficiencies of the naturally occurring hormone; and (3) G-CSF (Granulocyte-Colony Stimulating Factor) to stimulate production of white blood cells needed to fight infection. In the U.S., the FDA has

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than for conventional generic drugs, reflecting differences in market size and high fixed costs of entry for many biologics. Average price effects and rates of FOB uptake for innovator products are likely to be limited in the short run due to the low number and timing of entry of FOBs, limitations to perceived substitutability between innovator biologics and FOBs on the part of physicians and patients, incentives for limited price-based competition between FOBs and innovator products....”); Grabowski, *Entry and Competition*, at 449.

<sup>65</sup> See Grabowski, *White Paper* at 2.

<sup>66</sup> *Id.*; Heldman at 25, 27.

<sup>67</sup> Heldman at 25, 27; Brugger at 39; Urlep at 56 (“We have to invest into primary marketing to overcome this with our data, which we created during the development programs.”); Hospira (Wilkie Farr) Comment (12/22/08) at 2 (“Without an ‘interchangeable’ designation, biosimilar companies would be compelled to invest significant sums to market and promote biosimilars, thus driving up the cost to the consumer.”).

<sup>68</sup> Grabowski at 42.

<sup>69</sup> Brugger at 74.

<sup>70</sup> Linda Horton, *The European Experience with Follow-on Biologics Legislation at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues* (Nov. 21, 2008) at 3 [hereinafter “Horton Presentation”].

approved two biosimilar HGH products pursuant to the FD&C Act.<sup>71</sup> The following two sections describe the market competition for EPO and HGH.<sup>72</sup>

## 1. EPO Market Experience in the European Union

Panelists and commenters explained that seven EPO biologic manufacturers market their products in Germany, three of which are biosimilars (products 5-7):

- (1) Amgen's Aranesp,
- (2) Johnson & Johnson's Eprex/Erypo,
- (3) Roche's NeoRecormon,
- (4) Roche's Mircera,
- (5) Hospira's Retacrit,
- (6) Novartis' Binocrit, and
- (7) Shire's Dynepo.<sup>73</sup>

As of November 2008, the multiple biosimilar entrants had attained a combined market share in Germany of between 14 to 30 percent with price discounts estimated at about 25 percent off the branded price several years after entry.<sup>74</sup> The reported results of international sales from the first quarter of 2009 appear to confirm that pioneer firms retain a significant first mover advantage. For example, Amgen states that Aranesp's

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<sup>71</sup> See Appendix B for a discussion of the statutory authority that permits the FDA to approve a limited number of biosimilar products under the FD&C Act.

<sup>72</sup> Although the E.U. approved biosimilar filgrastim on February 13, 2009, market experience was too limited to include in this report. See Press Release, Sandoz, Sandoz Receives European Commission Approval for Biosimilar Filgrastim (Feb. 13, 2009), available at [http://www.sandoz.com/site/en/media\\_room/press\\_releases\\_news/090213.shtml](http://www.sandoz.com/site/en/media_room/press_releases_news/090213.shtml); Hospira Comment (May 11 2009) at 3, Amgen, Q1 2009 Earnings Call, at 19-20 (April 23, 2009). In Europe, the pioneer G-CSF products consist of Amgen's Neupogen (filgrastim), Amgen's Neulasta (pegylated filgrastim) and Chugai's Granocyte (lenograstim), while the biosimilar products consist of Teva's Tevagrastim, Ratiopharm Ratiograstim and Ratiopharm filgrastim, CT Arzneimittel's Biograstim, Novartis' Zarzio (marketed by Novartis' Sandoz division), and Filgrastim Hexal (marketed by Novartis' Hexal division).

<sup>73</sup> Hospira, Inc. ("Hospira") and STADA Arzneimittel AG co-market their product Retacrit/Silapo in Germany. Market shares for Novartis' Binocrit, Novartis' Epoetin alpha Hexal and Medice' Arzneimittel Putter GmbH&Co KG's Abseamed are represented together. On February 17, 2009, Shire plc. ("Shire") discontinued selling Dynepo in Europe for commercial reasons, and its marketing authorization was rescinded in March, 2009. See <http://www.emea.europa.eu/humandocs/PDFs/EPAR/dynepo/12666909en.pdf>.

<sup>74</sup> Bernstein Research Comment (9/29/08); Paul Heldman, *Follow-On Biologic Market: Initial Lessons and Challenges Ahead at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues* (Nov. 21, 2008) at 7 [hereinafter "Heldman Presentation"]; Heldman at 26-27; Lane at 36 ("on a unit basis [we] have actually captured 23 percent of the first gen market"); Novartis Comment (9/29/08) at 2-3. Some of the share estimates differ because some estimates are calculated based on units while others are based on different measures of sales. *Id.* See also Amgen, Q1 2009 Earnings Call, at 19-20 (April 23, 2009).

market share in dialysis patients has increased slightly even two years after biosimilar and other branded competitors have entered the market.<sup>75</sup>

## 2. HGH Market Experience in the European Union and the United States

Panelists and commenters also discussed the limited price competition and market share shift to biosimilars in the HGH markets in the E.U. and U.S. In April 2006, Novartis launched its biosimilar HGH product, Omnitrope, which referenced Pfizer's Genotropin, in Germany and Austria. In December 2006, BioPartner launched the second HGH product, Valtropin, in the E.U., which referenced Eli Lilly's Humatrope.

By leveraging its global R&D, Novartis launched Omnitrope in the United States in 2007.<sup>76</sup> The second HGH biosimilar entrant in the United States was Teva with Tev-Tropin.<sup>77</sup> There are five other branded HGH products in the U.S. market:

- Pfizer's Genotropin
- Eli Lilly's Humatrope
- Novo Nordisk's Norditropin
- Serono's Saizen
- Genentech's Nutropin (Genentech, majority-owned by Roche)<sup>78</sup>

As of November 2008, combined U.S. market shares of the two biosimilars amounted to about four percent.<sup>79</sup> Panelists' best estimates of the price discounts in the U.S. for HGH biosimilar drug products ranged from 10 to 40 percent off the branded HGH products' prices depending upon the purchaser, while branded HGH prices had increased.<sup>80</sup> As

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<sup>75</sup> See Amgen, Q1 2009 Earnings Call, at 19-20 (April 23, 2009) (stating that Hospira's Retacrit and the other biosimilars together account for only 5 percent market share).

<sup>76</sup> For a discussion of the novel issues involved with the approval of Omnitrope, see *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006); see generally FDA's Second Response to Omnitrope CPs; Letter from Janet Woodcock, Director, CDER, FDA to Petitioners (October 14, 2003), available at <http://www.fda.gov/ohrms/DOCKETS/dailys/03/oct03/102403/03p-0408-pdn0001.pdf> [hereinafter "FDA's First Response to Omnitrope CPs"]. When the FDA approved Sandoz's Omnitrope on May 31, 2006, it did not rate Omnitrope as therapeutically equivalent to and automatically substitutable for Genotropin. See Letter from Paulo Costa, President & CEO, Novartis Corp. to Frank Pallone, Jr., Chmn, and Nathan Deal, H. Subcomm. on Health (May 1, 2008) at 9-10, available at [http://energycommerce.house.gov/Press\\_110/110-ltr.050108.respto040308.Novartis.pdf](http://energycommerce.house.gov/Press_110/110-ltr.050108.respto040308.Novartis.pdf).

<sup>77</sup> Heldman at 23; Citigroup 2006 FOB Guidebook at 2; Bernstein Research Comment (9/29/08) at 12-13.

<sup>78</sup> *Id.*; FDA's Second Response to Omnitrope CPs at 7.

<sup>79</sup> Heldman at 28, Heldman Presentation at 3-6.

<sup>80</sup> See Heldman at 28, Heldman Presentation at 3-6; CBO S.1695 Report. Heldman notes that aggressive discounts offered in the market to PBMs and other payors are generally non-public and not captured in the WAC data available from IMS and other sources. Branded firms compete on prices not by lowering the list, WAC or AWP to all customers, but by offering discounts off those prices to the most price sensitive,

discussed above, pioneer manufacturers offer discounts to their most price sensitive, sophisticated, and largest purchasers; these discounts are negotiated individually and typically are not publicly available.<sup>81</sup> Both Novartis and Teva supported their biosimilar products with marketing and sales efforts.<sup>82</sup>

#### **D. Likely Pricing Effect of Interchangeable FOBs**

Panelists and commenters expressed a range of price discount predictions if and when technology allows interchangeable FOBs to enter the market. For ease of discussion, some panelists and commenters referred to interchangeable FOBs as “biogeneric” drugs. Panelists predicted that if biogeneric applicants could, for example, rely on analytical data rather than clinical trials to show equivalent efficacy, and not be required to engage additional comparability and immunogenicity trials, then biogenerics will generate greater consumer savings than biosimilars.<sup>83</sup> And conversely, if a biogeneric pathway were more costly and rigorous than the process for new drug approvals, panelists predicted no biogeneric FOB entrants would use such a pathway as “manufacturers would be better off pursuing a full approval.”<sup>84</sup>

One commenter explained that savings in marketing and selling expenses should translate into lower sales price for a biogeneric product than a biosimilar product.<sup>85</sup> An FOB manufacturer explained that only interchangeable biogeneric, not biosimilar, products offer the greatest price competition.<sup>86</sup> This increased price competition,

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sophisticated, and largest purchasers. *See* Heldman at 24-25; FTC PBM REPORT at 48-54; LEVY REPORT at 183; *see generally* CBO, *Research and Development in the Pharmaceutical Industry* at 48; CBO, *Increased Competition from Generic Drugs*, at 27-30.

<sup>81</sup> *See* FTC PBM REPORT at 48-54.

<sup>82</sup> *See* Urlep at 34; Lane at 36.

<sup>83</sup> *See* Brugger at 74 (“[W]hat is very important to us to make continued investment in this field is a very clear path towards interchangeability, and what that does is allows companies like ours to innovate in the analytical space and not in the clinical trial space. These clinical trials are a very crude way to detect similarities or differences between these very complex molecules, and the way that we will truly understand these complex macro molecules in the future is by innovating in this analytical space.”); Behrman at 77 (“I couldn’t agree ... more that the real advances will come in the analytics and the ability to, to the best of our ability, realize how similar or different these products are and may minimize or shorten or decrease the extent to which certain types of clinical trials are necessary.”).

<sup>84</sup> Hospira (Wilkie Farr) Comment (12/22/08) at 3 (“If a company pursuing the development of a biosimilar/biogeneric cannot reference any of the innovator’s preclinical or clinical data, there would be no incentive to embark on an abbreviated approval pathway.”).

<sup>85</sup> Hospira Comment (9/30/08) at 1; *but see* BIO Comment (9/30/08) at 3-4 (presumed biogenerics are more expensive to get approved and priced higher than biosimilars).

<sup>86</sup> GPhA Comment (9/30/08) at 1-2; *see also* Novartis Comment (9/29/08) at 3 (explaining that interchangeability would “enable direct, head-to-head competition to occur based on price factoring in the front-loaded investment in the research and development of an FOB without the additional cost of a ‘back-loaded’ investment in the advertising, promotion, and detailing of an FOB. Consequently, competing

however, is likely to be greater than price competition among biosimilars, but not as great as generic drug price competition seen with small-molecule generic drugs.<sup>87</sup>

However, at least one panelist disagreed stating, “[i]nterchangeability will not necessarily provide greater economic benefit from biosimilar market entry.” He asserted that this prediction is erroneous because it is based on the false assumption that biogeneric products would be “interchangeable” and approved without more clinical testing than biosimilars.<sup>88</sup> One commenter stated that not only was biogeneric entry not possible, but the effects on cost savings provided by biogenerics were too speculative to predict at this point.<sup>89</sup>

### **E. Conclusions About the Likely Market Impact of FOB Entry**

An abbreviated approval process for follow-on biologic drugs is likely to be an efficient way to bring a biosimilar drug product to market. The FOB applicant can save time and money by not engaging in the full pre-clinical and clinical tests and, as a result, it can enter the market at a price lower than the pioneer drug product.

Competition from FOB drug entry is likely to resemble brand-to-brand competition rather than brand-to-generic drug competition for small-molecule products. Two or three FOB manufacturers are expected to seek entry in large markets due to the significant time and expense expected to develop an FOB drug product. They are likely to introduce their drug products at price discounts between 10 and 30 percent of the pioneer products’ price to the most price-sensitive customers. Pioneer manufacturers are expected to respond aggressively and offer competitive discounts. This price competition is likely to lead to an expanded market and greater consumer access.

The lack of automatic substitution will slow significant market share acquisition by FOB products. The difficult and costly administration, training, payment, and reimbursement of specialty drugs makes it likely that there will be few entrants, despite the multi-billion dollar size market opportunities offered by many biologic products losing their patent protection in the next 10 years. Moreover, traditional payor incentives used in the retail pharmacy setting, such as co-pay differential and formulary tiering to incentivize utilization of low-priced drugs, are unlikely to be used in the specialized drug setting in which many biologics are dispensed, such as hospitals and outpatient clinics,

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FOBs that are designated as interchangeable can be anticipated to achieve more rapid and ultimately more substantial market share penetration than those that are not.”).

<sup>87</sup> See Amgen Comment (9/30/08) at 6; CBO S. 1695 Report; Momenta Comment (9/30/08) at 4 (“A designation of “interchangeability” by FDA would significantly increase the competitive impact of a follow-on biologic product and consequently the potential for cost savings.”); Novartis Comment (9/29/08) at 9, 11, 24.

<sup>88</sup> BIO Comment (12/22/08) at 1; Heldman at 24-28.

<sup>89</sup> BIO Comment (12/22/08) at 3; PhRMA Comment (9/30/08) at 1.

and other clinical settings. As a result, pioneer manufacturers are likely to retain 70 to 90 percent of their market share after FOB entry.

The likely effect of FOB entry contrasts markedly from small-molecule generic drug competition. Soon after small-molecule generic drug entry occurs, the branded product loses most of its market share. This loss of market share occurs because of state substitution laws and payor incentives that permit pharmacies to substitute a prescription for a branded product to a generic product without physician consent. When a market includes eight or more generic products, prices can be discounted up to 80 percent of the branded price.

The Commission is mindful that the likely competitive effects of FOB entry described in this chapter are based on agreement among pioneer manufacturers, potential FOB applicants, and payors as to future conditions. The likely competitive effects of FOB competition could change if technology breakthroughs occur, biosimilar safety issues arise, health insurance coverage expands, or payor and reimbursement strategies change, among others. In sophisticated industries such as biotechnology, external conditions can and do change and often alter expectations of profit-maximizing firms.<sup>90</sup> This industry, however, has shown significant ability to adapt and thrive under new market conditions.<sup>91</sup> The Commission expects the robust and dynamic market conditions of the biologic drug industry to continue with the entry of FOB drug products.

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<sup>90</sup> See Charles E. Phelps, *Managing the Market: Regulation and Technical Change in Health Care*, HEALTH ECONOMICS, at 498-546 (3d ed. 2003).

<sup>91</sup> See Iain M. Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFFAIRS 1:10-22, 14 (2004).



## CHAPTER 2 PATENT PROTECTION AND MARKET INCENTIVES ARE LIKELY TO CONTINUE TO PROVIDE ROBUST INNOVATION INCENTIVES AFTER ENTRY OF FOLLOW-ON BIOLOGIC DRUGS

### I. INTRODUCTION

The introduction of FOB competition raises the question of whether, in addition to patent protection and market-based pricing, pioneer biologic drug products need an exclusivity period, a “branded exclusivity period,” that restricts FOB competition by prohibiting the FDA from approving an FOB product for some period of time to promote innovation in biologic drug markets.<sup>92</sup> Pioneer biologic drug manufacturers have suggested that a 12- to 14-year branded exclusivity period is necessary to incentivize innovation.<sup>93</sup> The length of this branded exclusivity period is based on a model that estimates the time it takes a pioneer manufacturer to recoup its investment to develop and commercialize a typical biologic drug (the “Nature model”).<sup>94</sup>

This chapter explains that the main argument for a branded exclusivity period of 12 to 14 years is to compensate for the perceived failures of the patent system to reward, protect, and incentivize biologic drug innovation.<sup>95</sup> To understand whether such a branded exclusivity period is necessary, and the likely effects of such a period, this chapter summarizes the comments and relevant economic literature on how biologic drugs are developed and the role of the patent system in driving these innovations.

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<sup>92</sup> Other ways to incentivize innovation include tax credits for R&D costs similar to the tax credits used for orphan drugs. *See* Orphan Drug Act, 21 U.S.C.A. § 360aa-dd (2009). Alternatively, one commenter suggested that a new regulatory scheme be developed to allow for the reporting of R&D costs by pioneer manufacturers and then to have FOB entrants repay a share of these costs. *See* Essential Action Comment (12/22/08) at 4. This system may be difficult to establish and administer because FOBs are similar, not identical to the branded product, and may rely on different FDA findings of safety and effectiveness of the branded product to support regulatory approval.

<sup>93</sup> This report uses the term “branded exclusivity” rather than “data exclusivity” because current legislative proposals permit an FOB applicant to rely on FDA’s finding or conclusion that an approved pioneer drug is safe and effective. This reliance does not involve disclosure to the FOB applicant, or to the public, of the data in the pioneer manufacturers’ application. *See* FDA to Petitioners (May 30, 2006) at 6, *available at* <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>. Further, reliance on the FDA’s findings of safety and efficacy of the pioneer biologic provides much less of a benefit in the biologic context than in the small-molecule context, because the FOB will still have substantial R&D expenditures, including clinical testing. *See infra* Ch. 1 at 9, 14-15.

<sup>94</sup> Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 (June 2008).

<sup>95</sup> American Enterprise Institute (“AEI”) Comment (12/10/08) at 5 (“[D]ata exclusivity is a tool that comes into play when patents fail to provide reasonable protection for innovation.”); Henry Grabowski *et al.*, *Updating Prior Analyses and Responding to Critiques*, Duke Univ. Dept. Econ. Working Paper, No. 2008-10 (Dec. 22, 2008) at 3 (“[E]xclusivity periods are essential to compensate for some important shortcomings in patent protection for biologics.”); Duke University Comment (12/23/08) at 1 (“Data exclusivity periods . . . are an “insurance policy.”).

The patent system is the primary means by which the government grants exclusive rights to promote innovation. Patent protection and market-based pricing enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights.<sup>96</sup> Congress and the courts set patent policy with a conscious eye towards maintaining an appropriate balance with competition policy, which also promotes innovation, as the best means to benefit consumers.<sup>97</sup>

Nothing about the introduction of FOB drug products changes the relationship of pioneer biologic drug products to the patents protecting them. As a result, patent protection should continue to incentivize biotechnology innovation, even after enactment of an approval process for FOB drugs. Pioneer biologic drugs are covered by more and varied patents than small-molecule branded products, including manufacturing and technology platform patents. Moreover, there is no evidence that patents claiming a biologic drug product have been designed around more frequently than those claiming small-molecule products.

Even if the FOB manufacturer were to design around the patents claiming a pioneer biologic drug product and enter prior to patent expiration, the effect of FOB entry is unlikely to cause the precipitous decline in the pioneer product's revenues that generic drug entry causes. FOB drugs are likely to garner only 10 to 30 percent market share of an expanded market, rather than nearly 100 percent of the market share from a branded small-molecule drug manufacturer. The pioneer biologic drug manufacturer can continue to earn significant revenues years after FOB entry.

The use of patents to incentivize innovation is especially strong if the FOB approval process does not contain special features similar to the ones in Hatch-Waxman that incentivize an early start to patent challenges that is prior to FDA approval of the generic drug. (These issues are discussed in Chapters 3 and 4.) These early patent challenges are unique to the generic drug industry and, if applied in the FOB drug context, undermine the ability of the patent to incentivize innovation.

Market experience shows that pharmaceutical products already compete against other branded entrants and that this competition benefits consumers by increasing the pace and scope of innovation as well as price competition. Currently, pioneer or first-in-class branded products engage in a race with other branded competitors to bring products

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<sup>96</sup> F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, 3d Ed. 621 (1990).

<sup>97</sup> The Supreme Court has emphasized the "careful balance" embodied in the patent system: "From their inception, the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement through imitation are both necessary to invention itself and the very lifeblood of a competitive economy." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989).

to market.<sup>98</sup> Over the last three decades, the head start of the first-in-class drug product has decreased as the average lead time of the first-in-class product shrank from 8.2 years during the 1970s to 2.25 years in the 1990s. This limited head start for the first-in-class drug product has not dampened R&D incentives and may, in fact, be optimal for rewarding past innovation while allowing competition to incentivize future innovation.<sup>99</sup> Because FOB entry is likely to have a competitive effect similar to that caused by entry of another branded competitor, it is likely that FOB entry will have a similar effect on innovation.

Congress has implemented exclusivity periods to encourage the development of new and innovative drug products when the drug molecule is in the public domain, and therefore not patentable. The Hatch-Waxman Act provides a five-year exclusivity period to incentivize the development of new chemical entities and it provides a three-year exclusivity period for new clinical investigations (“NCI”) of small-molecule drugs. In other instances, Congress has implemented an exclusivity period when market-based pricing has not provided sufficient incentive to test drug products for children or small patient populations.

Central to each of these exclusivities is a public policy trade-off: a restriction on competition is provided in return for a development of a new drug product or new use of an existing product. A 12- to 14-year exclusivity period for pioneer drugs, however, departs sharply from this basic trade-off, because it does not spur the creation of a new product or indication. The product has already been incentivized through patent protection and market-based pricing.

The potential harm posed by such a period is that firms will direct scarce R&D dollars toward developing low-risk clinical and safety data for drug products with proven methods of action rather than toward new inventions to address unmet medical needs. Thus, a new 12- to 14-year exclusivity period imperils the efficiency benefits of an FOB approval process in the first place and it risks over-investment in well-tilled areas.

This chapter then summarizes a critique of the Nature model. The model as currently structured contains numerous methodological and conceptual weaknesses that render its results too imprecise and non-robust to inform discussions about the ideal length of any branded exclusivity period. A model that balances the benefits of FOB competition with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model’s approach.

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<sup>98</sup> See Joseph DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development*, 22 PHARMACOECONOMICS Supp 2:1-14, 10 (2004 ). Although this study examined pharmaceutical products primarily, it included several biologic drugs as well.

<sup>99</sup> F.M. Scherer, *Markets and Uncertainty in Pharmaceutical Development* 13 (FACULTY RESEARCH WORKING PAPERS SER., HARV. U. JOHN F. KENNEDY SCHOOL OF GOV’T, 2007), available at [http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/\\$File/rwp\\_07\\_039\\_scherer.pdf](http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-039/$File/rwp_07_039_scherer.pdf).

## II. THE IMPORTANCE OF PATENT PROTECTION TO THE NEW DRUG RESEARCH AND DEVELOPMENT PROCESS

### A. New Drug Research and Development Process

Pharmaceutical innovation for new drug products is lengthy, expensive, highly risky, and involves a multitude of public- and private-sector entities.<sup>100</sup> Pharmaceutical innovation begins with basic scientific research. Much of the funding of basic medical research comes from the National Institutes of Health or other government sources, angel investors and corporations, not venture capitalists.<sup>101</sup> This funding covers basic research up until proof of concept, which is usually demonstrated by preclinical findings.<sup>102</sup> This basic medical understanding of disease pathways and processes has led to the commercialization of two categories of biologic drugs: (1) recombinant proteins; and (2) monoclonal antibodies.<sup>103</sup>

Once proof of concept has been attained, private investment from angel investors, corporate, and venture capital funding continues the development of these inventions

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<sup>100</sup> See F.M. Scherer, *Pharmaceutical Innovation*, (John F. Kennedy School of Government, Harvard Univ., Working Paper No. RWP07-004, 2007) available at <http://ksgnotes1.harvard.edu/Research/wpaper.nsf/rwp/RWP07-004>; Scherer, *Markets and Uncertainty*, at 11; see also U.S. Cong., Office of Technology Assessment (“OTA”), *Pharmaceutical R&D: Costs, Risks and Rewards*, at 6 (1993), available at <http://www.princeton.edu/~ota> (follow “OTA publications” hyperlink and use search engine there to find article by title) [hereinafter “Pharmaceutical R&D”].

<sup>101</sup> Public policy to increase the U.S. expenditures for research, development and commercialization of federally-funded inventions led to enactment of The University and Small Business Patent Procedures Act of 1980 (also known as “The Bayh-Dole Act”), 35 U.S.C.A. § 200 *et seq.* (2009). This act provides universities and small businesses the right to patent federally funded inventions. Corporations and larger businesses were afforded these same rights pursuant to the Trademark Clarification Act of 1984. 15 U.S.C.A. § 1501 (2009); 35 U.S.C.A. § 210(c) (2009). Privatization of government-funded research was deemed necessary because of a market failure to allocate risk capital to early-stage inventions. Since passage of the Bayh-Dole Act, university-based research has increased by over 800%. See Lewis M. Branscomb and Philip Auerwald, *Between Invention and Innovation: An Analysis of Funding for Early Stage Technology Development*, prepared for Nat’l Inst. of Standards and Technology (“NIST”), Dept. of Commerce (2002), available at <http://www.atp.nist.gov/eao/gcr02-841/contents.htm>. While government funds are used on a variety of novel scientific research, corporate funding typically is incremental innovation to support its pre-existing core business, and to “advance its established product and process technologies to better serve existing markets.” *Id.* at 4.

<sup>102</sup> Jerry G. Thursby & Marie Thursby, *Enhanced: University Licensing and the Bayh-Dole Act*, SCIENCE, Aug. 22, 2003, at 1052, available at <http://www.sciencemag.org/cgi/content/full/301/5636/1052>.

<sup>103</sup> Steven Kozlowski, *Protein Therapeutics and the Regulation of Quality: A Brief History*, BIOPHARM INTERNATIONAL (Oct. 1, 2007), available at <http://biopharminternational.findpharma.com/biopharm/article/articleDetail.jsp?id=462759&sk=&date=&pageID=2>. In addition to these two classes of therapeutic drug treatments, three additional classes of biotechnological products include: (1) vaccines, which typically are preventative treatments but are under investigation for use as therapeutic treatments; (2) cell therapies and (3) gene therapies which are in clinical development.

through clinical development of a drug candidate.<sup>104</sup> After late stage clinical development, private corporations typically begin to scale-up manufacturing and marketing efforts.<sup>105</sup> The R&D process for developing biologic drugs lasts, on average, 10 to 12 years.<sup>106</sup>

Pioneer biologic manufacturers also engage in a race to screen, patent, and develop their products.<sup>107</sup> These races are often propelled by a new medical threat or scientific advances that suggest a new line of therapy.<sup>108</sup>

A study of first-in-class drugs approved by the FDA from the 1960s through the 1990s shows that increasingly, multiple firms target the same disease, therapy or biologic pathway, and as a result, nearly every therapeutic class has had multiple branded competitors. Branded competitors' R&D occurs in parallel. For example, in the 1990s, for all drug classes in which a first-in-class drug was approved, clinical testing for at least one branded competitor's drug occurred before FDA approval of the first-in-class drug.<sup>109</sup> The head start of the first-in-class drug product has decreased over the last three decades, shrinking markedly from 8.2 years during the 1970s to 2.25 years in the 1990s.<sup>110</sup>

Competition does not stop once FDA approval is obtained. Biologic drug manufacturers in particular seek to expand the market opportunity for their products by obtaining additional indications for diseases that share biologic pathways; for example, HGH indications for Turner's syndrome and pituitary dwarfism, Tumor Necrosis Factor ("TNF") inhibitors for both Crohn's Disease and rheumatoid arthritis, and Vasoendothelial Growth Factor ("VEGF") inhibitor for lung cancer and colorectal

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<sup>104</sup> See NIST, DEP'T. OF COMMERCE, BEYOND MEASURE: A PROFILE OF ATP HEALTH CARE INVESTMENTS (2003), available at <http://www.atp.nist.gov/atp/brochures/healthcare.pdf> (estimating that federal funding accounts for 21 to 25 percent of funding during the "valley of death" period between basic research and product development).

<sup>105</sup> See Branscomb, *Between Invention and Innovation*, at Figure 2, p. 33, see also Tanuja V. Garde, *Supporting Innovation in Targeted Treatments: Licenses of Right to NIH-funded Research Tools*, 11 MICH. TELECOMM. TECH. L. REV. 249, 277 (2005), available at <http://www.mttl.org/voleleven/garde.pdf>.

<sup>106</sup> See Joseph DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ. 151, 162, 166 (2003) (estimating that average time from synthesis of a compound to initial human testing is 52.0 months, from the start of clinical testing to marketing approval is 90.3 months, and the total time is approximately 142 months [11 years, 10 months] for small-molecule drugs); see also Grabowski, NATURE, at 481.

<sup>107</sup> DiMasi, *The Economics of Follow-on Drug Research and Development*, at 10.

<sup>108</sup> Scherer, *Markets and Uncertainty*, at 13.

<sup>109</sup> DiMasi, *The Economics of Follow-on Drug Research and Development*, at 9.

<sup>110</sup> *Id.*; Scherer, *Markets and Uncertainty*, at 13.

cancer. These incremental innovations lead to “improvements that over time can yield substantial benefits.”<sup>111</sup>

## **B. The Importance of Patent Protection Incentives for Innovation**

Patent protection fuels this R&D engine.<sup>112</sup> To obtain a patent, an invention (*i.e.*, a product, a process, machine, or composition of matter) must be novel, non-obvious, and useful. A patentee also must disclose clearly the invention. Economic literature has described how this property right enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur but for the prospect of a patent.<sup>113</sup>

The FTC, in its 2003 Report, “To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy,” described how innovation in the biotechnology and pharmaceutical industries is highly dependent on patent protection, more so than any other industry.<sup>114</sup> Stand-alone innovation in these two industries is costly and unpredictable, requiring significant amounts of pioneering research to discover and test new drug products. By preventing rival firms from free riding on discoveries, patents allow pioneer firms to recoup the substantial capital investments made to discover, test, and obtain regulatory approval of new drug products. Patents also are necessary to attract the capital to fund high-risk investment in the biotechnology industry.<sup>115</sup>

The FTC Patent Report explained how pharmaceutical and biotech firms use the patent information disclosures required by the patent statutes to direct their R&D into

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<sup>111</sup> See *e.g.*, AEI Comment (12/10/08) at 2 (post approval development of novel biologics continues as science evolves); see also John Calfee, *The Golden Age of Medical Innovation*, THE AMERICAN (March/April 2007), available at <http://www.american.com/archive/2007/march-april-magazine-contents/the-golden-age-of-medical-innovation>.

<sup>112</sup> See, *e.g.*, *Patent Reform: The Future of American Innovation*, Hearing Before the S. Comm. on the Judiciary, 110th Cong. (2007) (statement of Kathryn L. Biberstein, Senior Vice President, Alkermes, on behalf of the Biotechnology Industry Organization), available at <http://judiciary.senate.gov/hearings/hearing.cfm?id=2803>.

<sup>113</sup> F.M. Scherer & David Ross, INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE, 621 (3d ed. 1990); see also *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 2008 U.S. Dist. LEXIS 77343 at \*169-73 (D. Mass. Oct. 2, 2008 (“Of course, the public derives significant benefits from the innovation generated by the economic incentives in our patent system.”)).

<sup>114</sup> See FEDERAL TRADE COMM’N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (2003), Ch. 3 at 1 [hereinafter “FTC PATENT REPORT”].

<sup>115</sup> *Id.*, see also Arti K. Rai, *Knowledge Commons: The Cost of the Biopharmaceutical Industry*, FIRST MONDAY (June 2007) (“Small biotechnology firms rely on patents, often on technology that is far removed from an end product, for purposes of deterring misappropriation when they market their technology. Patents also help small biotechnology firms negotiate vertical R&D alliances with pharmaceutical firms. For their part, pharmaceutical firms rely on patents on end product drugs for purposes of recouping research and development costs. [footnotes omitted.]”), available at <http://firstmonday.org/htbin/cgiwrap/bin/ojs/index.php/fm/article/view/1909/1791>.

areas not claimed by patents. Patent disclosures can guide rival firms' efforts to "design-around" patents, so that they can develop non-infringing products to compete with the patented discovery and thus spur greater innovation.<sup>116</sup>

Patent protection also covers several components of biotechnology products, including claims drawn to:<sup>117</sup>

- the compound or molecule,
- methods of treatment (specific indications, route of administration),
- formulation and dosage form,
- product-by-process claims (products defined by the process used to make the molecule),
- manufacturing process (including cell lines used in the manufacturing process), and
- manufacturing technology (technology platforms and research tools used to make the molecule).

With one key difference, these are the same types of patent claims that claim small-molecule products. Process patents and technology platform patents are often more important for biologic drug products than for small-molecule drug products. Process patent claims are important because the "processes by which biologics are made are highly specific, complex, and determine many of the biologic's functional and structural characteristics. . . [that] can often be expected to affect the product's safety, purity, and efficacy profile, and thus are integral to the approval of the product itself."<sup>118</sup> Process claims, therefore, add a layer of patent protection that small-molecule drug products may not possess.<sup>119</sup>

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<sup>116</sup> *Id.* at 1-2.

<sup>117</sup> See BIO Comment (9/30/08) at 10-12.

<sup>118</sup> BIO Comment (9/30/08) at 12; see also Bruce S. Manheim *et al.*, 'Follow-On Biologics': Ensuring Continued Innovation In The Biotechnology Industry, 25 HEALTH AFFAIRS 2: 394-404, 397(March/April 2006) ("the identity of a [biologic] product is clearly dependent upon the process used to manufacture the product.").

<sup>119</sup> One commenter noted that not all biologic manufacturing processes are patented, and may restrain entry by FOBs because they are trade secrets in the possession of the branded manufacturers. Essential Action Comment (12/22/08) at 3, and fn. 3 (quoting Gregory Mandel, *The Generics Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement*, 11 Va. J.L. & Tech. at 66 (2006)). Trade secrets often cover methods of making biologic products. See *e.g.*, Letter from Director Steven K. Glason, FDA Center for Evaluation and Research ("CDER") to Petitioners (May 30, 2006) at 9, available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> [hereinafter "FDA's Second

Indeed, concern previously centered on the belief that biotechnology patent protection was too strong because of patent claims covering research tools used to assist in the drug discovery process. The concern was that patented research tools would actually obstruct commercialization of new products, thereby hindering follow-on innovation.<sup>120</sup> This problem has yet to materialize.<sup>121</sup>

### C. Patent Protection in the Biotechnology Industry

The introduction of FOB competition raises the question of whether pioneer biologic drug products should be granted an exclusivity period to incentivize innovation. This section summarizes the two competing arguments regarding the strength of patents to continue to incentivize biotechnology R&D in the face of FOB competition.

#### 1. Panelists' and Commenters' Arguments that Patents Are Unlikely to Incentivize Innovation in Light of FOB Competition

Panelists and commenters representing pioneer biologic drug manufacturers suggested that biologic drug patents are likely to provide less investment certainty than patents claiming small-molecule drug products because FOB products are likely to be similar to, not exact duplicates of, the branded drug product.<sup>122</sup> The panelists suggested that FOB competitors could develop biosimilar products by designing around the branded product's patents.<sup>123</sup>

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Response to Omnitrope CPs"]; Reinhardt Comment (10/19/08) at 2; Novartis Comment (9/29/08) at 2; Momenta Comment (9/30/08) at 40.

<sup>120</sup> FTC PATENT REPORT, at Ch. 3 at 1; Michael Heller *et al.*, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE at 698-701 (MAY 1, 1998) (posits the concern that while biomedical patents spur private investment to support innovation but risks paradoxically the proliferation of fragmented and overlapping intellectual property rights which may restrict the number of commercialized products for improving human health); Suzanne Scotchmer, *Standing On The Shoulders Of Giants: Cumulative Research And Patent Law*, JOURNAL OF ECONOMIC PERSPECTIVES, 5 AMERICAN ECONOMIC ASSOCIATION 1: 29-41 (1991); *see also* HHS, NIH, *Principles and Guidelines for Sharing of Biomedical Resources*, 64 Fed. Reg. No. 246, 72090 (December 23, 1999) (ensuring that the conditions imposed on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act).

<sup>121</sup> John Walsh *et al.*, *Effects of Research Tools Patents and Licensing on Biomedical Innovation*, PATENTS IN THE KNOWLEDGE BASED ECONOMY, 285-336 (2003); John Walsh *et al.*, *View From the Bench: Patents and Material Transfers*, 309 SCIENCE 2003-03 (September 23, 2005); Office of Industries, U.S. International Trade Comm'n, *Patenting Trends and Innovation in Industrial Biotechnology* (October 2008).

<sup>122</sup> *See, e.g.*, AEI Comment (12/10/08) at 5 (“[D]ata exclusivity is a tool that comes into play when patents fail to provide reasonable protection for innovation.”); BIO Comment (9/30/08) at 4; Duke University Comment (12/22/08) at 3.

<sup>123</sup> Norman at 156.



A commenter predicted that the pioneer drug manufacturer does not know whether its patent estate is going to cover the exact molecule that an FOB manufacturer produces.<sup>124</sup> Another commenter summed up this difficulty by suggesting that “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.”<sup>125</sup>

Panelists and commenters also suggested that the uncertain scope of patent protection was caused by recent rules of the U.S. Patent and Trademark Office (PTO) and Federal Circuit decisions narrowing of the claims to the biologic molecule.<sup>126</sup> A panelist suggested that Federal Circuit decisions and PTO practices have forced patentees to obtain “snapshot” claims that limit the claim scope of the compound patent to the exact amino acid sequence.<sup>127</sup> A panelist suggested that in light of these developments, the PTO is applying the written description requirements in such a way that “it is very difficult to get any kind of scope.”<sup>128</sup> Another panelist noted that for biologics, it is much more difficult to establish claims drawn to a broad genus that support current written description and enablement requirements.<sup>129</sup> Additionally, one panelist explained that the PTO recently issued written description guidelines supporting a more narrow interpretation of the written description requirement such that a greater percentage of homology is required in molecules patent claims covering DNA sequences.<sup>130</sup>

Some panelists also discussed the market effects from the Federal Circuit’s decisions scaling back the doctrine of equivalents -- a doctrine that allows for a finding of infringement when the infringing product does not fall within the literal scope of the patent claim but is equivalent to the claimed invention.<sup>131</sup> Panelists and commenters suggested that the practical effect of these current trends in patent law portends difficulty for a branded firm to broaden the scope of its patent claims to cover all equivalent products, especially if the biosimilar differs from the branded biologic by a small variation in amino acid sequences.

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<sup>124</sup> Kushan at 180.

<sup>125</sup> Manspeizer at 148-49; BIO Comment (12/22/08) at 5; *see also* Wyeth Comment (12/18/08) at 8..

<sup>126</sup> *See e.g.*, Wyeth Comment (12/18/08) at 8; Manheim, *Follow-On Biologics*.

<sup>127</sup> Seide at 150-52; BIO Comment (12/22/08) at 5-6 (citing case law).

<sup>128</sup> Kepplinger at 158-59 (further explaining that under the PTO’s current practice for a molecule patent claim to a method of use or function, the PTO will restrict the function claim to the narrow molecule and not broaden it across variations of that molecule.)

<sup>129</sup> Dow at 166-67.

<sup>130</sup> Kepplinger at 157-58; *see generally* Patent and Trademark Office, Written Description Training Materials (2008), available at <http://www.uspto.gov/web/menu/written.pdf>.

<sup>131</sup> *See* Goldman at 164-65, Kepplinger at 158-59; Manspeizer at 148-49.

Another panelist described that when a patent applicant narrows claims during the patent prosecution at the PTO, it has the collateral effect under prosecution history estoppel of surrendering future claims under the doctrine of equivalents that the patentee might try to claim against a biosimilar entrant.<sup>132</sup>

## **2. Panelists' and Commenters' Arguments that Patent Protection Provides Ample Incentives for Innovation**

FOB manufacturers suggested that these arguments were overbroad because of the number and scope of patents that pioneer manufacturers control relating to their biologic products. For example, FOB commenters and panelists explained how the molecule patents claiming branded products would likely be infringed by FOBs.<sup>133</sup> Thus, a “minor and immaterial sequence change is very likely to expose a follow-on biologic to an infringement risk.”<sup>134</sup> Another commenter explained that while “smaller biopharma products (such as peptides, fragments and small proteins) may have granted patents covering the full sequence of the product, Amgen’s recent success on EPO full sequence claims against Roche and Transkaryotic Therapies (different products and technologies) shows the power in such claims.”<sup>135</sup>

Some FOB manufacturers suggested that process patents will likely provide additional protection against infringing products, making it more difficult for FOB manufacturers to design around the patents and obtain FDA approval of an FOB product.<sup>136</sup> For example, one panelist suggested that the pioneer manufacturer may have patented the most commercially viable manufacturing methods and the FOB industry may not be able to devise “another commercially appropriate way to circumvent a process patent.”<sup>137</sup> In light of this problem, another commenter suggested that process “patents often provide a level of market protection because the biological origin of their discovery makes them necessary for a production of a product.”<sup>138</sup>

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<sup>132</sup> Dow at 166-67, 169; Manspeizer at 148-49.

<sup>133</sup> Hospira (Wilkie Farr) Comment (12/22/08) at 2 (“Biologics are large molecules, and product patents typically only claim their ‘active’ regions. [footnote omitted] These active regions engage the molecule with its surrounding environment and create the therapeutic effect. Thus, while biosimilars might be similar, but not identical, their functionality will likely require resolution of product claims covering the biologic’s active region, regions that will often be shared by both the reference biologic and the biosimilar.”); Leicher at 161-62; Winston & Strawn (“W&S”) Comment (12/22/08) at 4.

<sup>134</sup> Pearce at 169.

<sup>135</sup> Hospira (Wilkie Farr) Comment (12/22/08) at 3; *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 2008 U.S. Dist. LEXIS 77343 at \* 13 (D. Mass. Oct. 2, 2008); *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094 (Fed. Cir. 2003).

<sup>136</sup> Hospira (Wilkie Farr) Comment (12/22/08) at 2.

<sup>137</sup> Pearce at 144-45.

<sup>138</sup> Momenta Comment (12/22/08) at 8.

Another commenter suggested that additional barriers to FOB entry are created by well-known platform technology patents used in the research, development and manufacture of biopharmaceutical products.<sup>139</sup> This commenter explained that “[t]hese patents are extremely broad and tend to overlap with one another, providing brand biopharmaceuticals with wide-ranging protection over their drug products.”<sup>140</sup>

FOB manufacturers suggested that “[b]iologic patents are more likely to obtain patent term extensions under Section 156 [of the Patent Act] due to the long and complex patent prosecutions.”<sup>141</sup> These extensions ebb and flow with the PTO’s workload.<sup>142</sup> FOB manufacturers also suggested that biologics “are also more likely than chemical drugs to be covered by ‘submarine’ patents.”<sup>143</sup>

#### **D. Patent Protection is Likely to Continue to Provide Strong Incentives for Innovation after Introduction of Follow-On Drug Competition**

The patent system has a proven record of protecting and stimulating biotechnology innovation.<sup>144</sup> The introduction of FOB drug products does not alter the relationship of pioneer biologic drug products to the patents protecting them. Pioneer biologic drugs are covered by more and varied patents than small-molecule branded

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<sup>139</sup> Panelists explained the number of patents per biologic product, including platform patents, is substantial, resulting in significant “stacking” of patents (or royalties) compared to the small-molecule patent estates. *See* Dow at 185; Sauer at 261; Seide at 238; Duncan Bucknell Co. Comment (1/9/09) at 9; Momenta Comment (9/30/08) at 6-7; Wyeth Comment (9/30/08) at 4.

<sup>140</sup> Essential Action Comment (12/22/08) at 3, and fn. 3 (quoting Gregory Mandel, *The Generics Biologics Debate: Industry’s Unintended Admission That Biotech Patents Fail Enablement*, 11 Va. J.L. & Tech. at 66 (2006)); W&S Comment (12/22/08) at 5;.

<sup>141</sup> W&S Comment (12/22/08) at 3.

<sup>142</sup> Leicher at 162-63; Dow at 185.

<sup>143</sup> Hospira (Wilkie Farr) Comment (12/22/08) at 3. Submarine patents result from older patent applications that are not published. Because the applications are not made available 18 months after filing, competitors cannot use the applications to determine whether their FOB products in R&D are likely to infringe potential issued patents. This also creates uncertainty for competitors.

<sup>144</sup> F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, at 621 (3rd Ed., 1990); *see also Patent Reform: The Future of American Innovation, Hearing Before the S. Comm. on the Judiciary*, 110th Cong. (2007) (statement of Kathryn L. Biberstein, Senior Vice President, Alkermes) at 2; *Patent Reform Act of 2007: Hearing on H.R. 1908 Before the H. Subcomm. on Courts, the Internet, and Intellectual Property of the H. Comm. on Judiciary*, 110th Cong. 65 (2007) (statement of Kevin Sharer, CEO of Amgen), available at <http://judiciary.house.gov/hearings/April2007/Sharer070426.pdf>., *Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing Before the H. Comm. on the Judiciary, Subcomm. on Courts, the Internet, and Intellectual Property*, 110th Cong. (2007) (statement of Jeffrey P. Kushan on Behalf of BIO), available at <http://judiciary.house.gov/hearings/pdf/Kushan071030.pdf>.

products, including manufacturing and technology platform patents.<sup>145</sup> Patent cases between pioneer manufacturers reveal that patents such as process, manufacturing, and method of use claims can be infringed by a branded competitor.<sup>146</sup> These cases show that the range of patents claiming a biologic product provide a strong assurance that at least one of a biologic drug product's patents will cover an FOB drug product.

There is no evidence that the patents claiming the compound or molecule of pioneer biologic drugs have been designed around more frequently than those claiming small-molecule drug products. There are a variety of ways to draft claims broadly enough to cover the types of drug structure variations expected in follow-on biologics.<sup>147</sup> For example, patent claims reciting the amino acid sequence of a biologic drug compound or molecule can encompass not only the specific sequence, but also a broad genus of structurally and/or functionally related variants through the use of "percent identity claims." An example of a percent identity claim would be 'a protein comprising an amino acid sequence sharing at least 70% identity with the described amino acid sequence.'<sup>148</sup> The PTO's Written Description Guidelines specifically allow the use of percent identity claims.<sup>149</sup> The effect of these claims is that the patent covering the pioneer biologic drug can be broader than the actual product.<sup>150</sup> Using the example

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<sup>145</sup> *Id.*, see also Dow at 185; Sauer at 261; Seide at 238; Duncan Bucknell Co. Comment (1/9/09) at 9; Momenta Comment (9/30/08) at 6-7; Wyeth Comment (9/30/08) at 4.

<sup>146</sup> Bio-Technology Gen. Corp. v. Genentech, Inc., 267 F.3d 1325, 1333 (Fed. Cir. 2001) (reversing trial court's finding of invalidity for lack of enablement regarding method of production patent); see also Press Release, Genentech, Genentech Receives Final Notification Upholding Cabilly Patent in Reexamination Proceeding (Feb. 24, 2009), available at [www.gene.com](http://www.gene.com) (announcing PTO issuance of Notice of Intent to Issue a Reexamination Certificate confirming patentability of all claims of the Cabilly Patent (U.S. Pat. No. 6,331,415) claiming methods of making recombinant cells expressing both an immunoglobulin light chain and heavy chain used in genetically-engineered monoclonal antibodies).

<sup>147</sup> John R. Thomas, *Toward a Theory of Marketing Exclusivities* at 32-33 (2009) (forthcoming) ("Biotechnology products may commonly be defined through multiple techniques, including their structure, chemical or physical characteristics, and method of preparation, that in combination are capable of providing a potent shield against would-be competitors.").

<sup>148</sup> Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 44 (2007).

<sup>149</sup> PTO, WRITTEN DESCRIPTION TRAINING MATERIALS (2008), available at <http://www.uspto.gov/web/menu/written.pdf>.

<sup>150</sup> See, e.g., *Infigen, Inc. v. Advanced Cell Technology, Inc.*, 65 F. Supp.2d 967,975 (W.D. Wis. 1999) ("It is black letter law that claims are not limited to the embodiment described in the patent specifications. Moreover, a patent claim may encompass uses not anticipated by the inventor and therefore not described in the patent.") (citations omitted). This principle extends beyond percent identity claims. *Capon v. Eshhar*, 418 F.3d. 1349, 1359 (Fed. Cir. 2005) (reversing BPAI interpretation of written description and holding, "It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention."); *Invitrogen Corp. v. Clontech Labs.*, 429 F. 3d 1052, 1071-74 (Fed. Cir. 2005) (holding that disclosure of a known protein variant satisfied written description for claims encompassing engineered protein variants with shared function); *id* at 1073 ("Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise."),

above, an FOB drug product's molecule could differ by up to 30 percent and still infringe the patent protecting the pioneer product.<sup>151</sup>

The scope of drug compound or molecule patents depends on the claim language and patent prosecution. Although it is true that alleged competitors have been found not to infringe drug compound claims because of the way in which the claims were construed,<sup>152</sup> it is equally true that biotechnology drug product claims have been construed so that accused products have been found to infringe even when they have varied from the patentee's corresponding product.<sup>153</sup> For example, a pioneer manufacturer recently obtained a permanent injunction after a finding that its patents were infringed by a competitor that had altered the patented molecule slightly.<sup>154</sup> Other cases are pending as well.<sup>155</sup>

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*see generally* Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1 (2007) (a comprehensive review of federal court and PTO Board of Patent Appeals and Interferences decisions reveals no support for the proposition that since the Lilly decision, which purportedly tightened the written description requirements for biotechnology drug molecule claims, patentees have not been able to obtain patents with sufficiently broad scope.).

<sup>151</sup> Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 47 (2007).

<sup>152</sup> *Biogen, Inc. v. Berlex Labs*, 318 F.3d 1132, 1140-42 (Fed. Cir. 2003) (affirming trial court's finding that there was no literal infringement and vacating summary judgment of non-infringement under the doctrine of equivalents); *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 1569 (Fed. Cir. 1997) (reversing trial court's denial of defendant's JMOL in part because an element of the doctrine of equivalents was not met); *Novo Nordisk of N. America, Inc., v. Genentech, Inc.*, 77 F.3d 1364, 1367-71 (Fed. Cir. 1996) (vacating preliminary injunction on grounds that district court erred in finding literal infringement where "direct expression" of human growth hormone did not cover alleged infringers "cleavable fusion" process for producing the hormone); *Hormone Research Foundation, Inc., v. Genentech, Inc.*, 904 F.2d 1558, 1563-67 (Fed. Cir. 1990) (finding no literal infringement, vacating infringement under the doctrine of equivalents, holding that the patentee did not intend "corresponding to" and "similar" to have the same meaning, and ruling that "corresponding to" reflected true identity).

<sup>153</sup> *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) (reversing district court's claim interpretation in interference proceeding because it was "not the broadest, reasonable interpretation of the count.") (citing *Genentech, Inc. v. The Wellcome Found., Ltd.*, 29 F.3d 1555 (Fed. Cir. 1997)); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1219 (Fed. Cir. 1991) (affirming trial court's finding that certain claims covering purified and isolated DNA sequences encoding EPO and host cells transformed or transfected with a DNA sequence were valid and infringed and reversing finding that other claims were enabled); *Amgen, Inc. v. Hoffmann-LaRoche Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. 2008) (granting permanent injunction for infringement of claims directed to a specific amino acid sequence); *see also* *Amgen Inc. v. Hoechst Marion Roussel*, 579 F. Supp. 2d 199, 210 (D. Mass. 2008); *Chiron v. Genentech, Inc.*, 268 F. Supp. 2d 1126, 1138 (E.D. Cal. 2008); *Genentech, Inc. v. Insmad Inc.*, 436 F. Supp. 2d 1080, 1091-92 (N.D. Cal. 2006) (granting patent holder's partial motion for summary judgment and finding literal infringement of a patent claiming "Preparation of Human IGF via Recombinant DNA I Technology").

<sup>154</sup> *Amgen, Inc. v. F. Hoffmann La Roche, Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. Oct. 2, 2008).

<sup>155</sup> *See e.g.*, *Bayer HealthCare LLC v. Abbott Laboratories*, Civ. Action No. 6:08cv507 (E.D. Tex. Dec. 24, 2008), complaint available at <http://www.patentbaristas.com/wp/wp-content/uploads/2009/01/bayer.pdf>.

To the extent an FOB manufacturer will attempt to design around a pioneer manufacturer's patent, that effort is to be expected and encouraged. Competing branded manufacturers have been doing just that since the early days of biotechnology patents.<sup>156</sup> The purpose of the required patent disclosures is to assist rival firms to design around patents so that they can develop non-infringing products to compete with the patented discovery and thus spur greater innovation.<sup>157</sup> Of course, FOB manufacturers run the risk that the more their drug molecule differs from the pioneer product's molecule to avoid patent infringement issues, the greater the chance that its product will no longer be "similar" enough to the pioneer product to use the FOB approval process.

Finally, even if the FOB manufacturer were to design around the patents claiming a pioneer biologic drug product and enter prior to patent expiration, the pioneer manufacturer will continue to earn significant revenues after FOB entry. Pioneer manufacturers are likely to retain 70 to 90 percent market share following FOB entry. Moreover, the overall market is likely to expand following FOB entry, thereby diminishing the loss of revenue by the pioneer manufacturer. The effect on the pioneer manufacturer caused by FOB entry is not nearly as great as it is with small-molecule generic drug entry.

In sum, continued reliance on the patent system to stimulate biotechnology innovation is well-justified. This reliance is well-placed especially if the FOB abbreviated FDA drug approval process does not contain special regulatory features similar to the ones in Hatch-Waxman that incentivize patent challenges prior to FDA approval of the FOB drug and undermine the ability of the patent to incentivize innovation.

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Abbott countersued in Massachusetts: *Abbott Laboratories v. Bayer Healthcare LLC*, 09cv40002, U.S. District Court for the District of Massachusetts, 09cv40002, (D. Mass. June 5, 2008).

<sup>156</sup> BIO Comment (9/30/08) at 22 (citing industry experience over more than two decades of biotechnology patent litigation).

<sup>157</sup> FTC PATENT REPORT, Ch. 3 at 1-2.

### **III. OTHER CONSIDERATIONS DO NOT SUPPORT A 12- TO 14-YEAR BRANDED EXCLUSIVITY PERIOD**

Commenters and panelists also described the need for, and the likely effects of, a 12- to 14-year branded exclusivity period. The next two sections summarize these views and the need for a 12- to 14-year exclusivity period. The third section provides an analysis of these effects.

#### **A. Panelists' and Commenters' Views on the Likely Effects of a Branded Exclusivity Period**

Pioneer manufacturers suggested that a 12- to 14-year branded exclusivity period provides certainty about recoupment when R&D investment decisions are made.<sup>158</sup> Moreover, exclusivity only protects the pioneer manufacturer from the use of its own data by a potential FOB competitor for the length of the exclusivity period.<sup>159</sup>

To calculate the recoupment amount, pioneer manufacturers rely on an economic model (the “Nature model”) that calculates the time it takes for a manufacturer to recover fully its investment to develop and commercialize a typical biologic drug.<sup>160</sup> Some commenters have concluded that the Nature model supports a branded exclusivity period between 12.9 and 16.2 years in length.<sup>161</sup>

Pioneer manufacturers suggested that a branded exclusivity period substantially shorter than 14 years would be disastrous for innovation and patients.<sup>162</sup> They suggested that without substantial exclusivity, there will be a decrease in the number of “targets of opportunity” for which FOBs could reference.<sup>163</sup> In addition, R&D would shift away from new treatments for diseases, thus depriving the public of much needed treatments

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<sup>158</sup> Phillips at 100-01 (“[I]f there is no chance to recoup the capital outlay, then the investment won’t be made.”). This panelist also suggested that there is a dynamic effect to a branded exclusivity period in that it “is going to change the status quo for investment decisions made by innovator companies;” *see also* AEI Comment (12/10/08); Eli Lilly Comment (12/19/08) at 2; Wyeth Comment (12/18/08) at 2 (“Just as certainty spurs innovation and advances that benefit patients, lack of certainty in the pharmaceutical and biotechnology industries hinders innovation”).

<sup>159</sup> Johnson & Johnson Comment (3/17/09) at 6.

<sup>160</sup> Grabowski, *Follow-on Biologic*.

<sup>161</sup> Duke University Comment (12/22/08); PhRMA Comment (12/22/08).

<sup>162</sup> *See, e.g.*, BIO Comment (9/30/08) at 17 (“Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies, in order to secure the necessary resources from venture capital firms and other funding sources, must have some certainty that they can prevent free-riding on their investment in the development of new breakthrough therapies for a substantial period of time.”)

<sup>163</sup> Wyeth Comment (12/18/08) at 10.

for unmet medical needs, toward ‘safer’ bets such as new formulations or second generation molecules.”<sup>164</sup>

Others suggested that a branded exclusivity period should be similar to the actual amount of time that patented small-molecule products enjoy before generic entry occurs.<sup>165</sup> Under Hatch-Waxman, even though the maximum amount of branded exclusivity is five years, generic entry occurs, on average and depending upon the size of the market, between 11 and 13 years after FDA approval of the branded drug product.<sup>166</sup>

Although one panelist questioned why, if the exclusivity period were short, the pioneer manufacturer could not raise prices to make up for any shortfall in revenue and thus not be any worse off.<sup>167</sup> However, another panelist explained that the “the key driver of prices will be if you’re in a market where there’s competition or anticipated competition.”<sup>168</sup>

By contrast, commenters representing FOB manufacturers suggested that experience under Hatch-Waxman informed their view that a long exclusivity period would lengthen the time between innovations and do little to stimulate innovation. Instead, a 14-year branded exclusivity period may simply reduce the pace of innovation.<sup>169</sup> One commenter predicted that if the branded exclusivity period were that long then branded manufacturers would engage in minor product enhancement strategies which would multiply the costs of expanding monopoly protection.<sup>170</sup> Others noted that long exclusivity periods will eliminate or substantially delay the efforts by FOB manufacturers in making innovations in safety, convenience, cost, access, immunogenicity, interchangeability, or new indications for biologics.<sup>171</sup>

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<sup>164</sup> *Id.* at 9.

<sup>165</sup> BIO Comment (12/22/08) at 6.

<sup>166</sup> Henry Grabowski *et al.*, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, *MANAGERIAL AND DECISION ECONOMICS* 28 (2007) 491–502, at 493 (the study examined 251 products that encountered generic entry between 1995 and 2005).

<sup>167</sup> Heldman at 117; *see also* Essential Action Comment (12/22/08) at 2 (“[F]ree from competitive pressures they can set a price that allows them to earn profits, and not just recoup their R&D costs.”).

<sup>168</sup> Grabowski at 117-18 (“[P]rice is going to be driven by your interaction with payers and other competitors.”).

<sup>169</sup> Zuckerman Spaeder Comment (12/22/08) at 12.

<sup>170</sup> Teva Comment at 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.”).

<sup>171</sup> Brugger at 74; Behrman at 77-79; Grabowski at 80; Barr Comment (12/19/08) at 1-2 (the anticompetitive barrier to FOB competition is longer than just the term of the exclusivity period, as FOB cannot file its application until the day after the period expires, and entry is further delayed for year(s) while FDA reviews the FOB’s application.); Momenta Comment (12/22/08) at 1-3; Novartis Comment (9/29/08) at 10 (“With no market access, there is only limited incentive to make safe and effective



## **B. Panelists' and Commenters' Views on the Need for Branded Exclusivity to Incentivize Incremental Innovation**

The panelists and commenters also examined how the existence and length of an exclusivity period could affect incremental innovation. Pioneer manufacturers explained that there likely would not be incremental innovation without recoupment to recover these investments.<sup>172</sup> In this context, participants used the term “incremental innovation” to refer to actions such as the discovery of a new indication for a previously approved product, or an improved formulation for greater safety or convenience.<sup>173</sup>

A commenter suggested that a 12- to 14- year period of exclusivity is necessary to encourage post-FDA approval research. This commenter explained “that at the time a novel biologic is approved, little may be known of what that drug can do or of what can be achieved in connection with its biological target.”<sup>174</sup> Another commenter suggested that without an additional exclusivity period the number of post-approval clinical trials testing new uses of already approved biologic would drastically decrease due to the lack of certainty of an adequate return on investment. For example, instead of anti-cancer biologics being tested in a dozen or more indications in large scale, “Phase IV” clinical trials, no attempt would be made to broaden the use of approved biologic drugs.<sup>175</sup>

Another commenter explained that some extension of exclusivity for the pioneer product is necessary to effectively incentivize the development of new indications for, or other improvements to, existing products. Without such an extension, this commenter predicted that “healthcare practitioners may decide to use the FOB to treat the new indication regardless of whether the FOB was approved for that indication.”<sup>176</sup>

Another panelist suggested, however, that there likely would be a trade-off between the length of the initial branded exclusivity period and additional grants of exclusivity for new indications. He suggested that if additional branded exclusivity is granted, that the initial period be kept shorter to encourage the pioneer manufacturer to engage in the post-approval R&D.<sup>177</sup>

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competing products . . . expand the market with new indications . . . implement more efficient and cost-effective manufacturing that potentially can enable reductions in costs of goods.”).

<sup>172</sup> Grabowski at 128; Horton at 129-30; Philips at 132-33.

<sup>173</sup> See John E. Calfee, *Facing Reality on Follow-On Biologics*, AEI (2007), available at [http://www.aei.org/docLib/20070423\\_200704AHPOg.pdf](http://www.aei.org/docLib/20070423_200704AHPOg.pdf).

<sup>174</sup> AEI Comment (12/10/08) at 2.

<sup>175</sup> Wyeth Comment (12/18/08) at 9.

<sup>176</sup> BIO Comment (12/22/08) at 7-8.

<sup>177</sup> Brill at 133-34.

## C. Likely Competitive Effects of a Branded Exclusivity Period

### 1. The Innovation Benefits of FOB Competition

As discussed in Chapter 1, FOB manufacturers are likely to seek approval of biosimilar products whose market effects are likely to resemble those of pioneer biologic products rather than small-molecule generic products. Innovation benefits due to branded competition include a race among firms attacking an unmet medical need or investigating a promising therapy that results in increased dissemination of scientific knowledge, and a greater chance of developing a breakthrough product to benefit consumers.<sup>178</sup> The social value of the cumulative effects of incremental innovations can often exceed those of the original breakthrough.<sup>179</sup> These same benefits are likely with entry of FOB products.

Branded competitors also enhance their products to differentiate them from their competitors. This is a common dynamic in competitive markets. Automatic substitution of generic drugs distorts this product enhancement dynamic such that branded manufacturers are incentivized to change their products in minor ways to defeat automatic substitution.<sup>180</sup> These minor changes may not provide clinical or patient benefit. The lack of automatic substitution of FOB products, however, is likely to lessen this distortion in biologic drug markets.

### 2. Actual Pioneer Drug Manufacturer Exclusivity Can Inform the Length of a Branded Exclusivity Period

The head start that first-in-class branded products already experience against second-in-class products can inform the length of a branded exclusivity period for biologics. A subsequent branded competitor obtains limited benefits from the regulatory approval occasioned by the first-in-class product because its R&D efforts have been proceeding on a parallel path with those of the first-in-class manufacturer.<sup>181</sup> The head start of the first-in-class drug product has decreased over the last three decades as the average lead time of the first-in-class product shrank from 8.2 years during the 1970s to 2.25 years in the 1990s. This limited period of exclusivity for the first-in-class drug

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<sup>178</sup> See generally DiMasi, *The Economics of Follow-on Drug Research and Development*; Ian Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFF. 1:10-22 (2004).

<sup>179</sup> William J. Baumol, *THE FREE-MARKET INNOVATION MACHINE: ANALYZING THE GROWTH MIRACLE OF CAPITALISM* (2002) at 33 (capitalism benefits society not just through price competition but also through systematic innovation races among all firms in an innovating industry as they vie for consumers and dare not fall behind the others in new products and processes).

<sup>180</sup> See *Abbott Labs. v. Teva Pharm. USA, Inc.*, 432 F. Supp. 2d 408, 413 n.1 (D. Del. 2006) for an example of litigation alleging this type of strategy. See also Herbert Hovencamp, Mark D. Janis & Mark A. Lemley, *IP AND ANTITRUST*, § 12.5 (2006).

<sup>181</sup> See generally DiMasi, *The Economics of Follow-on Drug Research and Development*. Although this study examined pharmaceutical products primarily, it included several biologic drugs as well.

product has not dampened R&D incentives and may, in fact, be optimal for rewarding past innovation while allowing competition to incentivize future innovation.<sup>182</sup>

### 3. **FOB Entry is Unlikely to Occur Immediately upon Expiration of a Limited Period of Branded Exclusivity**

It is likely that few, if any, biologic products will experience FOB entry immediately upon expiration of a limited period of exclusivity. The generic drug approval process under Hatch-Waxman results in branded manufacturers enjoying approximately 11 to 13 years of *de facto* exclusivity prior to a generic drug entry.<sup>183</sup> This length of market exclusivity occurs despite the incentives within Hatch-Waxman for generic manufacturers to challenge branded patents prior to FDA approval of the generic drug. Indeed, this length of time is attributable mainly to patent protection and patent restoration.<sup>184</sup>

An approach that does not provide incentives to challenge a pioneer product's patents prior to FDA approval is likely to result in a longer period of *de facto* exclusivity than that which occurs under Hatch-Waxman for small-molecule drugs. To the extent patents are at issue, they would be resolved after any branded exclusivity period had expired and FDA approval had been acquired, similar to the way in which branded competitors currently resolve their patent disputes. It is unlikely that FOB manufacturers will expend the substantial resources to develop a biosimilar product and obtain FDA approval if it is likely to run afoul of a pioneer product's patents.

Moreover, expiration of a branded exclusivity period does not mean that FDA approval of an FOB will follow soon thereafter. Pioneer manufacturers are likely to use the citizen petition process to raise safety and efficacy concerns about FOBs, which will delay FOB approvals, as occurred with Omnitrope.<sup>185</sup> Additional delays to FDA approvals of FOB applications would likely occur were FDA required to issue guidance documents, including issuing draft guidance documents, soliciting public comments, and finalizing the guidance documents, before accepting or approving any FOB application for a particular class of branded biologic drugs.<sup>186</sup>

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<sup>182</sup> Scherer, *Markets and Uncertainty*, at 13.

<sup>183</sup> Grabowski, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, at 493.

<sup>184</sup> Charles Clift, *The Value of Patent Term Extensions to the Pharmaceutical Industry in the USA*, 5 J. GEN. MED. 201-208 (Apr. 2008).

<sup>185</sup> Barr Comment (9/30/08) at 12.; PhRMA Comment (9/30/08) at 19 (“As in the case of generic drugs, any regulatory approval pathway for FOBs would involve complex scientific and legal considerations that can and should be raised through appropriate mechanisms, such as citizen petitions. Innovator companies have extensive knowledge about their products, and are often in the best position to bring to FDA’s attention complex regulatory and scientific issues regarding appropriate approval standards.”).

<sup>186</sup> *See, e.g.*, H. 1548, 111th Cong. § 101(k)(2)(B)(iii) (2009) (guidelines required for assessing immunogenicity); *id.* at § 101(k)(4)(B) (guidelines required for assessing interchangeability); and *id.* at § 101(k)(5)(C) (guidelines required for Risk Evaluation and Mitigations Strategy).

Even if patent litigation were to start following FDA approval, pioneer manufacturers would likely have *de facto* exclusivity for several years after the period ends due to the time it takes to resolve complex patent litigation. The FTC 2002 Generic Drug Study calculated that obtaining a district court resolution of patent issues under the Hatch-Waxman Act took on average 25.5 months and that it took over 12 more months to obtain a court of appeals decision.<sup>187</sup> Given that the patent portfolios for biologic products are likely to include patents owned by third party entities, this time could be substantially extended.<sup>188</sup> Thus, the effect of patent litigation starting after FDA approval of an FOB would delay FOB entry beyond the expiration of a limited branded exclusivity period.

#### **4. Exclusivity Periods Have Been Used When Patent Protection Has Been Insufficient to Incentivize and Reward Innovation**

Congress has implemented exclusivity periods to encourage the development of new and innovative drug products when the drug molecule is in the public domain, and therefore not patentable.<sup>189</sup> Similarly, exclusivity periods have been used to incentivize the post-FDA approval clinical trials for new uses of existing drug products. For example, the Hatch-Waxman Act provides a five-year exclusivity period to incentivize the development of new chemical entities. It also provides a three-year exclusivity period for new clinical investigations (“NCI”) of small-molecule drugs.<sup>190</sup>

In other instances, Congress has implemented an exclusivity period when market-based pricing has not provided sufficient incentive to develop drug products for target populations. For example, 6-months of marketing exclusivity periods are awarded upon the showing of safety and effectiveness for children. A seven-year marketing exclusivity period is awarded to manufacturers of drug products that treat diseases affecting less than 200,000 persons in the United States.<sup>191</sup>

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<sup>187</sup> See FEDERAL TRADE COMM’N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (JULY 2002), at iiiii, available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

<sup>188</sup> See *infra* Chapter 3.

<sup>189</sup> See BIO Comment (5/1/09) at 7-9 (Benjamin Roin, *Unpatentable Drugs and the Standards of Patentability* 87 TEX. L. REV. (forthcoming)).

<sup>190</sup> See Appendix B for a description of the marketing exclusivities for small-molecule drug products.

<sup>191</sup> See Orphan Drug Act (“ODA”), 21 U.S.C.A. § 360aa *et seq.* (2009), 21 C.F.R. § 316 *et seq.*; FDA, Office of Orphan Products Dev’t, Cong. Findings For the ODA (“[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss; there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs.”) available at <http://www.fda.gov/orphan/oda.htm>. It is likely that the patents for orphan drugs and not the 7-year ODA exclusivity period provide the greatest incentive to innovators. See Robert Rogoyski, *The Orphan Drug*

Central to each of these exclusivities is a public policy trade-off: a restriction on competition is provided in return for a development of a new drug product or new use of an existing product. A 12- to 14-year exclusivity period, however, departs sharply from this basic trade-off, because it does not spur the creation of a new product or indication. The drug has already been incentivized through patent protection and market-based pricing.

To the extent that there are new biologic molecules that cannot obtain patent protection, an exclusivity period may be warranted. Because there is no evidence about the lack of patentability of new biologic products, nor that market forces have been insufficient to incentivize their development, the Commission has not recommended a length of an exclusivity period.

One benefit of an FOB approval process is that it provides an efficient way to advance scientific progress and commercialization of that scientific innovation. An FOB approval process eliminates unnecessary clinical tests and allows competition to generate better consumer products at lower prices. The potential harm posed by a 12- to 14-year exclusivity period is that firms will direct scarce R&D dollars toward developing low-risk clinical and safety data for drug products with previously proven efficacy rather than toward new inventions to address unmet medical needs. Thus, a new 12- to 14-year branded exclusivity period imperils the efficiency benefits of an FOB approval process in the first place.

In addition, a 12- to 14-year branded exclusivity period could undermine the patent system's disclosure function as pioneer manufacturers rely on trade secrets rather than patents to protect their inventions. Because the patent system requires public disclosure, it promotes the dissemination of scientific and technical information that would not occur but for the grant of a patent. The scientific community can then learn and design around the invention. The ability to design around is prevalent for patent claims covering the formulation or dosage of drug products, product-by-process claims, and process claims – all of which currently protect pioneer biologic products. To the extent that the branded exclusivity period replaces the need for the patent, the scientific community loses the disclosure of inventions that occurs when patents are granted and published, and innovation could be harmed.

#### **D. The Nature Model Fails to Inform Reliably the Length of a Branded Exclusivity Period**

Pioneer manufacturers have developed the Nature model to show that the optimal length of branded exclusivity should be approximately 14 years. The Nature model, as currently presented, contains numerous methodological and conceptual weaknesses that

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*Act and the Myth of the Exclusivity Incentive*, 7 COLUM. SCI. & TECH. L. REV 2 (2006), <http://www.stlr.org/volumes/volume-vii-2005-2006/rogoyski/>. According to one study, the majority of orphan drugs are protected by patents with both a broader scope than the disorder specific ODA, and a longer duration than the 7-year ODA exclusivity period. *Id.* at 18, Figure 1.

render its results too imprecise and non-robust to inform discussions about the length of an exclusivity period. A model that balances the benefits of FOB competition with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model's approach.<sup>192</sup>

Appendix A further explains and evaluates the assumptions underlying the Nature model. A brief summary of the problems includes:

- **Imprecision:** The estimates of costs and revenues used in the model are based on extremely small samples of drug products and are likely imprecise.
- **Inelastic Demand:** Most versions of the model currently assume that the overall quantity of the drug produced and sold will not expand with FOB entry although they assume that FOB entry will lead to lower prices.
- **Internal Inconsistency:** The ad hoc assumptions about the branded manufacturers' price decrease and market share decline following FOB entry are not necessarily consistent with the likely market dynamics of FOB competition.
- **Excessive Aggregation:**
  - The revenue estimates do not distinguish between the original and subsequent indications and formulations, so an independent analyst cannot modify the framework to calculate the break-even point for just the original indication and formulation.
  - The model is based on a portfolio of biologic drugs that includes blockbuster drugs as well as drugs with relatively less in sales and profit. The use of an average revenue stream likely produces an exclusivity period that overprotects the top-selling drugs which are the only drugs likely to face FOB entry when the branded exclusivity period ends.
- **Non-Robustness:** The model's results are extremely sensitive to small changes in the cost of capital<sup>193</sup> and other assumptions.

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<sup>192</sup> Such an approach would require, at a minimum, R&D cost information to which the FTC does not have access.

<sup>193</sup> The cost of capital is the annual rate of return that an investor would require. Grabowski, NATURE at 480.

## CHAPTER 3      COMPETITIVE EFFECTS OF A PRE-APPROVAL PATENT RESOLUTION PROCESS

### I.      INTRODUCTION

Patent protection fuels the biotechnology industry's R&D engine.<sup>194</sup> As discussed in Chapter 2, patent protection and market-based pricing enable biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights.<sup>195</sup>

Special procedures to provide an early start to resolving patent disputes between pioneer and FOB manufacturers prior to FDA approval of the FOB product are unlikely to be successful to facilitate FOB entry. Although special procedures govern patent litigation between branded and generic competitors over small-molecule drug products, these procedures are the exception, not the norm. In every industry, including the biotechnology industry, competing firms have engaged in patent litigation in which the patent holder initiates infringement litigation or the alleged infringer seeks a declaratory judgment of non-infringement or invalidity. In the biotechnology industry, this process usually begins following FDA approval of the competing drug product.<sup>196</sup>

The special procedures for small-molecule drugs were designed in 1984 to address the issue of "judgment proof" generic defendants. In this context, the profits of the alleged infringer (the generic entrant) are substantially less than the loss of profits by the branded product manufacturer, because of the substantial price differences between branded and generic products. Consequently, generic entrants in small-molecule drug markets are unlikely to be able to satisfy a potential treble damage award for infringing the branded manufacturer's patents.

This chapter explains that FOB entrants will not be similarly judgment proof. FOB entrants are not expected to offer the deep discounts seen in small-molecule drug competition. Rather, FOB entry is likely to resemble the market impact of entry by subsequent branded entrants. An FOB manufacturer is likely to introduce its FOB product at prices 10 to 30 percent lower than the pioneer manufacturer's price. Because

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<sup>194</sup> See *Patent Reform: The Future of American Innovation, Hearing Before S. Judiciary Comm.*, 110th Cong. (2007) (statement of Kathryn L. Bieberstein on behalf of the Biotechnology Organization) ("The biotechnology industry, fueled by the strength of the U.S. patent system, has provided jobs for over 200,000 people in the United States, and has generated hundreds of drug products, medical diagnostic tests, biotech crops, and environmental products."), available at [http://judiciary.senate.gov/hearings/testimony.cfm?id=2803&wit\\_id=6508](http://judiciary.senate.gov/hearings/testimony.cfm?id=2803&wit_id=6508) [hereinafter, "Bieberstein Statement"].

<sup>195</sup> F.M. Scherer & David Ross, *INDUSTRIAL MARKET STRUCTURE AND ECONOMIC PERFORMANCE*, 621 (3d ed. 1990).

<sup>196</sup> BIO Comment (9/30/08) at 22 ("Biotechnology patent disputes today can be adjudicated within a relatively stable doctrinal framework that is expected to solidify further as biotechnology matures both as a science as an industry.").

FOB entrants will earn greater profits, and will be able to satisfy potential damage awards, the market dynamics of FOB competition do not justify creation of a special regulatory system to protect pioneer manufacturers from judgment-proof defendants.

Although FOB market entry would be eased if an FOB manufacturer had complete certainty as to whether its product infringed the pioneer product's patents, a pre-FDA approval patent resolution process is unlikely to provide greater certainty than use of existing statutory patent resolution mechanisms.<sup>197</sup> A special pre-approval patent resolution process is not likely to succeed in raising and resolving all pertinent patent issues prior to FDA approval. Patents claiming the pioneer product may issue after a pre-approval process has begun and/or after FDA approval. In either situation, the FOB manufacturer will need to resolve these later-issued patents before commercial marketing. The FOB manufacturer's application and product also may change during the approval process such that by starting patent litigation prior to FDA approval would not ensure earlier resolution. Moreover, without a mechanism to enforce the rules of a pre-approval resolution process, there is no guarantee that litigation that is started prior to FDA approval will end earlier. Incorporating a pre-approval patent resolution process into a 12- to 14-year branded exclusivity period is unlikely to mitigate these problems.

Based on the experience under Hatch-Waxman, a pre-approval patent resolution process also is likely to lead to consumer harm, including the facilitation of anticompetitive conduct that defeats the purpose of starting the patent litigation early. In the Hatch-Waxman context, branded manufacturers have used the pre-approval patent regulations to delay generic entry. In addition, generic and branded competitors have entered into "pay-for-delay" patent settlements that delay entry, not encourage it. It is likely that a pre-approval patent resolution process in the FOB context could facilitate collusive agreements and/or provide the pioneer biologic drug manufacturer with competitively sensitive information about a significant potential competitor to which it otherwise would not have access.

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<sup>197</sup> To the extent that a pre-approval process is designed to address allegations of poor biotechnology patent quality, these issues may be better addressed in efforts to examine patent reform more broadly. Recent Congressional testimony addressed biotechnology issues in the context of patent reform. *See, e.g., Patent Reform in the 111th Congress: Legislation and Recent Court Decisions: Hearings Before the S. Judiciary Comm., 111th Cong.* (2009).



## II. THE LIKELY EFFECTS OF AN FOB PRE-APPROVAL PATENT RESOLUTION PROCESS

### A. Background on the Hatch-Waxman Pre-Approval Patent Resolution Process

Current law exempts the FOB manufacturer from patent infringement liability for work directed towards petitioning the FDA for product approval.<sup>198</sup> To be liable for infringement, an FOB manufacturer must take steps separate and apart from seeking FDA approval, in essence, it must import, make, use, sell, or offer to sell its product.<sup>199</sup> The FOB manufacturer, however, is unlikely to take these steps until it receives FDA approval. Consequently, to have patent litigation begin *before* FDA approval of the FOB, Congress must create an “artificial act of patent infringement” and a mechanism to resolve subsequent patent litigation (a “pre-approval patent resolution process”).

Hatch-Waxman established special procedures to incentivize generic small-molecule drug manufacturers to challenge invalid or narrow patents on branded products. These procedures allowed the patent resolution process to run concurrently with the FDA regulatory approval process. Of course, to the extent a generic applicant seeks entry on the day the last patent claiming the branded drug product expires, these procedures are not utilized.<sup>200</sup>

To effectuate the pre-approval patent resolution process, Hatch-Waxman requires branded manufacturers to list certain patents claiming the branded drug product in the FDA’s Orange Book. A generic applicant is then required to certify whether it seeks FDA approval prior to the expiration of any of the patents listed in the Orange Book that covers the referenced branded product. If it does, the generic company must provide notice to patent holders and the branded product manufacturer. The notice must include a detailed statement of the factual and legal basis supporting the applicant’s assertion that the listed patents are invalid or not infringed.

To incentivize early pre-approval litigation and resolution, if the branded manufacturer brings infringement litigation within 45 days from notice, the FDA cannot

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<sup>198</sup> 35 U.S.C.A. § 271(e)(1) (2009) (“It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.”).

<sup>199</sup> Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005).

<sup>200</sup> See Appendix B for a description of the patent resolution process in the Hatch-Waxman Act.

approve the generic application for 30 months.<sup>201</sup> If the branded manufacturer does not initiate litigation within 45 days, the FDA is free to approve the generic application in its normal course.

## **B. Commenters' and Panelists' Views on the Likely Effects of an FOB Pre-Approval Patent Resolution Process**

Panelists and commenters described the likely benefits of developing a pre-approval patent resolution process derived from the Hatch-Waxman Act. Panelists suggested patent infringement certainty would enhance their drug development activities.<sup>202</sup> They also suggested that a pre-approval patent resolution process is likely to preclude FOB at-risk launches, which occur when a company launches its product without knowing if all product-related patent issues are resolved.<sup>203</sup> Other panelists predicted that certainty is likely to attract venture capital resources,<sup>204</sup> and suggested that smaller companies may not be in a position to launch-at-risk because they are unlikely to attract investment funds without certainty.<sup>205</sup> Another panelist predicted that without a pre-approval resolution process, pioneer manufacturers would not be able to enforce injunctive relief against an FOB entrant and that this would lead to compulsory licensing of patents rather than removal of the product from market.<sup>206</sup>

Panelists and commenters described the likely effects of linking FDA approval to the outcome of patent litigation, as it is done under the Hatch-Waxman Act. Panelists representing pioneer manufacturers explained that if a court finds a pioneer product's patent to be valid and infringed, the FDA should not approve the infringing FOB product until the patent expires.<sup>207</sup> Another suggested that tying FDA approval to patent resolution

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<sup>201</sup> This "30-month stay" expires at the earliest of: (1) the date the patent(s) expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of the 30 months from receipt of notice of the paragraph IV certification.

<sup>202</sup> See, e.g., Amgen (9/30/08) Comment at 20 (certainty may increase FOB uptake if physicians are more likely to prescribe an FOB after the product has cleared patent hurdles); Essential Action Comment (12/20/08) at 7 ("should be to clear patent claims so that a) invalid patents do not delay investment in, or introduction of, generic or similar products; b) non-applicable patents do not delay investment in, or introduction of, generic or similar products; and c) all potential patent claims are resolved in advance of any applicable marketing exclusivities."); Manspeizer at 229; Leicher at 232; and Dow at 295-96.

<sup>203</sup> Hospira Comment (9/30/08) at 7 ("Due to the greater uncertainty surrounding the valid scope of patents and the lack of jurisprudence resulting from an immature biopharmaceutical industry as compared to a small molecule drug . . . this will operate as a significant disincentive to launch of a biogeneric and will thus operate as a disincentive to competition."); Seide at 238; and Siwik at 224-25.

<sup>204</sup> Amgen Comment (9/30/08) at 20; BIO Comment (9/30/08) at 20.

<sup>205</sup> Leicher at 232.

<sup>206</sup> Sauer at 227.

<sup>207</sup> *Id.* at 271.

would “keep follow-on biologics that infringe a patent off the market by preventing final FDA approval until patent expiry.”<sup>208</sup>

One panelist and commenter representing a potential FOB entrant suggested that linkage is unnecessary because existing patent law provides for robust protection of patent rights against infringement and is sufficient to deter inappropriate entry.<sup>209</sup> This panelist explained that launching-at-risk currently is the norm in the biotech industry.<sup>210</sup> He also explained that the generic small-molecule industry is the only industry that has an artificial act of infringement, and “that was a result of the state of the industry in 1984, and we don’t believe [it] is required with the state of the industry in 2008.”<sup>211</sup>

Another panelist noted that linkage may be unworkable because biologic patent portfolios often include patents that have been licensed to third parties. Infringing one of these patents may not lead to a permanent injunction, and thus should not preclude FDA approval.<sup>212</sup> Another panelist added that the patent holder may obtain an injunction notwithstanding the fact that they have licensed the patent to other parties.<sup>213</sup>

Participants also described the likely unintended consequences of a pre-approval patent resolution process, which include: delay of FOB entry, distortions to the parties’ incentives during the process, and increased costs.<sup>214</sup> For example, one panelist suggested that the process can cause unintended delay, noting that for small-molecule drugs, Hatch-Waxman has led to “serial litigation.”<sup>215</sup> Another panelist focused on the likelihood of wasteful litigation.<sup>216</sup>

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<sup>208</sup> Wyeth Comment (9/30/08) at 9; *see also* Wyeth Comment (12/18/08) at 13 (“In order to provide certainty to all parties concerning the outcome of any patent resolution mechanism, a linkage system is required.”).

<sup>209</sup> Novartis Comment (9/29/08) at 19; and Goldman at 231 (“Decoupling will avoid premature challenges to biotech patent estates ahead of the prospect of imminent commercialization, and current law provides robust protection for those rights when infringement occurs.”).

<sup>210</sup> Goldman at 230 (“There’s not a single product that hasn’t come on the market in which launching at risk hasn’t been a key issue. And companies are – all of us here have the ability to take that business risk into consideration and decide whether or not to launch at risk.”); *see also id.* (“[T]he need for an early resolution, early litigation because of the fear of launching at risk is not a serious one we contend.”); and Novartis Comment (9/29/08) at 19.

<sup>211</sup> Goldman at 230-31 (explaining that “[t]here’s no artificial act of infringement in the European scheme as well, so it’s a real aberration.”).

<sup>212</sup> Siwik at 273-74.

<sup>213</sup> Kushan at 276-77.

<sup>214</sup> Siwik at 224-25 (“[I]t’s important to have a mechanism in the bill for resolving certain patent disputes concurrent with FDA review, but the big but is, if the system doesn’t work, if whatever this patent mechanism is doesn’t work, I guess work in the sense that it can delay market launch.”).

<sup>215</sup> Goldman at 231 (“You litigate one patent followed by another patent, and that can really extend the litigation pre-approval.”).

Panelists also described how a pre-approval resolution process will distort parties' incentives. One panelist explained that the process will "create bounties on valid patents" by producing an incentive for an FOB to challenge patents before it has shown it can develop an approvable drug.<sup>217</sup> By starting the process early, that is prior to FDA approval, parties are encouraged to bring multiple litigations, where, if they brought litigation at the end of the process, there may be greater incentive to raise only the strongest patents.<sup>218</sup> Commenters also explained how if litigation begins too early, the FOB application and product also may change during the approval process such that an early start to litigation prior to FDA approval would not ensure an earlier resolution. Rather, an early start to litigation would lead to additional litigation upon finalization of the application and the FOB product.<sup>219</sup> Panelists also described how unnecessarily-early litigation processes will increase pioneer and FOB costs, explaining that a pre-approval patent resolution process likely will "bring[] on expensive litigation costs earlier when you might not want to do that."<sup>220</sup>

### **C. Analysis of the Likely Effects of a Pre-Approval Patent Resolution Process**

#### **1. The Likely Market Impact of FOB Drug Entry Does Not Warrant a Special Pre-Approval Patent Resolution Process**

The justification for special procedures akin to those in Hatch-Waxman for small-molecule drugs depends upon the context in which FOB competition is likely to proceed. As discussed in Chapter 1, FOB competitors are likely to seek approval of biosimilar

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<sup>216</sup> Kepplinger at 267 ("[I]t seems like one of the lessons from Hatch-Waxman, and many people have talked about it, is that there's quite a lot of litigation, and it seems like in designing the situation, we should be looking to try to reduce the litigation because it is just a lot of money that could probably be better spent on other things, like designing more pharmaceuticals.").

<sup>217</sup> Goldman at 242-43; Novartis Comment (9/29/08) at 18-19.

<sup>218</sup> Goldman at 231 ("[A]nd besides that, we also see in those cases that there's serial litigation. You litigate one patent followed by another patent, and that can really extend the litigation pre-approval. Post approval, there's no incentive for serial litigation. You would want to bring your best patents quickly to get the product off the market.").

<sup>219</sup> BIO Comment (9/30/08) at 21 ("Patent litigation would be premature if it were allowed to commence before a determination that the FOB application in question is complete and in condition for review without additional clinical studies."); *see also* Wyeth Comment (12/18/2008) at 13 ("[a] patent resolution proceeding should not be initiated at a point in time that is too early, when the details of the biosimilar product are not yet fully defined or manufacturing processes still are subject to change.").

<sup>220</sup> Goldman at 240-41 ("[I]t surprises me that . . . the companies that are worried about not having enough money are the ones that are advocating jumping into expensive litigation 30 months early. I would think that you would want to avoid that, the litigation . . . [Y]ou may in fact be bringing on expensive litigation costs earlier when you might not want to do that."); *see also* Siwik at 225.

products. The competitive dynamics of biosimilar entry are likely to resemble entry by a branded drug product, in which FOB competitors introduce their products at discounts between 10 and 30 percent of the pioneer products' price. This effect contrasts with the 80 percent discounts that occur with entry of multiple small-molecule generic products.<sup>221</sup> The competition prompted by biosimilar entry is unlikely to move more than 10 to 30 percent market share away from the pioneer manufacturer. This market share movement is substantially less than the market share gain that small-molecule generic drugs obtain due to state substitution of generic drugs. Because of smaller discounts and smaller market share, the FOB entrant is unlikely to be judgment-proof and thus able to pay any possible damages resulting from infringing a pioneer product's patents.

Because FOB entrants are likely to mimic the market effects of another branded product, the FOB and pioneer manufacturer can avail themselves of the existing patent litigation procedures that apply to every industry, except generic small-molecule drugs. Biologic drug manufacturers have successfully used this process to resolve patent litigation for decades.<sup>222</sup> It is the same process all patent holders use to resolve claims of infringement or validity – the patent holder initiates infringement litigation after the FDA has approved the potentially infringing drug product, or the alleged infringer seeks a declaratory judgment of non-infringement or invalidity. For example, the Supreme Court has addressed biotechnology patent disputes in *Merck KGaA v. Integra Lifesciences I, Ltd.* and *MedImmune Inc. v. Genentech, Inc.*<sup>223</sup> Lower courts also have addressed patent infringement litigation against competing products that had obtained FDA approval but had not yet been marketed.<sup>224</sup>

In other words, the patent holder can use existing court remedies to enforce its patent rights against an FOB, without developing special procedures that condition FDA approval on the outcome of patent litigation. Although the lack of a pre-approval patent resolution process increases the potential for at-risk launches by an FOB, a profit-maximizing FOB manufacturer is unlikely to enter the market “at-risk” if it believes it will

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<sup>221</sup> See, e.g., David Reiffen and M.R. Ward, “Branded Generics” As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 *MANAGERIAL AND DECISION ECONOMICS* 251, 264 (2005), available at [http://ftc.gov/be/healthcare/wp/12\\_Reiffen\\_BrandedGenericsAsAStrategy.pdf](http://ftc.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf)

<sup>222</sup> BIO Comment (9/30/08) at 22.

<sup>223</sup> *MedImmune Inc. v. Genentech, Inc.* 549 U.S. 118, 137 (2007) (holding that a licensee has standing to bring a declaratory judgment action for non-infringement); *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 206-08 (2005) (clarifying 35 U.S.C.A. 271(e)(1)).

<sup>224</sup> See, e.g., *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1219 (Fed. Cir. 1991) (affirming trial court's finding that certain claims covering purified and isolated DNA sequences encoding EPO and host cells transformed or transfected with a DNA sequence were valid and infringed and reversing finding that other claims were enabled); *Amgen, Inc. v. Hoffmann-LaRoche Ltd.*, 2008 U.S. Dist. LEXIS 77343 (D. Mass. 2008) (granting permanent injunction for infringement of claims directed to a specific amino acid sequence); see also, *Amgen Inc. v. Hoechst Marion Roussel*, 579 F. Supp. 2d 199, 210 (D. Mass. 2008); *Bayer HealthCare LLC v. Abbott Labs.*, Civ. Action No. 6:08cv507 (E.D. Tex. Dec. 24, 2008). *Abbott countersued in Massachusetts: Abbott Labs. v. Bayer Healthcare LLC*, 09cv40002, U.S. District Court for the District of Massachusetts, 09cv40002 (D. Mass. June 5, 2009).

be liable for substantial infringement damages, cause physician and patient confusion, or harm its reputation as a reliable FOB drug manufacturer.

## **2. A Pre-Approval Patent Resolution Process is Unlikely to Provide Certainty and is Likely to Disrupt Innovation Incentives**

A pre-approval patent resolution process is unlikely to achieve the certainty goals desired by pioneer and FOB manufacturers for three reasons. First, pioneer manufacturers with vulnerable patents have no incentive to have their patents invalidated or held not infringed by the FOB drug, especially if such a determination were to come several years before patent expiration or before FOB entry was imminent. In other situations, a pioneer manufacturer or third party may license its patents to other market participants where the license creates a revenue stream for the patent holder. If these patents are deemed invalid, the patent holder loses this revenue stream.

Experience under Hatch-Waxman shows that profit-maximizing manufacturers are likely to use a pre-approval regulatory process to delay a final court decision.<sup>225</sup> In other instances, pioneer manufacturers may seek to bring suit in a judicial district with a history or reputation of slow-moving proceedings or they may fail to participate in the process, thus requiring the generic firm to bring a declaratory judgment action.<sup>226</sup> Pioneer manufacturers also may attempt to hold back relevant patents during this pre-approval process if the regulations are subject to interpretation or the penalty for violating the rules provides an insufficient deterrent. These tactics can succeed because the FOB product has not been approved and the FOB manufacturer is unable to threaten market entry to further the process along.

By contrast, if litigation were to begin post-approval, the way in which branded biologic competitors resolve patent issues currently, a patent holder is likely to assert its strongest patents to keep the FOB product off the market. This process naturally focuses

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<sup>225</sup> Prior to 2003, if a branded manufacturer listed an additional patent in the Orange Book *after* the generic applicant filed its ANDA, more than one 30-month stay could be generated. The generic applicant was required to re-certify to this later-listed patent, and if, upon notice of the generic's re-certification, the brand-name company sued within 45 days, then FDA approval of the generic's previously filed ANDA was stayed for *an additional* 30-months from the notice date or until a court decision in the newly instituted patent litigation. FTC GENERIC DRUG STUDY at iii. In 2003, Congress amended the Hatch-Waxman Act to address this problem, "allowing lower-priced generic products to enter the market more quickly." Joint Explanatory Text to the MMA Conference Agreement, H.R. Conf. Rep. No. 108-391, at 836 (2003), *reprinted in* 2004 U.S.C.C.A.N. 2187. Now, a generic applicant who amends a pending ANDA to include Paragraph IV certifications to later-listed patents is not subject to a 30-month stay on the amended certification. 21 C.F.R. § 314.94(a)(12)(vi). This conduct is not unexpected. *See* Robert H. Bork, THE ANTITRUST PARADOX 347 (1978) ("The modern profusion of [ . . . ] governmental authorities offers almost limitless possibilities for abuse.").

<sup>226</sup> *See, e.g.,* Teva Pharm., USA, Inc. v. FDA, 182 F.3d 1003 (D. C. Cir 1999), *see also* Siwik at 289 ("[I]n Hatch-Waxman we learned that there are rules, but if there are no sticks, the rules are going to go out the window.").

litigation on the strongest patents, and reduces unnecessary pre-approval litigation regarding patents that may not be asserted after FDA approval.<sup>227</sup>

Moreover, without special pre-approval processes, there would be no need to change the declaratory judgment standards or rules. Even if the pioneer manufacturer did not initiate patent infringement litigation, the newly-approved FOB entrant would have standing to seek a declaration that the pioneer manufacturer's patents are invalid or not infringed.

Second, a start to litigation prior to FDA approval does not guarantee that patent issues will be resolved earlier than if litigation begins after FDA approval. Patents claiming the pioneer product may issue after a pre-approval process has begun, but before FOB approval. Patents also may issue after FOB approval. In either situation, the pioneer manufacturer, or third party, will need to bring additional litigation to enforce these later-issued patents, removing the certainty sought by the parties. The FOB's application and product also may change during the approval process, such that early patent litigation would no longer apply to the approved product. The litigation would be about a "moving target." Moreover, without an enforcement provision, even with a pre-approval process there is no guarantee that litigation will begin pre-approval. Until the FOB product is approved, patent infringement litigation may be premature.

Third, patent litigation under Hatch-Waxman shows that a pre-approval process is likely to invite numerous patent challenges. In the Hatch-Waxman context, nearly every branded drug faces a pre-approval patent challenge.<sup>228</sup> Similarly, in the FOB context, a pre-approval patent resolution process may incentivize FOB manufacturers to challenge all of a pioneer product's patents in hope of exposing and exploiting weaknesses in the patent portfolio. In contrast, the absence of a pre-approval patent resolution process is likely to incentivize FOB manufacturers to direct their product development resources to those areas in which the pioneer product's patents are likely to be invalid or not infringed.

### **3. A Pre-Approval Process is Unlikely to be Workable and is Likely to Cause Harm**

At a minimum, a pre-approval process must include two components: (1) notification requirements, including when notification begins; and (2) identification of patents to be litigated in the pre-approval period, which could include only "necessary" patents. The following sections describe how these procedures are unnecessary, could lead to anticompetitive outcomes, and defeat the purpose of a pre-approval process to obtain early resolution of potential patent infringement issues.

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<sup>227</sup> To the extent that the branded company brings suit in a slow-moving venue, the FOB has a variety of tools to force expeditious resolution of its case.

<sup>228</sup> Norman at 201.

In addition, strong enforcement of the governing regulations for the pre-approval process will be necessary to deter abuse by the participants that seek to use the process to obtain competitive advantages. It is likely that a self-policing process will not work and that FDA will be asked to referee the process, much like it has been forced to do with the Hatch-Waxman process.

**a. Notice Provisions are Unnecessary and Could Raise Anticompetitive Concerns**

To be effective, a pre-approval patent resolution process will need to incorporate two major types of notice: (1) the pioneer manufacturer will need to provide notice to potential FOB manufacturers of patent claims covering its pioneer products; and (2) the FOB manufacturer will need to provide notice to the pioneer manufacturer of its FDA application.<sup>229</sup>

**(1). Patents Claiming the Pioneer Drug Product are Publicly Available**

Although the first type of notice is likely to help the FOB identify which patent claims its product may infringe, it is unnecessary given that granted patents and post-2000 patent applications are published by the PTO.<sup>230</sup> FOB manufacturers can use existing databases to perform a patent search, as companies in many industries do, to determine patent claims that its product may infringe.<sup>231</sup> This search would apply to patents owned by the pioneer manufacturer and any applicable third parties.

In addition, the Patent Act currently requires patent holders to provide notice of potentially infringed patents. A patentee cannot recover damages for infringement until it (1) marks the product; or (2) provides the alleged infringer with actual notice of the infringement.<sup>232</sup> If the product, or its packaging, is not physically marked with applicable patent numbers, then the patentee can give notice either by sending a warning letter to the

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<sup>229</sup> Wyeth Comment (12/18/2008). Some panelists explained that there should be “[f]ull disclosure by all participants early in the patent resolution mechanism,” calling for patent holders to provide “full disclosure of the patents at issue in any dispute” while FOBs would provide “full disclosure of their application for regulatory approval, including all manufacturing process details.” *Id.*

<sup>230</sup> Patent applications filed on or after November 29, 2000 are published eighteen months after the effective filing date of the application. One commenter noted the existence of “submarine” patent applications, a subset of patent applications filed before November 29, 2000 that are not published until the patent is granted. Applications with an effective filing date on or after June 8, 1995 expire 20 years from filing. Applications with an effective filing date before June 8, 1995 expire 17 years from patent grant. *See Hospira Comment (9/22/08)* at 4-5. While this can present issues of extended patent terms for old technology, this problem applies across the industry and likely does not outweigh the likely anticompetitive effects of a notice provision.

<sup>231</sup> *See* <http://www.uspto.gov/main/patents.htm>.

<sup>232</sup> 35 U.S.C.A. § 287(a) (2009).



alleged infringer, or by bringing a suit for infringement.<sup>233</sup> The notice must identify the patent(s) and specifically allege infringement.<sup>234</sup> For process patents only, an additional “request for disclosure” applies. Before it sells its product, a competitor or potential competitor may request a patent holder to produce all process patents that the patent holder believes could be infringed by the competitor’s product.<sup>235</sup> These notice procedures would apply to follow-on biologic drugs even if there were no pre-approval patent resolution process.

A patent listing system also is likely to lead to anticompetitive unintended consequences. For example, Hatch-Waxman’s notice provision led to the delay of generic entry until the notice provisions were amended by the Act’s 2003 Amendments. As discussed above, a branded manufacturer must list certain patents in the FDA’s Orange Book.<sup>236</sup> The generic then files a certification regarding each patent. If the branded manufacturer then brings an infringement action within 45 days, FDA approval of the ANDA automatically is stayed for 30 months.<sup>237</sup>

Over time, branded manufacturers began successively to list later-issued patents in the Orange Book. A number of these later-listed patents did not meet the FDA’s requirements for listing patents in the Orange Book and were subsequently found to be invalid or not infringed.<sup>238</sup> This strategy allowed the branded manufacturer to obtain additional 30-month stays delaying FDA approval of generic drugs. Congress remedied this problem in the Medicare Modernization Act by limiting branded drug companies to a single 30-month stay, but only after consumers lost substantial competition from generic drugs during the periods of these “stacked” 30-month stays.

## **(2). Notice of the FOB’s Application Raises Competitive Concerns**

The FOB manufacturer’s notice to the pioneer manufacturer of its FDA application and additional manufacturing information raises two concerns – one administrative and one anticompetitive. First, there is a difficulty in determining to whom the notice should be provided. Biologic drug patents implicate more than the pioneer manufacturer; they also

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<sup>233</sup> *American Medical Sys., Inc. v. Medical Eng’g Corp.*, 6 F.3d 1523, 1538 (Fed. Cir. 1993).

<sup>234</sup> *Amstead Indus., Inc. v. Buckeye Steel Castings Co.*, 24 F.3d 178, 185-87 (Fed. Cir. 1994) (finding lack of notice where the letter did not specifically charge the recipient with infringement and did not identify an infringing device).

<sup>235</sup> 35 U.S.C.A. § 287(b)(4) (2009).

<sup>236</sup> See 21 U.S.C.A. § 355(b)(1) (2009) and Appendix B for a detailed description of the Hatch-Waxman abbreviated drug approval process.

<sup>237</sup> 21 U.S.C.A. § 355(j)(2)(A)(vii)(IV) and § 355(j)(5)(B)(iii) (2009).

<sup>238</sup> Fed. Trade Comm’n, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 18* (July 2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

implicate universities and third parties. If notice is provided only to the pioneer manufacturer, an early start to patent resolution may not involve all of the relevant parties and patents, thus defeating the purpose of the pre-approval process. Conversely, if notice is provided to all parties, it may overly complicate the process and deter early resolution. Indeed, one panelist suggested “[t]he whole issue of notice should be as simple as possible, but some of the issues are more complex than we see even in the more complex drug situations.”<sup>239</sup> This complexity is likely to reduce the effectiveness of a notice requirement and raise questions over whether sufficient notice had been provided in a timely manner.

In addition, requiring the FOB manufacturer to provide a detailed description of the product and manufacturing processes to the pioneer manufacturer and other third parties could facilitate anticompetitive conduct.<sup>240</sup> As discussed in Chapter 1, the FOB manufacturer is likely to compete against the pioneer product with a similar, but not identical, product. The FOB product could be an improvement over the pioneer product in terms of reduced dosing, increased effectiveness, or fewer side effects. In other cases, the FOB product manufacturer may have discovered a way to manufacture an FOB product more efficiently than the pioneer manufacturer. In either scenario, the firms are likely to be significant rivals and engage in head-to-head competition.

Forced sharing of information between rivals about the timing and content of the FOB’s application and manufacturing processes (and other related matters) could facilitate collusion.<sup>241</sup> For example, this information could facilitate agreements to delay entry, allocate markets, or fix prices. Experience under Hatch-Waxman has shown that generic and branded competitors have entered into “pay-for-delay” patent settlements that delay entry. In other situations, the anticompetitive harm could stem from providing the pioneer manufacturer with competitively sensitive information that it otherwise would not be able to obtain. The pioneer manufacturer may then have an opportunity to act on this information prior to the approval of the FOB and thus, can pre-empt the innovation and price competition that is likely to occur with FOB entry. This harm is lessened, although not eliminated, with patent litigation after FDA approval because the FOB can enter quickly and blunt any harm that could be caused by a sharing of competitively significant information.

Moreover, sharing this type of information may be unnecessary to the extent that the FOB manufacturer claims that the pioneer manufacturer’s patents are invalid. In these

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<sup>239</sup> Seide at 266.

<sup>240</sup> Kushan at 257-58 (“[T]he notice should include a detailed description of the FOB’s product, including the amino acid sequence produced, the nucleic acid sequence, expression technologies, process technologies, manufacturing process information, molecular structure, formulation, patent certifications, molecular identity and intended uses.”).

<sup>241</sup> Fed. Trade Comm’n and U.S. Dep’t of Justice, ANTITRUST GUIDELINES FOR COLLABORATIONS AMONG COMPETITORS 12 (2000).

situations, the pioneer manufacturer has no need for detailed information relating to the FOB's method of manufacturing.<sup>242</sup>

Confidentiality provisions that limit access to information about the FOB product to persons involved in the pre-approval patent litigation process are likely to be ineffective to safeguard against these potential anticompetitive harms. Biotechnology patent litigation is a complex endeavor that requires not only patent attorneys, but medical, scientific, manufacturing, and business personnel with intimate knowledge about the pioneer product's patent claims. There is no way to cordon off a patent infringement analysis regarding the FOB drug product from the personnel that know the most about the pioneer product.<sup>243</sup>

**b. Identification of a Subset of Patents to Resolve During the Pre-Approval Patent Resolution Process Defeats the Purpose of a Pre-Approval Resolution Process**

A pre-approval patent resolution process will need to account for the broad range of patents claiming a pioneer product and their multiple owners. As described in Chapter 2, the types of patents that are likely to claim the biologic product include compound or molecule patents, method of treatment, formulation and dosage form patents, and manufacturing process and technology platform patents. Due to the nature of biologic drugs, these portfolios may include patents owned by the pioneer manufacturer,<sup>244</sup> as well as third-party owned patents that are licensed either exclusively or non-exclusively to the pioneer manufacturer.

Panelists representing pioneer manufacturers proposed that a pre-approval patent resolution process resolve all of the patents claiming a pioneer product.<sup>245</sup> Another panelist noted that the process should include third-party patents, reasoning that if the patent resolution process does not cover third-party patents, then the generic will be susceptible to launch-at-risk on those patents.<sup>246</sup>

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<sup>242</sup> Patent law places the burden of proof of demonstrating infringement on the patent holder. The patent holder may not need the FOB's application to establish infringement if the FOB's product already is approved. In addition, a notice provision is likely to have the effect of shifting the burden of proof such that the FOB has to demonstrate that it does not infringe the patent, rather than under patent law having the patent holder show that its patent has been infringed.

<sup>243</sup> Of course, these arguments apply with equal force in the opposite scenario if the FOB manufacturer were to obtain confidential information regarding the branded product.

<sup>244</sup> The pioneer manufacturer-owned patents may be out-licensed further to additional third parties.

<sup>245</sup> Kushan at 237.

<sup>246</sup> Seide at 238 ("The technology platform patents are very important . . . and so there has to be some way of resolving third-party patents as well if they're known.").

As a counterpoint, panelists said that litigating all patents potentially infringed by the FOB product could lead to delay. If the process is not tailored, litigation costs could outweigh benefits for some FOB companies.<sup>247</sup> Commenters representing FOB manufacturers explained that the process should be limited to “necessary” patents (*i.e.*, patents that would most likely prevent the FOB from entering the market). One commenter explained that “it is in the generic’s interest to immediately litigate only those patents that would prevent the generic company from launching until questions of validity, enforceability, or infringement are resolved. Litigation on all remaining patents would take place after the generic product actually enters the market.”<sup>248</sup>

It is unclear how a regulatory process could determine which patents are “necessary.” Resolving infringement issues for a subset of “necessary” patents may streamline that particular litigation, but it is likely to lead to future uncertainty. A patent not deemed “necessary” does not mean that the patent is invalid and/or not infringed by the FOB manufacturer. The patent holder can still assert these “unnecessary” patents following FDA approval of the FOB. Retaining these later “unnecessary” patents is unlikely to create the certainty that a pre-approval patent resolution process is intended to create. As noted above, additional patents that block FOB entry may issue after the pre-approval process has started, thus complicating identification of “necessary” patents and frustrating the overall objective of the pre-approval process to obtain certainty regarding patent infringement issues.

Furthermore, a two-tier resolution system whereby some patents are “necessary” and litigated pre-approval, while others must wait until after FDA approval, will likely create additional litigation regarding the determination of “necessary” versus “unnecessary” patents. Such litigation will create additional costs detrimental to consumer welfare. Moreover, as discussed above, Hatch-Waxman created the incentive for the branded manufacturer to “stack” patent notification to obtain multiple 30-month stays. Here, too, limiting the process to a subset of patents may create incentives for the brand to withhold certain “necessary” patents to retain their rights after FDA approval of the FOB product.

### **c. Enforcement Provisions May Harm Innovation and Competition**

An enforcement provision is likely to be necessary to ensure that the notice and patent identification requirements are adhered to during the pre-approval resolution process. Without such an enforcement mechanism, the pre-approval process is unlikely to be adhered to, and likely to cause unintended consequences that delay FOB entry.

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<sup>247</sup> Siwik at 226.

<sup>248</sup> Barr Comment (9/30/2008) at 10; CCPM Comment (9/30/2008) at 8; GPHA Comment (9/30/08) at 6; Teva Comment (9/30/08) at 6; Leicher at 260 (“If you limit it to the key patents that are built around the product that the brand company controls, I think you’ve got it simplified.”).

Several panelists and commenters suggested that a “sue-or-lose” provision in which a pioneer manufacturer, or third party, could lose its patent enforcement rights if it did not participate in the patent resolution process, is necessary to ensure the integrity of the pre-approval patent resolution process.<sup>249</sup> One panelist said that without a penalty provision, the rules likely will not be enforced, noting that if the pioneer manufacturer holds back patents until the end of the exclusivity period, or launch, then any likely effect of early resolution will not be achieved.<sup>250</sup>

Panelists representing pioneer manufacturers opposed a sue-or-lose provision or a provision in which damages are limited for lack of participation in the process.<sup>251</sup> One commenter said that it likely would lead to gaming, “the patent owner would be forced to decide whether to sue based on the information it obtained from the FOB applicant. That applicant, in turn, would have an incentive to convince the patent owner not to bring a suit.”<sup>252</sup> Another panelist explained that a sue-or-lose provision would take away a valuable property right from the patent holder for failure to comply with a regulatory obligation.<sup>253</sup>

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<sup>249</sup> Schultz at 290; Essential Action Comment (12/20/2008) at 6 (“[I]nitial registrants should be required at the time of the application to indicate any granted or filed patents that they believe apply to the biologic for which they seek marketing approval. This should include both patents granted to the registrant or which have been licensed to them. They should be required to update this list for any new patent filings, within a statutorily defined period, perhaps 30 days. Failure to disclose should forfeit the right to enforce.”).

<sup>250</sup> Siwik at 289 (“If the overall scheme is fair and balanced, maybe we don’t need to worry about huge sticks to make people participate, but in Hatch-Waxman we learned that there are rules, but if there are no sticks, the rules are going to go out the window. There were statutory definitions of what patents could go in the Orange Book, and there were a few companies that abused that, and a list of other patents triggered a lot of 30 month stays, and a lot of litigation delays, but no penalties for doing it.”).

<sup>251</sup> Goldman at 287; Kushan at 293 (current laws exists to manage parties who timely fail to enforce their patent rights); PhRMA Comment (12/22/08) at 5.

<sup>252</sup> PhRMA Comment (12/22/08) at 5 (The proposal also “could create artificial incentives to litigate, which would waste time and money and impose burdens that would not be beneficial for the patent or the judicial system.”).

<sup>253</sup> Seide at 288.

Based on experience with the patent resolution process in Hatch-Waxman, examples of the need for enforcement could include:

- If the patent holder's notice fails to include all of the patents or all of the "necessary" patents claiming the pioneer product;
- If the patent holder fails to update the notice to include patents issued after the patent litigation has begun;
- If the FOB applicant fails to provide a sufficiently detailed description of the FOB product, its method of manufacture, or the materials included in the manufacturing; or
- If either the pioneer manufacturer or FOB applicant fails to provide information in a timely manner.

Experience under Hatch-Waxman also demonstrates that the FDA will be pulled into these disputes and asked to resolve substantive patent issues to enforce the rules in any patent resolution process.<sup>254</sup> Under Hatch-Waxman, the FDA has been asked to determine whether patents are correctly listed in the Orange Book. The FDA has consistently maintained that it does not have the patent expertise to do so.<sup>255</sup> Its resources are likely to be best deployed in examining the safety and effectiveness of FOBs, not in policing a patent resolution process for which it has little experience and expertise.

If the FDA were not involved, an enforcement provision could be designed so that if a party did not sue under the patent resolution process in a timely manner, it would lose its rights to later enforce the patent under provision of the Patent Act. This provision is beneficial because in order for the process to have integrity, there must be a mechanism to compel parties to participate. On the other hand, it is likely to be an unduly harsh remedy in the face of uncertainty as to a determination of "necessary" patents to include in a notice or the extent of detail in the FOB applicant's notice describing its product and its method of manufacturing. Such a remedy may also unnecessarily affect the patent holder's right to

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<sup>254</sup> See, e.g., *Sandoz, Inc. v. F.D.A.*, 439 F. Supp. 2d 26 (D.C. Cir. 2006) (denying generic competitor's motion for injunctive relief against FDA re-listing brand patents); *Purepac Pharm. Co. v. TorPharm, Inc.*, 354 F.3d 877, 886-88 (D.C. Cir. 2004) (upholding FDA decision to delist a patent incorrectly listed for the wrong drug). *Dr. Reddy's Labs., Inc. v. Thompson*, 302 F. Supp. 2d 340, 355 (D.N.J. 2003) (upholding FDA delisting of an expired patent and not to award exclusivity to an ANDA applicant who filed a paragraph IV certification before the patent's expiration);

<sup>255</sup> See, e.g., *American Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001) (recognizing that the FDA "has refused to become involved in patent listing disputes, accepting at face value the accuracy of NDA holders' patent declarations and following their listing instructions"); *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191, 196 (D. D.C. 2002) ("The duty to ensure that the Orange Book only lists patents that actually claim approved drugs . . . lies with NDA holders.") (citing *Watson Pharm., Inc. v. Henney*, 194 F. Supp. 2d 442, 445-46 (D. Md. 2001) ("In making its decision to list a patent . . . it is entirely appropriate and reasonable for the FDA to rely on the patentee's declaration as to coverage, and to let the patent infringement issues play out in other, proper arenas, as is the clear intent of the Hatch-Waxman Amendments.")).

assert the patent in unrelated contexts. Resolving these uncertainties (and others) is likely to delay resolution of patent issues and, thus, defeat the purpose of a pre-approval patent resolution process.<sup>256</sup>

In sum, although there may be legitimate issues about invalid or not infringed patents blocking FOB drug entry, these issues are best handled post-FDA approval when the parties' incentives are not distorted by a pre-approval process. In other words, post-FDA approval, the FOB manufacturer will seek to begin commercial marketing and the pioneer manufacturer will seek to obtain a preliminary injunction to block FOB drug entry.

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<sup>256</sup> For example, if the rules required a pioneer manufacturer to provide a list of patents within 30 days, but one patent is left off and corrected on day 31, does this omission limit enforceability against that FOB manufacturer? There are countless ways in which parties may inadvertently violate the rules for which a "sue-or-lose" provision would extinguish their patent rights.

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## CHAPTER 4      LIKELY COMPETITIVE EFFECTS OF A MARKET EXCLUSIVITY PERIOD FOR FOLLOW-ON BIOLOGICS

The Hatch-Waxman Act provides a 180-day marketing exclusivity period to the first generic drug applicant that seeks FDA approval prior to the expiration of patents relating to the branded drug product.<sup>257</sup> No other generic manufacturer may obtain FDA approval to market its product until the first generic has sold its product for 180 days or has forfeited the exclusivity period.

The 180-day exclusivity period incentivizes generic manufacturers to challenge the patents claiming a branded drug product. One court has explained that the 180-day exclusivity rewards the first generic applicant for the expense and effort involved with patent challenges.<sup>258</sup> A court finding of patent invalidity benefits not only the challenger, but also subsequent generic applicants whose entry is no longer blocked by the patent. Thus, the 180-day marketing exclusivity period prevents immediate free-riding by subsequent generic applicants on a favorable outcome that results from the first applicant's patent challenge. As subsequent generic firms enter, generic prices can drop to 80 percent off the branded price, depending upon the number of entrants.<sup>259</sup> The exclusivity period permits the first generic entrant to recoup its patent litigation costs before the substantial price drop caused by multiple generic entrants.

This chapter summarizes the commenters and panelists views on the need for, and the likely effects of, providing FOB manufacturers with incentives to develop their products by restricting entry of competing products during an FOB exclusivity period. It then explains that an exclusivity period is unnecessary to encourage the development and marketing of biosimilar products. Biosimilar products are likely to earn substantial profits without regulatory exclusivity periods. Moreover, European and U.S. experience with biosimilars shows that sufficient profit incentives already exist to encourage biosimilar entry.

An exclusivity period is likely to be unnecessary to encourage the development of interchangeable biosimilar drug products because potential market opportunities appear robust. The competitive dynamics that justified the 180-day exclusivity period for small-molecule generic drugs are unlikely to be present with the entry of interchangeable biosimilar drugs.

It also is unclear that an exclusivity period will successfully incentivize a manufacturer of a biosimilar product to develop an interchangeable FOB product. Biosimilar manufacturers are likely to make this additional investment based on a

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<sup>257</sup> 21 U.S.C.A. § 355 (j)(5)(B)(iv)(I) (2009).

<sup>258</sup> *Mova v. Shalala*, 140 F.3d 1060, 1074 (D.C. Cir. 1998).

<sup>259</sup> See David Reiffen & Michael Ward, "Branded Generics" As A Strategy To Limit Cannibalization of Pharmaceutical Markets, 28 *MANAGERIAL AND DECISION ECONOMICS*, 251, 264 (2005), available at [http://ftc.gov/be/healthcare/wp/12\\_Reiffen\\_BrandedGenericsAsAStrategy.pdf](http://ftc.gov/be/healthcare/wp/12_Reiffen_BrandedGenericsAsAStrategy.pdf).

consideration of, among other things: the cost, expected prices, capacity constraints, and the extent and effect of state substitution laws. This situation contrasts significantly with small-molecule generic competition seen under Hatch-Waxman in which generic manufacturers enter initially with an interchangeable product. Unlike FOB manufacturers, generic manufacturers do not market a “similar” product first and replace it with an “interchangeable” product later.

Not only do market dynamics counsel against an FOB exclusivity period, but the anticompetitive delay in entry evidenced in small-molecule generic drug markets is likely to be repeated if an exclusivity provision for interchangeable FOBs is implemented.<sup>260</sup> The current 180-day exclusivity period exacerbates the problem of “pay-for-delay” settlements that prevent generic entry.<sup>261</sup>

Awarding an FOB exclusivity period on a “first-to-approve” rather than a “first-to-file” basis does not lessen the potential harm. These anticompetitive consequences are likely to result if the period can be extended, the period does not run immediately upon its award, or if a firm has the ability to delay triggering the running of the period through, for example, a patent settlement, acquisition, merger, or agreement.<sup>262</sup>

## **I. NECESSITY OF AN EXCLUSIVITY PERIOD TO ENCOURAGE DEVELOPMENT OF FOLLOW-ON BIOLOGIC DRUGS**

The question arises whether an FOB manufacturer needs an incentive beyond market-based pricing to develop an interchangeable FOB drug, such as a limit on when subsequent interchangeable FOB drug entry can occur (an “FOB exclusivity period”). This limitation would allow the first interchangeable FOB manufacturer to recoup its development expenses.<sup>263</sup> One commenter indicated that “most companies contemplating biogenerics will be reluctant to invest the significant resources required to

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<sup>260</sup> See FDA/Center for Drug Evaluation and Research, *180-Day Generic Drug Exclusivity* (2001), available at [http://www.fda.gov/cder/about/smallbiz/generic\\_exclusivity.htm#COURT](http://www.fda.gov/cder/about/smallbiz/generic_exclusivity.htm#COURT) (“This 180-day exclusivity provision has been the subject of considerable litigation and administrative review in recent years...”).

<sup>261</sup> See *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs: Hearing Before the Subcomm. on Commerce, Trade, and Consumer Protection of the H. Comm. on Energy and Commerce*, 111th Cong. (2009) (Prepared Statement of the Federal Trade Commission), available at <http://www.ftc.gov/os/2009/03/P859910payfordelay.pdf>.

<sup>262</sup> For an example of how exclusivity periods can be extended, see discussion *supra* in Chapter 3 regarding stacking of 30-month stay provisions under Hatch-Waxman.

<sup>263</sup> See, e.g., Momen Comment (12/22/08) at 7 (“The discovery and understanding of the biology of a pathway often allows for patent protection that not only covers the therapeutic protein or antibody itself, but offers the potential to claim coverage of other therapeutic proteins and antibodies that regulate the biological landscape in which the biologic acts.”); *id.* at 7; Pearce at 169; Hospira (Wilkie Farr) Comment (12/22/08) at 2; Leicher at 161-62.

determine interchangeability if there is no possibility for recouping the costs that come with patent challenges.”<sup>264</sup>

By contrast, other commenters and panelists suggested that there was no need for an FOB exclusivity period because potential market profits would provide sufficient incentives to enter with a follow-on product.<sup>265</sup> Another commenter explained that if the market did not provide sufficient incentives on its own, an FOB exclusivity period would not do so either. An applicant would already have the assurance of *de facto* exclusivity, because there would not likely be a second or subsequent entrant, and *de jure* exclusivity would add nothing to the economic calculus.<sup>266</sup>

One potential FOB entrant explained that if a company invests a huge amount of money developing FOB products, it is unwise to put up further barriers in the form of exclusivity granted to other FOBs against its ability to get a return on investment.<sup>267</sup> Others panelists stressed that an additional incentive to foster FOB entry is no longer needed because the environment in 2008 is much different that it was in 1984, when Hatch-Waxman was enacted and there were no established generic competitors, thus an incentive was necessary to jump start the industry.<sup>268</sup>

Other panelists questioned why an FOB exclusivity period was needed in the United States, the largest drug market in the world, when follow-on drug manufacturers in Europe have not needed exclusivity to incentivize biosimilar entry. One panelist noted that European regulatory structure does not provide market exclusivity for biosimilars or

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<sup>264</sup> Teva Comment (9/30/08) at 6; *see also* Barr Comment (9/30/08) at 8 (“market exclusivity is necessary to encourage companies to develop generic biologics” and that “generic companies need an incentive to undertake costly and time-consuming patent disputes – disputes needed for pre-patent expiration generic market entry.”); GPhA (9/30/08) at 5 (generic marketing exclusivity 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.”); W&S Comment (12/22/08) at 2.

<sup>265</sup> Norman at 197 (“to recognize why someone following on after the trail has already been blazed should need any incentive other than the market in and of itself. The market provides plenty incentives for people to do what reasonable persons do every day”); Zielinski at 196 (The “market dynamic itself will be sufficient incentive, because fewer entrants, and less price discount, so FOBs can make it up in sales.”); *see also Competition in the Pharmaceutical Marketplace: Antitrust Implications of Patent Settlements: Hearing Before the S. Comm. On the Judiciary*, 107th Cong. (2001) (statement of Orin Hatch, Chairman, (S. Comm. On the Judiciary) (“Is it necessary or advisable to retain the 180-day exclusivity period given the enormous financial incentives to challenge patents on blockbuster drugs?”).

<sup>266</sup> Eli Lilly Comment (12/22/08) at 5.

<sup>267</sup> Allan at 194, 207.

<sup>268</sup> Miller at 198-99; *see also* Amgen Comment (9/30/08) at 19 (“[T]he generic industry is in a very different place today than it was at the time the Hatch-Waxman pathway for approval of generic drugs was adopted. In 1984, the industry was not yet established and success of the generic business model was uncertain.”).

“for any generic of any kind, including small molecule.”<sup>269</sup> This panelist also concluded that because many generic companies do not make the 180-day period the cornerstone of their business model, the 180-day marketing exclusivity period is not necessary to encourage entry.<sup>270</sup> A commenter also noted that the large number of biosimilar products under development in Europe, where no market exclusivity is provided for biosimilar products, indicates that market exclusivity in the United States may be unnecessary.<sup>271</sup>

## II. MARKETING EXCLUSIVITY LIMITED TO INTERCHANGEABLE FOLLOW-ON BIOLOGICS

Panelists suggested that any regulatory exclusivity period be limited to interchangeable FOBs (*e.g.*, biogenerics), which may cost more to develop than biosimilar drug products.<sup>272</sup> One panelist indicated that demonstrating interchangeability may require clinical trials. The trials will be complicated and expensive if there are multiple interchangeable products.<sup>273</sup> A commenter suggested that a “short period of exclusivity for the first to market could provide an incentive to companies entering the biogeneric market; however, companies will not likely rely on winning exclusivity to invest in the products because the development time and investment for biogenerics is so great.”<sup>274</sup>

Some panelists suggested that there are likely to be few, if any, interchangeable FOB entrants because of the additional expenses to develop and obtain approval of interchangeable products.<sup>275</sup> In contrast, another panelist predicted that the *availability* of an FDA approval process for interchangeability would prompt the development of the necessary analytics needed to prove interchangeability.<sup>276</sup>

If there were an FOB exclusivity period, panelists described how experience under Hatch-Waxman provided insights into how best to structure the exclusivity to

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<sup>269</sup> Barkoff at 204-05; *see also* Zielinski at 206; Teva Comment at 5 (“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.”).

<sup>270</sup> Barkoff at 205-06.

<sup>271</sup> *See* Amgen Comment (9/30/08) at 19.

<sup>272</sup> Hospira Comment (12/22/08) at 7 (“[t]he R&D investment for a biogeneric is significantly greater and could approach \$100 million”); *see also* Berhman Presentation at 13; Momenta Comment (9/30/08) at 3; Schultz at 191-92.

<sup>273</sup> Allan at 194.

<sup>274</sup> Hospira Comment (12/22/08) at 7.

<sup>275</sup> Shultz at 194-95.

<sup>276</sup> Brugger at 74.

avoid unintended anticompetitive effects that delayed entry. One panelist suggested that an FOB exclusivity period should restrict only other interchangeable FOBs, not other biosimilars, from coming to market during that period of time.<sup>277</sup>

One commenter posited that the Hatch-Waxman 180-day marketing period was designed to incentivize generic drug applicants to engage in patent litigation because of the concern that other generic drug applicants would free-ride on this litigation investment.<sup>278</sup> One panelist suggested that placing a bounty system on intellectual property rights through the awarding of marketing exclusivity for patent challenge is not in the public interest.<sup>279</sup> Other commenters suggested that FOB exclusivity “be based on product approval rather than patent challenge” such that it does not create a “perverse incentive to challenge the innovator’s patent early and often, regardless of the merit of the challenge.”<sup>280</sup>

### **III. ANALYSIS OF LIKELY COMPETITIVE EFFECTS OF AN FOB EXCLUSIVITY PERIOD**

An FOB exclusivity period is unnecessary to encourage the development and marketing of biosimilar products. Market forces to incentivize the development of these products appear robust. Indeed, several panelists and commenters noted that the multi-billion dollar size of the market opportunities, the European experience of HGH and EPO biosimilar entrants, and the U.S. EPO biosimilars provide strong evidence to predict that regulatory incentives are unnecessary to encourage biosimilar products in the United States.<sup>281</sup> Moreover, they are likely to face less competition than small-molecule generic drug manufacturers because of the high entry costs.

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<sup>277</sup> Shultz at 201-02; *see also* Barr Comment (9/30/08) at 8 (if there were an exclusivity period that it “not prevent the immediate approval of a non-interchangeable, but comparable, generic biologic product” and that it be awarded “to the first interchangeable product to be approved by FDA, rather than to the company that filed the first application seeking approval of such a product, as happens under Hatch-Waxman”); Mylan Comment at 9 (exclusivity provided only to the first biogeneric would not prevent or delay the FDA’s approval of a biosimilar product); Novartis Comment (12/22/08) at 18 (“[t]o date, none of the U.S. legislative proposals for FOBs would grant exclusivity to a non-interchangeable FOB. An interchangeability designation is currently considered the most effective way to introduce head-to-head market-based competition with currently-licensed PHS Act biologics.”); Teva Comment (10/8/08) at 8.

<sup>278</sup> BIO Comment (9/30/08) at 24-25 (“patent litigation over one FOB product will not necessarily apply to another FOB product,” and the risk of litigation free-riders faced in the generic small-molecule context will be much diminished in an FOB context); *see also* PhRMA Comment (9/30/08) at 21 (“[it] is not clear that regulatory exclusivity would be need to encourage patent challenges under an FOB regulatory pathway.”).

<sup>279</sup> Norman at 201.

<sup>280</sup> Amgen Comment (9/30/08) at 24 (expressing concern that “excessive patent litigation spawned by the 180-day exclusivity provision” would increase the cost of producing new treatments and cures); *see also* Schultz at 192.

<sup>281</sup> *See* Grabowski at 39; Heldman at 22-32; Heldman Presentation at 3-9; Lane at 36-37, 40; Urlep at 34; Zielinski at 211; Amgen Comment (9/30/08) at 19 (“It appears from the number of biosimilar products under development in Europe, where no market exclusivity is provided for biosimilar products, that market

An FOB exclusivity period also is unlikely to be necessary to encourage the development of interchangeable biosimilar drug products for several reasons. First, the conditions that justified the 180-day exclusivity period for small-molecule generic drugs under Hatch-Waxman are unlikely to be present. Interchangeable FOB drug prices are unlikely to fall as much (either in real terms or as a percentage of the pioneer product's price) as they do when multiple small-molecule generic drugs enter the market. In the small-molecule generic drug context, the first generic entrant is able to recoup its patent litigation costs before entry of additional generic drugs. Additional generic entry substantially decreases the generic price, in some cases, up to 80 percent off the referenced product's price. It is likely, however, that few interchangeable FOB entrants will enter the market, and prices will not fall as much as they do following small-molecule generic drug entry.

Second, it is unclear whether subsequent interchangeable entrants would be able to "free-ride" on the first interchangeable's FDA approval or patent litigation expense and thus enter the market once the first interchangeable product is approved. It is expected that FDA approval of interchangeable products (and accompanying patent litigation) is likely to be more complicated than generic drug approval. Unlike generic small-molecule drugs where several generic drug products often await FDA approval once a patent expires or is found invalid or not infringed, this complexity is likely to diminish the prospect that a "queue" of interchangeables will be ready for approval once the first interchangeable product is approved. Thus, the circumstances that justified a 180-day marketing exclusivity period for generic drugs are unlikely to be present for interchangeable FOB drug products.

Third, it is uncertain that cost will justify an FOB exclusivity period. It may not cost substantially more to show that a biosimilar product is interchangeable with the referenced branded product than an initial finding of biosimilarity. If technology advances such that it is relatively inexpensive to determine interchangeability, an exclusivity period is unnecessary.

Fourth, it is unclear that an FOB exclusivity period will successfully incentivize a manufacturer of a biosimilar product to develop an interchangeable FOB product. Biosimilar manufacturers are likely to make this additional investment based on a consideration of, among other things, the cost, expected prices, capacity constraints, and the extent and effect of state substitution laws. This situation contrasts significantly with small-molecule generic competition seen under Hatch-Waxman in which generic manufacturers enter initially with an interchangeable product. Unlike FOB manufacturers, generic manufacturers do not market a "similar" product first and replace it with an "interchangeable" product later.

Not only is an FOB exclusivity period not justified by market conditions but the delay in generic entry evidenced in small-molecule generic drug markets is likely to be

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exclusivity for biosimilars in the United States may not be necessary."); Bernstein Research Comment at 12.

repeated in biologics markets if an exclusivity provision for interchangeable products is implemented. These anticompetitive consequences are likely to result if the period can be extended, the period does not run immediately upon its award, or if a firm has the ability to delay triggering the running of the period through, for example, a patent settlement, acquisition, merger, or agreement.<sup>282</sup> In addition, each of these problems is likely to be present even if the exclusivity is awarded on a “first-to-file” rather than a “first-to-apply” basis.

For example, pioneer manufacturers and FOB applicants could settle patent litigation such that a payment is made to the first interchangeable FOB entrant to settle the patent dispute and defer its entry. This settlement could create a bottleneck that blocks subsequent interchangeable FOB from obtaining FDA approval because the first-approved product’s exclusivity period has not run. This outcome results in significant harm to consumers who not only lose the benefit of the first interchangeable product’s entry but also the second product’s entry. Furthermore, in this circumstance, the rationale for the FOB exclusivity period is undermined by proof that the subsequent applicant did not need an additional incentive to perform all the steps necessary to enter the market, yet is blocked from the market by the first interchangeable product.

In theory, various regulatory fixes could require an interchangeable FOB manufacturer to forfeit its exclusivity period. These forfeiture events could include when: (a) it fails to trigger the running of the period by launching the interchangeable FOB product immediately following a final court decision in its favor on the patents at issue; (b) it has not been sued by the branded manufacturer, or (c) its patent suit is taking too long to resolve and a subsequent interchangeable applicant is approvable by the FDA.

The problem with these fixes is that each one blocks entry of a subsequent interchangeable product for a period of time and thereby denies consumers price competition and increased innovation. They also require the FDA to expend significant resources monitoring patent registrations and certifications, litigations, and marketplace activity that is outside its core missions and competencies.<sup>283</sup> Further, such a marketing exclusivity provision will inevitably generate lawsuits against the FDA regarding award,

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<sup>282</sup> For an example of how exclusivity periods can be extended, *see* discussion in Chapter 3 regarding stacking of 30-month stay provisions under Hatch-Waxman.

<sup>283</sup> 21 U.S.C.A. § 355(b)(1); *see, e.g.*, *Teva Pharm. USA, Inc. v. Leavitt*, 548 F. 3d 103, 106-07 (D.C. Cir. 2008); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 124 (D.C. Cir. 2006); *Sandoz, Inc. v. F.D.A.*, 439 F. Supp. 2d 26, 30 (D.C. Cir. 2006); *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1348–49 (Fed. Cir. 2003); *Pharma Inc. v. Thompson*, 296 F.3d 227, 242–43 (4th Cir. 2002); *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1373-74 (Fed. Cir. 2002); *Mylan Pharm., Inc. v. Thompson*, 268 F.3d 1323, 1331-32 (Fed. Cir. 2001); *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001) (recognizing that the FDA “has refused to become involved in patent listing disputes, accepting at face value the accuracy of NDA holders’ patent declarations and following their listing instructions”); *see also Prepared Statement of the Federal Trade Commission Before the Hearing before the S. Comm. on Commerce, Science, and Transportation*, 107th Cong. (2002) (statement of Timothy J. Muris, Chairman, FTC), available at <http://www.ftc.gov/os/2002/04/pharmtestimony.htm>.

timing, scope and termination of the marketing exclusivity periods as has occurred regarding the 180-day provision of the Hatch-Waxman Amendments.<sup>284</sup>

For these reasons, an FOB exclusivity period is unlikely to benefit consumers either with an increase in the pace or scope of innovation or additional price competition. An FOB exclusivity period is likely to delay FOB competition in the case when a second interchangeable FOB applicant is ready to be approved, but cannot enter until the first-approved interchangeable product's exclusivity has expired.

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<sup>284</sup> See, e.g., *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1065 (D.C. Cir. 1998); *Apotex, Inc. v. FDA*, No. 06-5105, 2006 U.S. App. LEXIS 10561 (D.C. Cir. Apr. 24, 2006), *aff'd* *Apotex, Inc. v. FDA*, No. 06-5105, 2006 U.S. App. Lexis 14086 (D.C. Cir. June 6, 2006) (“This case is the latest flare-up in a long running dispute between the Food and Drug Administration (FDA) and several generic manufacturers as to what qualifies under the Hatch-Waxman act as “a decision of a court . . . holding [a challenged] patent to be invalid or not infringed.”).



## APPENDIX A

Economists have developed a framework to calculate the time it takes for a branded biologic drug manufacturer to recover fully its investment to develop and commercialize a typical biologic drug. This framework is referred to as the “Nature model” because it first appeared in an article by Dr. Henry Grabowski in the journal *Nature Reviews: Drug Discovery*.<sup>1</sup> The original Nature model, along with subsequent suggested changes, has been used as the basis for an estimation of the optimal length of a branded exclusivity period.<sup>2</sup>

This appendix describes the Nature model and explains the methodological and conceptual weaknesses that render its results too imprecise and non-robust to inform discussions about the length of a branded exclusivity period. A model that balances the benefits of FOB competition with the costs of potentially forsaking marginal branded drug development projects would be more informative than the Nature model’s approach.<sup>3</sup>

The appendix is organized as follows: Section I describes the original Nature model’s data inputs and the operation of the model; Section II describes the comments about, suggested changes to, and subsequent sensitivity analysis performed on the original Nature model; Section III describes the current weaknesses with the model; and despite these weaknesses, Section IV presents one correction to the elasticity and internal consistency flaws of the model along with new results based on these corrections.

### I. Description of the Nature Model

The Nature model calculates the break-even point for a branded manufacturer’s biologic portfolio as the point at which the net present value of the cumulative cash flows of the portfolio equals zero. The stream of cash flows upon which this calculation is based has the following six components.

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<sup>1</sup> Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479 (June 2008) [hereinafter “NATURE”].

<sup>2</sup> Subsequent calculations and adjustments to the Nature model include: Henry Grabowski *et al.*, *Updating Prior Analyses and Responding to Critiques*, DUKE UNIV. DEPT. ECON. WORKING PAPER, No. 2008-10 (Dec. 22, 2008) (hereinafter “Updating Analyses”); Matrix Global Advisors Comment (12/22/08); Alex Brill, *Proper Duration of Data Exclusivity for Generic Biologics: A Critique*, MATRIX GLOBAL ADVISORS, LLC, WHITE PAPER (2008).

<sup>3</sup> Such an approach would require, at a minimum, R&D cost information to which the FTC does not have access.

## **A. Total Pre-Approval Research and Development Costs per Approved Biologic Drug**

The first input of the Nature model is an estimate of the pre-approval R&D costs per approved biologic drug based on work by DiMasi and Grabowski.<sup>4</sup> The original Nature model and subsequent calculations rely on estimates of the total R&D costs for a typical investigational drug, adjusted for the probability of FDA approval, to calculate an estimate of the total R&D costs for a FDA-approved branded biologic drug. The R&D cost estimates are based on the proprietary data for 17 biologic drugs. The cost estimates are the weighted average costs in each phase of development (*i.e.*, preclinical, Phase I, Phase II, and Phase III) across the 17 drugs, where the weights are the probabilities of entering each phase.<sup>5</sup> The estimated real (*i.e.*, in 2005 dollars) costs for each phase are: \$59.88 million (preclinical), \$32.28 million (phase I), \$31.55 million (phase II), and \$45.26 million (phase III). These costs would be spent over an average 13 year period prior to approval, so that the future value of these costs at the time of approval (using a discount rate of 11.5%) is \$374.70 million.

Because every molecule developed is not approved (*e.g.*, clinical testing may show that it is not safe and/or effective), the total R&D estimate is adjusted for the probability of success. The R&D cost per investigational molecule is converted to an estimate of the R&D cost per *approved* molecule by dividing the \$374.70 million by the estimated probability of success (30.2%). The overall estimate of the total pre-approval R&D costs at launch (using a discount rate of 11.5%) for a typical approved biologic drug is \$1.24 billion. Using a discount rate of 12.5%, the estimate of pre-approval R&D costs is \$1.33 billion.

## **B. Launch and Plant Transition Costs**

The second input of the Nature model is an estimate of the costs of launching production of the new drug. The Nature model and subsequent calculations assumed that the branded manufacturer will spend \$25 million over the two years prior to launch to convert existing manufacturing capacity to the production of the new drug.<sup>6</sup> It is also assumed that the branded manufacturer will incur additional “launch-related expenditures equal to 10% and 20% of first year’s sales” in the two years prior to launch, respectively.<sup>7</sup> Using a discount rate of 11.5%, the future value of these costs at the time of launch is roughly \$70 million. Therefore, if the discount rate is assumed to be 11.5%, the typical branded biologic firm is estimated to be “in the

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<sup>4</sup> Joseph DiMasi & Henry Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAG. DECIS. ECON. 469 (2007).

<sup>5</sup> The phase probabilities, as well as the development times, are estimated from a separate database of 522 biologic drugs.

<sup>6</sup> Grabowski, NATURE, at 483, Note 6, Box 3.

<sup>7</sup> *Id.* at 483, Note 9, Box 3.

hole” roughly \$1.31 billion per approved new drug at the time of launch (\$1.24 billion plus \$70 million based on a 11.5% discount rate).

### **C. Post-Approval R&D Costs**

The third input of the Nature model is an estimate of the costs for post-approval R&D of new indications and formulations. The Nature model and subsequent calculations assumed that these costs are \$24.5 million per year for the first 8 years after approval based on post-approval R&D expenses of traditional small-molecule drug companies.

### **D. Revenues**

The fourth input of the Nature model is an estimate of the revenue stream used to recover the pre-approval R&D costs, launch and transition costs, and post-approval R&D costs. The Nature model’s revenue estimates are based on revenues from a sample of 30 biotechnology drugs. The 30 drugs are ranked into quintiles and the mean amounts for the top four ranked quintiles are then used to calculate the average revenue profile for a typical branded biologic drug. The Nature model excluded the bottom quintile because these drugs “may not have representative R&D cost profiles.”<sup>8</sup>

The timing of the revenues for the hypothetical portfolio is assumed to match that of the “average new drug introduction in the 1990s.” After the maximum revenues are achieved in the tenth year after launch, revenues are assumed to decline by 3.5% per year due to “obsolescence and therapeutic class competition.”<sup>9</sup> The revenue stream represents worldwide sales and is denominated in 2005 dollars.<sup>10</sup>

### **E. Contribution Margin**

The fifth input of the Nature model is an estimate of the operating profit margin, or contribution margin, of the brand drug. After the brand drug is launched, its revenues cover its operating costs each year with the remaining operating profit contributing to the recoupment of the investment costs. The original Nature model assumes that the contribution margin for the biologic portfolio is -30% in the first year after launch, +20% in the second year after launch, and +50% thereafter. The steady-state 50% margin is used because it is “in line with the contribution margins realized by the eight largest biotechnology firms with multiple products on the market.”<sup>11</sup>

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<sup>8</sup> *Id.* at 485.

<sup>9</sup> *Id.*

<sup>10</sup> *Id.* at 486.

<sup>11</sup> *Id.* at 486.

## F. Discount Rate/Cost of Capital

The final input of the Nature model is an estimate of the cost of capital for a biologic drug, *i.e.*, the rate of return required by investors to compensate for the risk involved in developing the brand drug. The original Nature model uses two rates to “capitalize forward” the R&D cost stream to the launch date and discount the profit stream back to the launch date: 11.5% and 12.5%. These rates are justified as “reflective of the equity cost of capital for larger publicly listed biotechnology firms with multiple products on the market in recent periods.”<sup>12</sup> These rates are based on estimates of the real cost of capital over time for an unspecified sample of biotech firms calculated in previous research using the capital asset pricing model (12.5% in 1994, 12.0% in 2000, and 10.0% in 2004).<sup>13</sup> The original Nature model uses the average (11.5%) and maximum (12.5%) of these three rates in its calculations.

These six components are used to calculate the point at which R&D costs are recouped through post-approval cumulative profits as shown in Table 1 below (which assumes a discount rate of 11.5%). The typical biologic product starts out at launch \$1.31 billion “in the hole.” During each year after launch, it earns an operating profit (assumed to be negative in the first year) which is its contribution margin times its revenue (minus any post-approval R&D). To properly compare profits in different years, this profit stream is discounted back to the launch date. If 11.5% is used as the discount rate, the cumulative profit stream covers the initial R&D expenditures late in the 13<sup>th</sup> year after launch (*i.e.*, 12.9 years after launch).<sup>14</sup> If 12.5% is used as the discount rate, this break-even point occurs 16.2 years after launch.

Based on these two calculations, Grabowski concludes that the exclusivity period for a branded biologic should last 12 and 16 years after launch: “entry through abbreviated filings should be delayed until the representative NBE [New Biologic Entity] has had the opportunity to earn risk-adjusted break-even returns.”<sup>15</sup>

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<sup>12</sup> *Id.*

<sup>13</sup> DiMasi, *The Cost of Biopharmaceutical R&D*, at 474.

<sup>14</sup> Grabowski, *NATURE*, at 486.

<sup>15</sup> *Id.* at 487.

**Table 1: Break-Even Analysis w/ Discount Rate = 11.5%** (all amounts in millions)

Year	R&D	Revenue	Margin	Post-approval R&D	Launch/Plant	Profit	NPV Profit	Cumulative NPV
0	-\$1,243				-\$70	-\$1,313	-\$1,313	-\$1,313
1		\$128	-0.3	-\$24.5		-\$63	-\$60	-\$1,372
2		\$243	0.2	-\$24.5		\$24	\$20	-\$1,352
3		\$328	0.5	-\$24.5		\$140	\$106	-\$1,245
4		\$413	0.5	-\$24.5		\$182	\$124	-\$1,121
5		\$506	0.5	-\$24.5		\$229	\$140	-\$981
6		\$577	0.5	-\$24.5		\$264	\$145	-\$836
7		\$648	0.5	-\$24.5		\$300	\$148	-\$688
8		\$676	0.5	-\$24.5		\$314	\$139	-\$550
9		\$713	0.5			\$357	\$141	-\$409
10		\$713	0.5			\$357	\$127	-\$282
11		\$688	0.5			\$344	\$110	-\$172
12		\$664	0.5			\$332	\$95	-\$77
13		\$641	0.5			\$320	\$82	\$5
14		\$618	0.5			\$309	\$71	\$76
15		\$597	0.5			\$298	\$62	\$138
16		\$576	0.5			\$288	\$53	\$191
17		\$556	0.5			\$278	\$46	\$237

## II. Summary of Comments

Commenters raised several issues about the inputs, the operation of the model, and the inferences that can be drawn from the model. Alex Brill arrived at different results by varying some of the model’s assumptions.<sup>16</sup> First, he suggested that 10% is a more accurate estimate of the cost of capital for biotech firms, rather than 11.5% or 12.5%.<sup>17</sup> Second, he posited that 60%, rather than 50%, is a more accurate estimate of the contribution margin for a large biotech firm.<sup>18</sup> Using these assumptions, he calculates a break-even point nine years after FDA approval of the branded biologic drug.

Brill also explained that the break-even point should not be used as a proxy for the optimal exclusivity period because a branded biologic product is likely to continue earning positive profits even after FOB entry.<sup>19</sup> If exclusivity is granted so that no FOBs can enter until the average branded manufacturer has recouped its R&D costs, then the branded manufacturer will earn “profits that exceed the required rate of return expected by investors.”<sup>20</sup> If true, this

<sup>16</sup> Brill, *Proper Duration of Data Exclusivity*.

<sup>17</sup> *Id.* at 8 (citing DiMasi, *The Cost of Biopharmaceutical R&D*).

<sup>18</sup> *Id.* at 8-9(citing an alternate source of financial data more recent than that used in the Nature model).

<sup>19</sup> *Id.* at 10.

<sup>20</sup> *Id.*

could lead to consumer harm through the delay of FOB entry. As an illustration, Brill used the 10%/60% discount rate/margin assumptions, along with assumptions from the Congressional Budget Office about the market share and price declines that branded biologic drugs are likely to face with FOB entry.<sup>21</sup> This illustration shows that a branded manufacturer would break-even ten years after approval even if FOB entry occurs in the eighth year after FDA approval of the branded drug.

Another commenter argued that the use of a portfolio approach in estimating the revenue stream may result in an exclusivity period that is too long and overprotects the branded biologic drugs that are most likely to face FOB competition. Although a branded manufacturer and its capital partners may diversify by investing in many investigational drugs (some of which will become very successful and profitable and others that will be approved, but have relatively small revenues), potential FOB entry is only a credible concern for the most successful of these drugs. The portfolio used in any break-even calculation to determine exclusivity periods should only include those drugs for which FOB entry is likely when the period of exclusivity expires. The original Nature model and subsequent calculations exclude only the bottom quintile of biologic drugs when constructing the portfolio. This commenter suggested that drugs with less than \$250 million in sales are unlikely to face FOB competition, thus implying that the bottom two quintiles should be excluded from the break-even calculation, as the drugs in the second lowest quintile have peak sales of \$100 million.<sup>22</sup>

Following the roundtable and in response to Brill's critique, Grabowski questioned Brill's assumption about total market revenues when FOBs enter the market; cited additional research suggesting that the true cost of capital may be higher than originally presented in the Nature model; suggested that the true contribution margin may be lower than originally presented; and provided additional analysis showing how relaxing other assumptions in the model would lead to longer break-even times.<sup>23</sup>

Brill also provided post-roundtable comments that included additional alternative interpretations of CBO's assumptions regarding branded manufacturer market share declines following FOB entry.<sup>24</sup> In addition to his original calculation (which assumes total market revenues do not change), he presented additional break-even calculations that assume a perfectly inelastic demand. One of these assumes a steady-state price decline of 40% as before and the other assumes a steady-state price decline of 20%. A final calculation assumes no price decline and simply a loss of market share to the FOB entrant. As in his original analysis, all of these

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<sup>21</sup> Congressional Budget Office ("CBO"), Cost Estimate (S.1695), *Biologics Price Competition and Innovation Act of 2007 S. 1695, As Ordered Reported by the S. Comm. on Health, Education, Labor, and Pensions on June 27, 2007* (June 25, 2008), available at <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf>.

<sup>22</sup> Zuckerman Spaeder Comment (12/22/08) at 10.

<sup>23</sup> Grabowski, *Updating Analyses*, at 13.

<sup>24</sup> Matrix Global Advisors Comment (12/22/08).

calculations assume seven years of branded exclusivity, a contribution margin of 60%, and a cost of capital of 10%. With these assumptions, he finds that the branded manufacturer breaks-even nine to 14 years after launch.

Finally, one commenter surmised that the Nature model was “fraught with peril.” He suggested that: “Aside from a possibly nonrepresentative sample, the exercise involves numerous assumptions about the cost of capital, profit margins, and prices after the first follow-on enters the market. Reasonable changes to these assumptions can easily affect the results by 30–40 percent.”<sup>25</sup>

### **III. Problems with the Break-Even Model - Analysis**

The problems with the Nature model fall into three types: (1) problems with the “inputs” to the model (*i.e.*, problems with the underlying components); (2) problems with the incorporation of FOB entry into the model after a period of exclusivity; and (3) problems with the interpretation and use of the results.

#### **A. Problems with the Input Assumptions**

The first input to the Nature model is the estimate of pre-approval R&D costs for a representative biologic drug. The problem with this estimate is that it is based on a sample of only 17 drugs. No variance information is presented for the sample.<sup>26</sup> Unless the R&D costs within each clinical phase are essentially identical across the drugs, it is likely that the confidence interval around the R&D cost estimate is large and, thus, the R&D cost estimate is less likely to be accurate. Further, 13 of the 17 drugs were developed by one firm and the sample is restricted to therapeutic recombinant proteins and monoclonal antibodies, so it is possible that the sample is non-random and not representative of biologic drugs overall.

Another important input into the model is the revenue stream of the representative biologic drug. There are two potential problems with the revenue stream used in the Nature model.<sup>27</sup> First, the revenue stream includes sales from post-approval indications and formulations in addition to the original indication/formulation.<sup>28</sup> The revenue stream associated with the original indication/formulation is not provided, so one cannot calculate the break-even point of the original indication/formulation with the data in the model.

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<sup>25</sup> American Enterprise Institute Comment (12/10/08) at 6.

<sup>26</sup> DiMasi, *The Cost of Biopharmaceutical R&D*.

<sup>27</sup> The FTC was unable to determine how the Nature model factors in sales of biologic products outside the United States, including potential sales of biologic products in European markets prior to their approval in the U.S., and European market revenues for the pioneer’s branded product after biosimilar entry. Accordingly, there could be additional weaknesses in the Nature model concerning its treatment of international revenues.

<sup>28</sup> Grabowski, NATURE, at 483, Box 3, Note 5.

Second, the revenue stream assumes “therapeutic class competition.”<sup>29</sup> The time frame of the therapeutic class competition is not stated in the original Nature model, but Grabowski’s post-conference comment suggests that the therapeutic class competition is assumed to begin in the tenth year after approval of the brand drug.<sup>30</sup> Thus, the original Nature model implies that a “first-in-class” branded drug will recoup its R&D costs even if therapeutic class competition occurs. And because entry of FOBs is likely to have the same market effect as entry by branded competitors, this assumption leads to the conclusion that the branded exclusivity period for the first-in-class branded drug should be less than 12 to 16 years.

In addition, like the R&D cost estimates, the revenue estimates are based on a small sample. The model relies on 24 biologic drugs to estimate the revenue stream. These are the drugs in the top four quintiles of the distribution and the spread in average peak revenues between the top and second-to-bottom quintiles (\$2 billion to \$100 million) suggests a large variance in this distribution. Like the R&D cost estimates, it is likely that the confidence interval around the estimated revenue stream is large and, thus, the revenue estimates are less likely to be accurate. In addition, it is unknown whether the 24 drugs are a random sample of biologics. If not, or if they substantially overlap with the 17 drugs used to estimate the R&D costs, the revenue estimates may be biased like the R&D cost estimates.

Furthermore, an implicit assumption of the Nature model is that there is no correlation between R&D costs and revenues, so that an average R&D cost stream and an average revenue stream can be used to make inferences about average profitability. However, R&D costs and revenues may be positively or negatively correlated, making the variance of the profit estimates smaller or larger, respectively, than suggested by independent samples. Since the samples used to estimate R&D costs and revenues are not disclosed, it is impossible to determine if this ameliorates or exacerbates the measurement error.

Another important component in the model is the assumed cost of capital. Despite the disagreement over the appropriate cost of capital for a biologic firm, the model assumes a constant cost of capital throughout the entire product life cycle. Investments in biologic R&D during the early stages of research (*e.g.*, preclinical R&D) might have a higher cost of capital reflecting their relative risk, while investments during the later stages (*e.g.*, phase III and post-approval) might have a lower cost of capital reflecting the relative certainty of the return.<sup>31</sup> As a result, this could substantially change the total capitalized amount to be recouped.

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<sup>29</sup> *Id.* at 485.

<sup>30</sup> Duke University Comment (12/22/08) at 5 (“Specifically, in the Nature article I assume that, starting ten years following launch of the innovator biologic, revenues will begin to decline due to obsolescence at a rate of 3.5% per year. The introduction of new branded biologics by competitors (branded competition with other “first generation” and “second generation” products) is a likely source of this obsolescence.”)

<sup>31</sup> See *e.g.*, Office of Technology Assessment, United States, Congress Edition, *Pharmaceutical R&D: Costs: Risks and Rewards*, (1994) at 66.



Apart from the estimation errors associated with the R&D cost and revenue inputs and the cost of capital assumptions, it is unclear whether the use of sample means or a portfolio approach is appropriate. The samples of drug projects used to create the R&D cost and revenue estimates are biologic development projects that were actually pursued. At least initially, all of these projects were perceived as potentially profitable ventures or else they would not have been funded. Introducing a FOB pathway might make some of these formerly profitable projects unprofitable. If the R&D cost and revenue figures are independent, the use of sample means in the Nature model imply that the exclusivity period should be set so that development of projects that are above the profit mean continue to be pursued while those below the profit mean are abandoned. If the R&D cost and revenue estimates are not independent (*e.g.*, more expensive projects are associated with larger expected sales), it is not clear which projects would be abandoned with a FOB pathway determined using the R&D cost and revenue mean estimates. A better approach to determining the optimal length of a branded exclusivity period would balance the benefits of FOB competition with the costs of potentially forsaking marginal branded development projects.

## **B. Problems Incorporating FOB Entry into the Break-Even Model**

The versions of the model that explicitly incorporate FOB entry contain two questionable assumptions that may bias the results. First, in most of the calculations that incorporate FOB entry, it is assumed that the price of the branded drug will gradually decline after FOB entry so that it is 40% below its pre-FOB price in four years. This assumption corresponds roughly to the CBO's assumption that the FOB price will be 40% less than the pre-FOB branded price four years after entry. Of course, the latter does not necessarily imply the former, as it is theoretically possible for the FOB's price to be 40% less than the branded drug's pre-FOB price even if the branded drug's price falls by more or less than 40%.

The assumption that the branded drug price will match the FOB price represents the least profitable scenario for the branded manufacturer: the scenario in which the branded drug and the FOB are perfect substitutes.<sup>32</sup> Still, the 40% branded price decrease assumption is ad hoc and is not necessarily consistent with the CBO assumption that the branded drug's market share will eventually decline by 35%. In the calculations of Grabowski and Brill, competition between the branded manufacturer and the FOB firm following FOB entry is not modeled explicitly. It is reasonable to expect that the branded drug's price decrease and market share decrease are inter-related and are jointly determined. In other words, the assumption that the branded drug's share declines by 35% in large part determines what price decreases are possible. The analysis below provides one example of how the Nature model can be corrected to account for this relationship.

The second questionable assumption concerns overall revenues after FOB entry. In some variations of the model, it is assumed that overall market revenues stay the same after FOB entry. In other words, it is assumed that the branded manufacturer faces a demand for its drug that is unitary elastic so that price decreases and the resulting increases in the quantity demanded

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<sup>32</sup> Matrix Global Advisors Comment (12/22/08) at 3 (“Given the desire to impose conservative assumptions, the Brill model assumes the price decline of innovator drugs is equal the FOB price.”).

exactly offset producing no change in overall market revenue. For profit-maximizing firms, this is impossible as profit-maximizing firms (with positive marginal costs) always price in the elastic portion of the demand they face.

In other variations of the model, it is assumed that overall revenues decline by the same fraction as the price which is equivalent to assuming that the demand for the branded drug is perfectly inelastic (*i.e.*, a price decline results in no change in the quantity produced and sold). A profit-maximizing firm facing a perfectly inelastic demand will increase its price to infinity, as it can sell the same amount at a higher and higher price. This result also is impossible. Branded manufacturers set prices in the elastic portion of the demands they face for the drugs they produce, as do all profit-maximizing firms.<sup>33</sup>

This latter assumption is problematic because it assumes away the primary benefit of establishing an abbreviated pathway for follow-on biologics, namely, to reduce the price of biologic drugs so more people can have access to them. Furthermore, this assumption of inelastic demand directly contradicts the contribution margins used in the model. The Lerner Index dictates that for any profit-maximizing firm, its profit margin over marginal cost will equal the inverse of (the absolute value of) the price elasticity of demand for the demand the firm faces for its product. This condition holds for all profit-maximizing firms, not just monopolists, as it is derived from the first-order necessary condition for profit-maximization. Thus, any profit-maximizing firm that has positive marginal costs and a finite, positive margin over marginal cost must be facing an elastic demand (at least locally around the profit-maximizing price). The contribution margins used in the model are not necessarily equal to the margins over marginal cost used in the Lerner Index (*e.g.*, they may include some overhead costs). However, the assumption of finite contribution margins necessarily implies finite margins over marginal cost and, thus, demand that is elastic, not perfectly inelastic. Below, we correct the model's calculations using the Lerner Index with the contribution margin serving as a proxy for the margin over marginal cost.

### **C. Problems in the Interpretation and Use of the Results**

Apart from the problems with the underlying assumptions of the model, the results of the model are prone to misinterpretation. First, the inclusion of post-approval R&D costs and revenues in the break-even analysis makes it easy to misinterpret the results if one is using the analysis to determine the extent of the exclusivity period for branded biologics. If a fixed exclusivity period is set to recoup the costs of pre-approval and post-approval R&D, then the exclusivity period provides no marginal incentive to the branded firm to conduct post-approval R&D.

Theoretically, the preceding issue could be resolved if one were able to separate the revenues from post-approval indications and formulations from the revenues for the original indication and formulation. However, even if one were able to correct this problem and all of

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<sup>33</sup> Dennis W. Carlton and Jeffrey M. Perloff, MODERN INDUSTRIAL ORGANIZATION, at 93 (4th ed. 2005).

the previous problems, a more fundamental problem with the general model remains: small changes in the input assumptions yield large swings in the resulting break-even period.

This last point can be illustrated by considering Grabowski's post-conference comment that the actual cost of capital for biotech firms may be as high as 13-15%. Recall that the Nature model originally found that a representative biologic portfolio would break even in the 13<sup>th</sup> year if the cost of capital was 11.5% and would break even in the 17<sup>th</sup> year if the cost of capital was 12.5%. Using identical assumptions to the original Nature model, but increasing the cost of capital to 13.25% produces a break-even point in the 23<sup>rd</sup> year. If the cost of capital is greater than or equal to 13.7%, and all of the other assumptions in the original model are retained (including no FOB entry at any point), the representative biologic portfolio *never* breaks even. The fact that the representative biologic portfolio *never* breaks even when using a cost of capital greater than or equal to 13.7%, even though Grabowski's post-roundtable comments suggest 14-15% is a plausible cost of capital for biotech firms, casts doubt on the accuracy and reliability of the model.

#### **IV. Correcting Problems in the Nature Model Does Not Improve Its Usefulness**

As discussed above, the break-even calculations of the Nature model suffer from many problems. Some of these problems can be corrected. In particular, the assumptions of unitary elastic and perfectly inelastic demand can be discarded to make the model's elasticity assumptions consistent with its contribution margin assumptions. Second, the model's consistency problems in the post-FOB world can be corrected by applying a reasonable and flexible competition model. The corrections described below are not exhaustive and simply represent one way these problems can be addressed. In fact, the assumption of Cournot FOB/branded competition is likely wrong, but is a reasonable approach that is consistent with the assumption made by both Grabowski and Brill that the FOB and branded drugs will have the same price after FOB entry. However, the corrections illustrate that the elasticity and consistency problems are not innocuous, but instead have a significant impact on the results. These corrections do not address the more fundamental problems of imprecision and non-robustness. As such, even with these corrections, we find the break-even framework uninformative in the debate about proper exclusivity periods for branded biologic drugs.

First, regarding the elasticity assumption, assume that the contribution margin of the branded manufacturer is equal to the branded manufacturer's margin over marginal cost  $(p - mc)/p$ . These two margins are probably not equal, as the former includes some overhead costs, but the contribution margin is the best proxy for the margin over marginal cost that is readily available. From the Lerner Index, the price elasticity of demand for the branded manufacturer's drug is  $(-1 \text{ times})$  the inverse of the contribution margin. In other words, the assumption of a contribution margin of 50% implies an elasticity of  $-2$  and a contribution margin of 60% implies an elasticity of  $-5/3$ . Let the subscript 1 denote the period before FOB entry and let the subscript 2 denote the period after FOB entry. Following Grabowski and Brill, we assume that the branded drug's price following FOB entry is the same as the FOB's price.<sup>34</sup> Let  $\alpha$  be such that  $p_2$

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<sup>34</sup> This is likely a conservative assumption as the branded manufacturer may be able to price above the FOB and any

$= \alpha p_1$ . For example, a steady-state price decline of 40% following FOB entry implies that  $\alpha = 0.6$ . The price elasticity of demand ( $\varepsilon$ ) is the ratio of the percentage change in quantity with a corresponding percentage change in price. Using an approximation of the elasticity and normalizing  $q_1 = 1$ , this implies:

$$(1) \quad \varepsilon = \frac{\frac{q_2 - q_1}{q_1}}{\frac{p_2 - p_1}{p_1}} \Rightarrow q_2 = \varepsilon(\alpha - 1) + 1$$

This implies that the total market (*i.e.*, branded + FOB) revenue after FOB entry is:

$$(2) \quad R_2 = p_2 q_2 = \alpha[\varepsilon(\alpha - 1) + 1]R_1$$

The profit-maximizing branded manufacturer's marginal cost will equal its marginal revenue before FOB entry:

$$(3) \quad mc = mr = p_1 \left( 1 + \frac{1}{\varepsilon} \right)$$

Therefore, assuming the branded manufacturer's marginal cost does not change after FOB entry, the branded manufacturers's post-FOB margin will be:

$$(4) \quad \frac{p_2 - mc}{p_2} = \frac{\alpha - \left( 1 + \frac{1}{\varepsilon} \right)}{\alpha}$$

Second, a model of the competition between the branded firm and the FOB entrants is needed to characterize prices and market shares that are consistent with each other. There are a number of models that could be used, but the Cournot model seems most appropriate in the current context for the following reasons:

- All versions of the Nature model that incorporate FOB entry assume that the branded firm and the FOB will have the same price after FOB entry. This assumption is likely incorrect as it is likely that the brand and FOBs will not be perfect substitutes and the brand may continue to price higher than the FOBs. However, this assumption is used because it represents the least profitable scenario for the branded manufacturer.

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ability to do so likely would allow the branded manufacturer to break-even sooner.

- Most analysts expect that the price of biologics will decline as more FOBs enter, which is a characteristic of the Cournot model.<sup>35</sup>
- The Cournot model is flexible and requires limited assumptions to implement. It is robust across most types of demand and cost functions. Other potential models (e.g., differentiated Bertrand) require more assumptions to implement. However, if feasible to implement, a monopolistic competition model would be more accurate, as it would capture the differentiation between the brand drug and the FOB that is likely to characterize competition after FOB entry.

The Cournot analogue to the Lerner Index dictates that a firm's margin over marginal cost will equal (the absolute value of) the inverse of the price elasticity of demand times the firm's market share. Therefore, after FOB entry, the branded manufacturer's margin is:

$$(5) \quad \frac{p_2 - mc}{p_2} = -\frac{s}{\varepsilon}$$

where  $s$  is the branded manufacturer's market share. Substituting the branded manufacturer's marginal cost as calculated in (3) above, we can solve for the branded manufacturer's post-FOB price as a function of the branded pre-FOB price:

$$(6) \quad \frac{p_2 - \left[ p_1 \left( 1 + \frac{1}{\varepsilon} \right) \right]}{p_2} = -\frac{s}{\varepsilon} \Rightarrow p_2 = \frac{(\varepsilon + 1)}{(\varepsilon + s)} p_1$$

In other words, if the competition between the branded firm and the FOB firms is consistent with the Cournot model, assumptions about the brand's pre-FOB margin (which determines  $\varepsilon$ ) and the brand's post-FOB market share uniquely determine the brand's price decrease after FOB entry. The CBO's assumption of a steady-state market share decline of 35% and the assumption of a 50% margin imply a 26% branded manufacturer price decrease. If a 60% margin is used instead, the branded manufacturer's price decrease is roughly 34%. Using these values in the break-even calculations produces the following break-even times:

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<sup>35</sup> See, e.g., Alexis Ahlstrom *et al.*, *Modeling Federal Cost Savings of Follow-On Biologics*, Avalere Health LLC (Mar. 2007) available at

[http://www.avalerehealth.net/research/docs/Follow\\_on\\_Biologic\\_Modeling\\_Framework.pdf](http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf).

**Table 2: Year After Launch in Which Branded manufacturer Breaks-Even (Data Exclusivity = 7 Years)**

Margin/Cost of Capital	Lerner ( $\epsilon = -1/\text{margin}$ ); 35% share decline; Cournot competition	Unitary elasticity; 35% share decline; 40% price decline	Perfect inelasticity; 35% share decline; 40% share decline
50%/10%	14	Never	Never
50%/11.5%	34	Never	Never
50%/12.5%	Never	Never	Never
60%/10%	10	11	14
60%/11.5%	14	17	Never
60%/12.5%	24	Never	Never

When the elasticity assumption is corrected and the price and share declines are made internally consistent, the results are much different than in previous versions of the Nature model. For example, Grabowski concludes that “notably, with an exclusivity period of 7 years, the *only* combination of assumptions that yields a breakeven point of less than 50 years is the one used by Brill.”<sup>36</sup> On the contrary, with an exclusivity period of seven years, there is only one set of assumptions (of those most commonly used) that does not result in the branded manufacturer breaking-even.

However, even when the elasticity assumption is corrected and the price and share declines are made internally consistent, the break-even period varies from 10 years to infinity. Small changes to the margin and cost of capital assumptions cause large swings in the results. Under the original assumptions of a 50% margin and a 11.5% cost of capital, the brand biologic breaks even after 34 years if the exclusivity period is seven years. Increase the cost of capital assumption to 13.7% and the brand would *never* recoup its investments, even if exclusivity were perpetual and FOB’s *never* entered. Note also that these large swings in the results occur even when one assumes the underlying cost and revenue estimates are measured without error. If one were to incorporate the large estimation errors that likely exist because of the small samples on which the estimates are based, the range of plausible results would only expand. A model that produces such vastly different results with small and reasonable changes in the underlying assumptions is unreliable as a basis for policy.

<sup>36</sup> Grabowski, *Updating Prior Analyses*.

## APPENDIX B

### I. FDA's Drug Approval Processes

The Food and Drug Administration (“FDA”) approves prescription drug medicines for marketing in the United States through two separate and distinct product approval pathways, depending on the drug’s method of manufacture. The first pathway applies to small molecule drugs and the second pathway applies to biologic drugs.

Small molecule drugs are manufactured by chemical synthesis. The FDA’s Center for Drug Evaluation and Research (“CDER”) approves small molecule drugs pursuant to the Federal Food, Drug, and Cosmetic Act (“FD&C Act”).<sup>1</sup> To obtain FDA approval, the small molecule drug manufacturer, or company sponsor, must complete the requirements of a full New Drug Application (“NDA”), including a showing of medical benefit over patient risk.<sup>2</sup>

Biologic products are derived from living matter (*e.g.*, purified from blood) or manufactured in living cells (*e.g.*, yeast, *e.coli*, or mammalian cells) using recombinant DNA biotechnologies.<sup>3</sup> The FDA’s Center for Biologics Evaluation and Research (“CBER”) approves biologic drugs for marketing pursuant to the Public Health Safety (PHS Act).<sup>4</sup> To obtain FDA approval, the company sponsor must complete the

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<sup>1</sup> 21 U.S.C.A. § 301 *et seq.* (2009).

<sup>2</sup> A full NDA is also known as a 505(b)(1) application, referring to FD&C Act § 505(b)(1). 21 U.S.C.A. § 355(b)(1) (2009).

<sup>3</sup> Although biologics must be approved through the BLA process, which center at the FDA performs the review is more complicated. CBER regulates allergenic extracts (*e.g.*, for allergy shots and tests), blood and blood components, gene therapy products, devices and test kits, human tissue and cellular products used in transplantation, and vaccines. The FDA transferred review of all recombinant proteins and monoclonal antibodies, except for hormones such as human growth hormone and insulin, to CBER. Then in 2003, the FDA transferred certain therapeutic biologic products from CBER to CDER. FDA, *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research available at <http://www.fda.gov/cber/transfer/transfer.htm>*. Accordingly, CDER regulates monoclonal antibodies designed as targeted therapies in cancer and other diseases, cytokines (types of proteins involved in immune response), growth factors (proteins that affect the growth of a cell), enzymes (types of proteins that speed up biochemical reactions), such as thrombolytics (used to dissolve blood clots), immunomodulators (agents that affect immune response). Additionally cell therapies and gene therapies are reviewed by the FDA’s Cellular, Tissue and Gene Therapies. 42 U.S.C.A. § 262 (2009).

<sup>4</sup> FDA's broad regulatory authority over biologic issues, including approval of biologic drug products resides in the PHS Act. The PHS Act also provides the FDA with the authority to: (a) protect the public against threats of emerging infectious diseases, (b) to promote the safe and appropriate use of biological products, (c) inspect manufacturing facilities of biologics before product approval is granted, and thereafter, on a regular basis, (d) monitor the safety of biological products after they are marketed (e) suspend biologic licenses where there exists a danger to public health, (f) prepare or procure products in the event of shortages and critical public health needs, and (g) prevent the introduction or spread of communicable diseases within the country. FDA, *Frequently Asked Questions About Therapeutic Biological Products, available at <http://www.fda.gov/cder/biologics/qa.htm>*.

requirements of a Biologics License Application (BLA). The FD&C Act also regulates biologic products because most biologic products also meet the FD&C Act's definition of "drugs".<sup>5</sup>

The small molecule and biologic pathways have one main difference: the FDA may approve generic small molecule drugs using an abbreviated pathway, but no abbreviated process exists for follow-on biologic drugs.

### **A. New Drug Approvals**

Although new small-molecule drug applicants file an NDA and new biologic drug applicants file a BLA, the development and regulatory approval process is similar for both categories.<sup>6</sup> For example, both small molecule and biologic drug applicants must establish medical benefit over patient risk.<sup>7</sup> The applicant, or company sponsor, also must prove the product is safe and effective. To do so, the applicant submits an NDA or BLA that contains the following information: (a) preclinical analytical tests, preclinical studies, and formulation studies; (c) an Investigational New Drug Application ("IND") to initiate human clinical testing; (d) adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for its intended use; (e) approval and validation of manufacturing facilities used in production of the pharmaceutical product; (f) drug manufacture and analytical methods; and (g) proposed product packaging and labeling.<sup>8</sup>

The preclinical phase of any new drug development typically begins with assays and large scale screening of compounds against targets of interest. Once a lead

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<sup>5</sup> FD&C Act defines "drug" as "(B) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C.A. § 321(g)(1) (2009). For historic reasons, recombinant human insulin and recombinant human growth hormone ("HGH") were approved under section 505 of the FD&C Act, not under the PHS Act. *See* FDA, *FDA 101: Biological Products*, available at <http://www.fda.gov/-consumer/updates-/biologics062608.html>; *see generally*, FDA's Center for Biologic Drug Evaluation ("CBER") webpage, available at <http://www.fda.gov/cber/about.htm>.

<sup>6</sup> *See* FDA's Center for Drug Evaluation and Research ("CDER") webpage, available at <http://www.fda.gov/cder/biologics/qa.htm>; *see also* FDA, *The New Drug Development Process: Steps from Test Tube to New Drug Application Review*, available at <http://www.fda.gov/cder/handbook/develop.htm>.

<sup>7</sup> Behrman at 17, 19 ("the [FDA's] review of any application, be it drug, be it a biological product, makes an assessment of what is in the best interest of the public given the available information. There will always be uncertainty. There is uncertainty about the simplest small molecule drugs."); *see id* ("Although medical products are required to be safe, safety does not mean zero risk, since all medical products are associated with some level of risk. A safe biological product is one that has reasonable risks, given the patient's condition, the magnitude of the benefit expected, and the alternatives available. The choice to use a biological product involves balancing the benefits to be gained with the potential risks.").

<sup>8</sup> *See* 42 U.S.C.A. § 262; 21 U.S.C.A. § 321 *et seq.*; and 21 C.F.R. 601.2.



compound is isolated, preclinical safety trials are conducted, as well as trials in predictive animal models. This preclinical phase typically takes one to five years.<sup>9</sup> After preclinical tests are completed, a drug sponsor submits the results in an IND to the FDA for approval before human clinical trials begin.

Human clinical trials typically consist of three phases. In Phase I clinical trials, a small group of healthy human patients are given the drug to determine if the drug is safe in humans.<sup>10</sup> In Phase II clinical trials, a small sample of the intended patient population are given doses of the drug to provide a preliminary assessment of the efficacy of the drug for a specific clinical indication, find dose tolerance, and determine the optimal dose range. Safety data also is collected in Phase II as it is in all phases of drug testing.<sup>11</sup> Phase III studies are initiated if Phase I and Phase II studies indicate the drug is safe, and has some efficacy in the targeted patient population. Phase III clinical trials are designed to gather sufficient data in a broad target population in order to establish safety and efficacy for a particular indication.<sup>12</sup>

The time needed to conduct these trials varies based on factors such as indication, availability of reliable biomarkers to measure efficacy, patient size, and ease of patient accrual. Phase I trials generally take one to two years. Phase II trials, including a full dose ranging study take two to three years. Phase III trials are the longest, taking approximately three to five years. Time variability, however, is significant as efficacy burdens vary. For example, it takes less time to collect the data using an accepted biomarker, such as blood cell levels, to measure efficacy of a treatment than it does for to collect data measuring disease free progression, mortality and morbidity data. Drug products also are subject to marketing exclusivities, described in more detail below.

## **B. Abbreviated Drug Approvals for Follow-on and Generic Products**

Prior to 1984, no process existed for abbreviated approval of generic small-molecule drugs. Generic versions of drugs approved after 1962 could only be approved pursuant to either a full New Drug Application or a “paper NDA” application under Section 505(b)(2) of the FD&C Act.<sup>13</sup> As a result, few companies developed generic drugs because of the high cost to perform the required clinical trials.<sup>14</sup>

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<sup>9</sup> See e.g., Ernst Berndt, *et al*, *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA*, NBER Working Paper No. W11425, (June 2005), available at <http://ssrn.com/abstract=745818>.

<sup>10</sup> See 21 C.F.R. §312.21(a) (2008).

<sup>11</sup> *Id.* §312.21(b).

<sup>12</sup> *Id.* §312.21(c).

<sup>13</sup> See H.R. Rep. 98-857(I), 1984 U.S.C.C.A.N. 2647; Letter from Janet Woodcock, Director, CDER, FDA to Petitioners (October 14, 2003) at 6, available at <http://www.fda.gov/ohrms/DOCKETS/dailys/03/oct03/102403/03p-0408-pdn0001.pdf> [hereinafter “FDA’s First Response to Omnitrope CPs”]. Generic drugs applications of drugs approved pre-1962 were approved

In 1984, Congress enacted the Hatch-Waxman Amendments to the FD&C Act (“Hatch-Waxman”) which established an abbreviated regulatory pathway to approve generic drug versions of drugs approved under that act. Hatch-Waxman provided the FDA with discretionary authority to not require generic applicants duplicate the safety and efficacy trials of the reference drug. Rather the Hatch-Waxman Act authorized the FDA to rely on its prior findings of safety and efficacy of previously approved drug products when the agency later reviewed the generic drug’s application.<sup>15</sup> The Hatch-Waxman Act reflected Congress’ attempt to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs.”<sup>16</sup>

### 1. The Section 505(b)(2) “Paper NDA” Pathway

The 505(b)(2) or “paper NDA” pathway is a partially-abbreviated pathway for drugs that are similar to, but not copies of, a reference small-molecule drug. This pathway pre-existed the Hatch-Waxman Act. A 505(b)(2) applicant relies on one or more safety or efficacy investigations that were not conducted by the 505(b)(2) applicant, and for which the 505(b)(2) applicant has not obtained a right of reference, *e.g.*, reliance on results in the published literature. This pathway is especially useful for new dosage forms, strengths, rates of administrations, dosing regimens and new indications.

The 505(b)(2) pathway permits the FDA to rely “to the greatest extent possible on what is already known about a drug” so as to avoid requiring drug sponsors to conduct and submit studies that “are not scientifically necessary.” FDA has stated that many of the drugs approved via the 505(b)(2) route would never have reached the market, or would have been significantly delayed, without this pathway.<sup>17</sup> Indeed, five significant FDA-identified harms could occur without the 505(b)(2) pathway: (1) diversion of industry resources that could otherwise be used to undertake innovative research; (2) increased drug costs; (3) strain on FDA review resources; (4) slowing of the process for drug approval with no corresponding benefit to the public health; and (5) significant ethical concerns raised by requiring duplicative studies that subject human beings and animals to medically and scientifically unjustified testing.<sup>18</sup>

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pursuant to the Drug Efficacy Study (“DESI”) program upon a showing that they were duplicates of the reference drug. The DESI system was obviated by Hatch-Waxman provisions.

<sup>14</sup> Post-1962 approved drugs whose patents had expired and were available for generic manufacturers, included five best selling drugs: Valium, Motrin, Inderal, Dyazide, and Lasix. *See* H.R. Rep. 98-857(I), 1984 U.S.C.C.A.N. 2647 at 2650; FDA’s First Response to Omnitrope CPs at 6.

<sup>15</sup> 21 U.S.C.A. § 355(j)(2)(A)(ii) – (iv) (2009).

<sup>16</sup> FDA’s First Response to Omnitrope CPs at 2 (citing *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), *Bristol-Myers Squibb Co. v. Royce Labs, Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995)).

<sup>17</sup> *Id.* at 4, citing approximately 80 drug approvals via the 505(b)(2) process.

<sup>18</sup> *Id.* at 3-4; H. REP. 98-857 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, at 2687 (“The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. FDA considers such retesting to be unnecessary and wasteful because the drug has already

## 2. The 505(j) ANDA Pathway

As discussed above, in 1984, Congress created an abbreviated pathway for approval of generic small-molecule drugs, this also is known as the 505(j) ANDA Pathway. Hatch-Waxman was designed to facilitate competition from lower-priced generic drugs, while maintaining incentives for pharmaceutical companies to invest in developing new drugs.<sup>19</sup> It also gave FDA discretionary authority to review an abbreviated new-drug application (“ANDA”) for generic small molecule drugs.<sup>20</sup> This “reflected Congress’ attempt to balance the need to encourage innovation with the desire to speed the availability of lower cost alternatives to approved drugs.”<sup>21</sup>

Under the Hatch-Waxman Act, a generic drug applicant only is required to show that its product includes the same active ingredient(s) and is bioequivalent to a reference drug, but it does not need to replicate the clinical trials and other testing of the reference product.<sup>22</sup> This process typically involves bioequivalency trials in healthy human volunteers, showing that a generic drug has the same levels of the same active pharmaceutical ingredient as the reference branded product. Because reference and ANDA drugs must have the same or similar API, dosage forms, strength, route of administration, labeling, quality, performance and intended use duplicate clinical trials are unnecessary. State substitution laws allow for the substitution of a bioequivalent generic product for the branded reference drug at the retail pharmacy without the doctor’s involvement.

## 3. Patent Restoration and Patent Listings for New Drug Products

Before Hatch-Waxman, 505(b)(2) applicants could not begin preclinical or clinical trials until after patents expired on the relevant branded product without risking infringement of the branded product’s patents. The risk of patent infringement coupled with the FDA generic approval process, in effect, extended the term of the branded company’s patent protection and delayed market entry by follow-on applicants’ versions of branded pharmaceutical drug products.<sup>23</sup> Hatch-Waxman limited the applicant’s

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been determined to be safe and effective. moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.”); Behrman at 24-25.

<sup>19</sup> The Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. § 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act”) and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, 21 U.S.C.A. § 355(j) and 35 U.S.C.A. § 271(e).

<sup>20</sup> 21 U.S.C.A. § 355(j) (2009). *See* 21 U.S.C.A. § 355(j)(2)(A)(ii)-(iv) (2009).

<sup>21</sup> FDA’s First Response to Omnitrope CPs at 2.

<sup>22</sup> 21 U.S.C.A. § 355(j)(2)(A)(ii) – (iv) (2009).

<sup>23</sup> *See* FTC GENERIC DRUG STUDY at 7. The “Bolar Amendment” passed as part of the Hatch-Waxman, reversed the Federal Circuit’s decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858

infringement liability so that it could begin the research, development, and manufacture of a drug product intended for FDA approval without infringing the branded product's patents.

Before 1984, branded pharmaceutical companies asserted that the effective terms of the patents covering their drugs were shortened due to the delays in the FDA approval process. To maintain incentives for branded drug product innovation in the face of generic competition, Congress included in the Hatch-Waxman Amendments patent restoration provisions that apply to drugs approved under both the FD&C Act and the PHS Act.<sup>24</sup> The extension period is calculated on the basis of length of time required to study and gain approval of the patented product. A maximum of five years can be restored to the patent. In all cases, the total patent life for the product with the patent extension cannot exceed 14 years from the product's approval date, or in other words, 14 years of potential marketing time. If the patent life of the product after approval has 14 or more years, the product would not be eligible for patent extension.<sup>25</sup>

Additionally, Hatch-Waxman provided operational provisions to encourage simultaneous running of the patent resolution process with any regulatory approval process, including marketing exclusivity periods.<sup>26</sup> To accomplish this, Hatch-Waxman amended the FDA's new drug approval process to require that the reference branded company list all of the reference drug's patents, and patent extensions.<sup>27</sup> Once these

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(Fed.Cir.1984), and provided that "[I]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention...solely for uses reasonably related to the development and submission of information [to support a market approval to the FDA]"; 35 U.S.C.A. § 271(e)(1); *Merck v. Integra*, 545 U.S. 193 (2005)(Section 271(e)(1) provides a wide berth for use of patented drugs in activities related to federal regulatory process, including uses reasonably related to the development and submission of any information to the FDA); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (It is not an act of infringement to use or import into the United States patented invention solely for uses reasonably related to the development and submission of information to the FDA for product approvals).

<sup>24</sup> See H. REP. 98-857 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647 at 2687; PhRMA, *Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong and Predictable Intellectual Property Rights*, (April 22, 2002); FTC Generic Drug Study at 7.

<sup>25</sup> See 35 U.S.C.A. § 156. See also FDA CDER, *Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program*, available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069959.htm>.

<sup>26</sup> FDA's First Response to Omnitrope CPs at 6.

<sup>27</sup> Section 505 of the Hatch-Waxman Amendments requires an NDA applicant, including some 505(b)(2) applicants, to submit to the FDA (for publication in the Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") the identifying all US patents that claim the drug substance, methods of formulating, composition of matter, and of method of using the drug and which could be infringed.

patents are listed in the Orange Book it is incumbent upon the follow-on applicants to certify how these patents relate to its drug product.<sup>28</sup>

If an ANDA or 505(b)(2) NDA applicant certifies that a referenced drug patent information has not been filed in the Orange Book, or that such patent has expired, then the FDA may approve the application immediately, provided other requirements are met.<sup>29</sup> If the applicant certifies that it will not launch its product until after the referenced product's patents expire, the FDA may approve the application effective on the date the patent expires.<sup>30</sup> However, if an applicant makes a certification under Paragraph IV, Hatch-Waxman requires that the applicant to also provide notice to both the patent holder and the NDA filer.<sup>31</sup> Once the ANDA filer has provided such notice, a patent holder (usually the referenced branded company) must bring an infringement suit within 45 days to trigger the 30-month stay of FDA approval of the application. Hatch-Waxman provides a 30-month stay of FDA approval with a detailed statement of the factual and legal basis for the applicant's assertion that the patent is invalid or not infringed. If suit is not filed by that date, the FDA may approve the application. If patent infringement litigation is initiated by the branded product company within the 45-day period, then the FDA approval of the application is stayed until the earliest of: (1) the date the patent(s) expire; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of the 30 months from receipt of notice of the paragraph IV certification.<sup>32</sup>

#### **4. Marketing Exclusivities**

Under the Hatch-Waxman Act, FDA enforces five types of exclusivity: (1) new chemical entity – five years; (2) new clinical investigation – three years; (3) orphan drug – seven years; (4) pediatric – six months; and (5) ANDA patent challenge exclusivity –

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<sup>28</sup> Both 505(b)(2) and 505(j) applicants must certify to each reference listed patents when they file their drug applications, stating either that: (1) under Paragraph I that such patent information has not been filed; or (2) under Paragraph II that such patent has expired; or (3) under Paragraph III the date on which such patent will expire, or (4) under Paragraph IV such patent is invalid or will not be infringed by the new drug . No ANDA or 505(b)(2) NDA will be approved by the FDA until all the listed Orange Book patents on the reference drug have expired, or have been successfully challenged by an applicant, or any applicable 30-month stay has expired. 21 C.F.R. 314.107; 21 U.S.C.A. § 355(j)(7)(A); 21 U.S.C.A. § 355(j)(2)(A)(vii); 21 U.S.C.A. § 355(j)(2)(A)(vii)(IV); *see also* H. REP. 98-857 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647 at 2655 (“the committee recognizes that in some instances an applicant will have to make multiple certifications with respect to product or controlling use patents. For example, if the product patent has expired and a valid controlling use patent will not expire for three years, then the applicant must certify that one patent has expired and the other will expire in three years.”).

<sup>29</sup> These are often referred to as Paragraph I and II certifications. 21 U.S.C.A. § 355(j)(5)(B)(i)-(ii); 21 U.S.C.A. § 355(b)(2)(A)(i)-(ii).

<sup>30</sup> 21 U.S.C.A. § 355 (j)(5)(B)(iii).

<sup>31</sup> 21 U.S.C.A. § 355(j)(2)(B).

<sup>32</sup> 21 U.S.C.A. § 355(j)(5)(B)(iii).

180 days. The first four apply only to New Drug Application (“NDA”) filers. The fifth applies only to Abbreviated New Drug Application (“ANDA”), *i.e.* generic, filers. The Orange Book lists all exclusivities granted to each approved-drug product.

New chemical entity (NCE) exclusivity provides five years of exclusivity, from the date of approval of the first NDA, for new drug applications containing new chemical entities never previously approved by FDA, either alone, or in combination.<sup>33</sup> An NCE is a drug that contains “no active moiety previously approved by the FDA.”<sup>34</sup> No ANDA or 505(b)(2) application may be submitted during the five-year NCE period, except that such applications may be submitted after four years if they contain a certification of patent invalidity or non-infringement (*i.e.*, paragraph IV certifications).

NCE exclusivity is the only exclusivity that bars the FDA from even accepting applications for review (as opposed to allowing the submission and review of such applications and simply delaying FDA approval). The five-year exclusivity period does not bar the FDA from accepting another full competitor NDA if the sponsor of the second application has done all of the work itself. As a practical matter, NCE exclusivity delays competition for more than five (or four) years because, once the application has been submitted, it typically takes the FDA at least an additional year to review and approve the ANDA.

New clinical investigation (NCI) exclusivity grants three years of exclusivity for certain changes to a drug product.<sup>35</sup> It prohibits FDA from approving an application for the same product for three years.<sup>36</sup> This exclusivity begins at the approval of the product, and is limited to the changes in the product supported by the new clinical studies. To obtain NCI exclusivity, the application or supplement must contain reports of new clinical investigations conducted by the sponsor. Several requirements apply, including that the study be clinical (*i.e.*, in humans, not animals), that it be new (and generally not

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<sup>33</sup> A “new chemical entity” or “NCE” is a drug that contains no active ingredient (including any ester or salt thereof) previously approved under section 505(b); 21 U.S.C.A. § 355, FD&C Act § 505 (c)(3)(D)(ii)-(iv), § 505(j)(5)(D)(ii)-(iv). The 5 year exclusivity provision of the Hatch-Waxman Act applies only to drug products approved under section 505(b) of the FD&C Act and not biologics. *See* FD&C Act. § 505(c)(3)(E)(ii).

<sup>34</sup> 21 C.F.R. § 314.08(a) (2008). An active moiety is “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule responsible for the physiological or pharmacological action of the drug substance.” *Id.* CDER makes NCE exclusivity determinations on all relevant applications. CDER reviews all relevant applications, with or without a request from the applicant, for an exclusivity determination. There is no requirement to apply.

<sup>35</sup> 21 C.F.R. § 314.108(b)(4)-(5).

<sup>36</sup> Unlike the five-year exclusivity for NCE, which bars submission of an application, the three-year exclusivity bars approval of an application, so that the agency can accept an application and review it during this time period. Like NCE exclusivity, new clinical investigation exclusivity will not bar approval of a full NDA where the applicant has done the work to support the same change for a drug product.

used for another drug approval purpose), and that it be essential to approval (*i.e.*, not merely interesting and useful).

Seven years of exclusivity also is available for Orphan drugs (*i.e.* drugs that treat a patient population with a target population less than 200,000).<sup>37</sup> The Orphan Drug Act of 1983 established an exclusivity period designed to provide an incentive to pharmaceutical manufacturers to develop drugs to treat rare diseases or conditions affecting relatively small numbers of persons. An orphan drug is defined as one treating a disease or condition which affects less than 200,000 persons in the United States or affects more than 200,000 persons but for which there is "no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

Obtaining orphan drug status is a two-step process. First, the applicant must apply for, and receive, orphan-drug designation from the Office of Orphan Products Development at the FDA. Orphan designation qualifies the sponsor of the product for the tax credit and marketing incentives of the Act in exchange for developing the drug for a rare disease or condition. Second, like any other new drug, the orphan-designated drug must submit its full NDA for safety and efficacy review.

If the NDA is approved for the indication for which the orphan designation was granted, the developer of an orphan product receives seven years of market exclusivity following the approval of the product by the FDA. Orphan drug exclusivity protects the drug for the approved orphan indication against all other competitors. Unlike other exclusivities, orphan exclusivity protects the orphan drug even from a second full NDA for the same indication submitted by another applicant. Exclusivity applies only to the indication for which the drug has been designated and approved, however, so that a second application for the same drug for a different use could be approved by the FDA.

Any small molecule or biologic drug product can also obtain an additional six months of marketing exclusivity for demonstrating the safety, dosing and efficacy of the product in children.<sup>38</sup> Congress provided for a six-month pediatric exclusivity period in response to a perceived need for an incentive to encourage companies to complete and submit studies on the pediatric uses of drugs. Pediatric exclusivity attaches to all the applicant's formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contains the same active moiety.

This is a broad grant because it attaches not only to the specific product that was studied in the pediatric population, but to all drug products (formulations, dosage forms, and indications) with the same active moiety. To balance this broad grant of exclusivity, the FDA requires pediatric studies of all drugs that contain the active moiety. This does

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<sup>37</sup> 21 U.S.C.A. § 360aa-dd.

<sup>38</sup> 21 U.S.C.A. § 355a. The FDA grant of 6 months exclusivity is added to any existing marketing exclusivity or patent protection. This exclusivity incentivizes firms to conduct pediatric drug studies.

not mean that a sponsor must show that the drug is safe or effective in the pediatric population to obtain pediatric exclusivity. Instead, the goal simply is to develop a maximum amount of pediatric information as a result of the grant of exclusivity. Pediatric exclusivity may therefore be granted upon acceptance of the pediatric study reports.

Pediatric exclusivity is unique because it attaches to the end of all existing marketing exclusivity and patent periods. This distinguishes it from other types of exclusivity and patent periods, which run concurrently. For example, if a drug sponsor has five-year NCE exclusivity (which is valuable because it bars competitors from even submitting applications to the FDA); the six-month pediatric exclusivity will provide six additional months of NCE exclusivity. If the drug sponsor has three years of new clinical investigation exclusivity, which bars the FDA from approving a competing application, the six-month pediatric exclusivity will provide six additional months of the same protection. If the drug sponsor has a patent, FDA-enforced exclusivity will be added at the end of the patent term.

The Hatch-Waxman Act grants 180 days of marketing exclusivity to certain generic drug applications. The statute provides an incentive of 180 days of market exclusivity to the “first” generic applicant who challenges a listed patent by filing a paragraph IV certification and therefore runs the risk of having to defend a patent infringement suit. As a practical matter, if multiple ANDA filers file paragraph IV certifications on the same day and all are found acceptable for filing, multiple applicants may share the 180-day exclusivity. The statute provides that the first application to file a substantially complete ANDA containing a paragraph IV certification to a listed patent will be eligible for a 180-day period of exclusivity beginning either from the date it begins commercial marketing of the generic drug product, or from the date of a court decision finding the patent invalid, unenforceable or not infringed, whichever is first. These two events – first commercial marketing and a court decision favorable to the generic – are often called “triggering” events, because under the statute they can trigger the beginning of the 180-day exclusivity period. Approval of the ANDA alone has no effect on triggering the 180-day patent exclusivity period.

If there is no court decision, and the first applicant does not begin commercial marketing of the generic drug, there may be prolonged or indefinite delays in the beginning of the first applicant’s 180-day exclusivity period. Until an eligible ANDA applicant’s 180-day exclusivity period has expired, the FDA cannot approve subsequently submitted ANDAs for the same drug, even if the later ANDAs are otherwise ready for approval and the sponsors are willing to immediately begin marketing. Therefore, as a practical matter, an ANDA applicant who is eligible for exclusivity is often in the position to delay all generic competition for the branded drug.

In 2003, the Medicare Modernization Act amended the Hatch Waxman Act, to provide an 180-day market exclusivity period to the first generic company that seeks FDA approval to market at product prior to the expiration of certain patents relating the branded drug product. No other generic manufacturer may obtain FDA approval to



market its product until the first generic applicant has sold its product for 180 days, unless the later generic applicant wins a patent challenge against the branded company.<sup>39</sup>

The Hatch-Waxman Act also provides marketing exclusivity incentives to any NDA holder based on the level of innovation represented by the drug product. Any “new chemical entity” receives five years of marketing exclusivity. During this five-year period, the FDA may not review any 505(b)(2) or 505(j) applications that reference this new chemical entity. However, if an ANDA files a paragraph II certification against this NCE, exclusivity is limited to four years.<sup>40</sup> The FDA may not approve this application until after seven and one half years or patent litigation is resolved.<sup>41</sup>

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<sup>39</sup> There are provisions for a generic company to forfeit the exclusivity period, which occur in limited circumstances.

<sup>40</sup> 21 U.S.C.A. §355(c)(3)(E)(iii); 21 U.S.C.A. §355(j)(5)(F)(iii).

<sup>41</sup> 21 U.S.C.A. § 355(j)(5)(F).

**APPENDIX C**  
**PUBLIC COMMENTS**  
**FTC ROUNDTABLE ON COMPETITION ISSUES INVOLVING**  
**FOLLOW-ON BIOLOGIC DRUGS**  
**NOVEMBER 21, 2008**

NAME	TITLE OF COMMENT
<b>American Association of Retired Persons</b> (David P. Sloane)	12/22/2008
<b>American Enterprise Institute</b> (John E. Calfee)	12/10/2008 • <i>When Patents Are Not Enough: Data Exclusivity for Follow-On Biologics</i>
<b>Amgen, Inc.</b> (David W. Beier)	9/30/2008
<b>Barr Pharmaceuticals, Inc.</b> (Bruce L. Downey)	9/30/2008
<b>Barr Pharmaceuticals, Inc.</b> (Bruce L. Downey)	12/19/2008
<b>Bayer HealthCare LLC</b> (Sandra S. Oliver)	10/2/2008
<b>Bernstein Research</b> (Ronny Gal)	12/9/2008 • <i>Eight Thoughts on Biosimilars</i>
<b>Biotechnology Industry Organization</b> (John M. Taylor, III)	9/30/2008
<b>Biotechnology Industry Organization</b> (John M. Taylor, III)	12/22/2008
<b>Biotechnology Industry Organization</b> (Sandra J. P. Dennis)	2/24/2009

NAME	TITLE OF COMMENT
<b>Biotechnology Industry Organization</b> (Sandra J. P. Dennis)	2/24/2009 • <i>Unpatentable Drugs and the Standards of Patentability, Benjamin N. Roin, (May 1, 2008)</i>
<b>Biotechnology Industry Organization</b> (Sandra J. P. Dennis)	2/24/2009 • <i>Biosimilars, Data Exclusivity, and the Incentives for Innovation: A Critique of Kotlikoff's White Paper, Henry C. Grabowski and Joseph DiMasi, (February 2009)</i>
<b>Biotechnology Industry Organization</b> (Sandra J. P. Dennis)	2/24/2009 • <i>Data Exclusivity Period Length and Federal Government Savings from Enactment of the Biologics Price Competition and Innovation Act of 2007, Joseph Golec, John A. Vernon, and Ted Buckley, (January 28, 2009)</i>
<b>Coalition for a Competitive Pharmaceutical Market</b> (Annette Guarisco)	9/30/2008
<b>CVS Caremark Corporation</b> (David Golding)	12/22/2008
<b>Duke University</b> (Henry C. Grabowski)	12/22/2008
<b>Duke University</b> (Henry C. Grabowski)	12/23/2008 • <i>Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques, (December 22, 2008)</i>
<b>Duncan Bucknell Company</b> (Duncan Bucknell)	1/9/2009
<b>Eli Lilly and Company</b> (Douglas K. Norman)	12/19/2008
<b>Essential Action</b> (Sarah Rimmington)	12/20/2008
<b>Generic Pharmaceutical Association</b> (Lisa K. Layman)	9/30/2008

NAME	TITLE OF COMMENT
<b>Hospira, Inc.</b>	5/19/2009
<b>Hospira, Inc.</b> (Lori N. Bowman)	9/30/2008
<b>Hospira, Inc.</b> (Lori N. Bowman)	12/22/2008
<b>Johnson &amp; Johnson, Inc.</b>	3/17/2009 • <i>Executive Summary, Achieving the Right Balance between Innovation and Competition: The Role of Data Exclusivity</i>
<b>Johnson &amp; Johnson, Inc.</b>	3/17/2009 • <i>Achieving the Right Balance between Innovation and Competition: The Role of Data Exclusivity</i>
<b>Matrix Global Advisors, LLC</b> (Alex M. Brill)	12/22/2008
<b>Momenta Pharmaceuticals, Inc.</b> (Bruce A. Leicher)	9/30/2008
<b>Momenta Pharmaceuticals, Inc.</b> (Bruce A. Leicher)	12/22/2008
<b>Mylan, Inc.</b> (David Rice)	1/5/2009
<b>Novartis Corporation</b> (Robert E. Pelzer)	9/29/2008
<b>Novartis Corporation</b> (Robert E. Pelzer)	12/22/2008
<b>Office of Health Economics</b> (Adrian Towse)	12/31/2008
<b>Pharmaceutical Care Management Association</b> (Missy Jenkins)	9/26/2008

<b>NAME</b>	<b>TITLE OF COMMENT</b>
<b>Pharmaceutical Research and Manufacturers of America</b> (Billy Tauzin)	9/30/2008
<b>Pharmaceutical Research and Manufacturers of America</b> (Billy Tauzin)	12/22/2008
<b>Robert J. Reinhart</b>	10/19/2008
<b>Talecris Biotherapeutics</b> (Bruce Bunyan)	9/30/2008
<b>Teva Pharmaceuticals USA</b> (David T. Sanders)	10/8/2008
<b>Willkie Farr &amp; Gallagher LLP on behalf of Hospira, Inc.</b> (Kelsey I. Nix)	12/22/2008
<b>Winston &amp; Strawn LLP</b> (James F. Hurst,.)	12/22/2008
<b>Wyeth</b> (Matthew D. Eyles)	9/30/2008
<b>Wyeth</b> (Matthew D. Eyles)	12/18/2008
<b>Zuckerman Spaeder LLP</b> (William B. Schultz)	12/22/2008

**Primary Source:** <http://ftc.gov/os/comments/healthcarecompissues/index.shtm>

**APPENDIX D:**  
**PARTICIPANTS AT FTC ROUNDTABLE,**  
**NOVEMBER 21, 2008**

<b>NAME</b>	<b>AFFILIATION</b>
Alexis <b>Ahlstrom</b>	Avalere Health LLC
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Rachel E. <b>Behrman</b>	U.S. Food and Drug Administration
Alex M. <b>Brill</b>	American Enterprise Institute; Buchanan, Ingersoll & Rooney PC
Steven B. <b>Brugger</b>	Momenta Pharmaceuticals, Inc.
Edward <b>Buckley</b>	Biotechnology Industry Organization
Kenneth J. <b>Dow</b>	Johnson & Johnson, Inc.
Suzanne B. <b>Drennon</b>	Federal Trade Commission
Christopher J. <b>Garmon</b>	Federal Trade Commission
David <b>Golding</b>	CVS Caremark Corporation
Ken <b>Goldman</b>	Novartis Corporation
Mark A. <b>Goshko</b>	Teva Pharmaceutical Industries Ltd.
Henry C. <b>Grabowski</b>	Duke University
Pamela Jones <b>Harbour</b>	Federal Trade Commission
Paul <b>Heldman</b>	Potomac Research Group
Linda R. <b>Horton</b>	Hogan & Hartson LLP

APPENDIX D

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John A. <b>Lane</b>	Hospira, Inc.
Bruce A. <b>Leicher</b>	Momenta Pharmaceuticals, Inc.
David A. <b>Manspeizer</b>	Wyeth
Suzanne T. <b>Michel</b>	Federal Trade Commission
Steven B. <b>Miller</b>	Express Scripts, Inc.
Douglas K. <b>Norman</b>	Eli Lilly and Company
Naomi <b>Pearce</b>	Hospira, Inc.
Audrey <b>Phillips</b>	Johnson & Johnson, Inc.
Hans <b>Sauer</b>	Biotechnology Industry Organization
William B. <b>Schultz</b>	Zuckerman Spaeder LLP
Rochelle K. <b>Seide</b>	Schwegman, Lundberg & Woessner PA
Christine J. <b>Siwik</b>	Rakoczy Molino Mazzochi Siwik LLP
Mateja <b>Urlep</b>	Novartis AG (Sandoz Ltd.)
Michael S. <b>Wroblewski</b>	Federal Trade Commission
Bryan C. <b>Zielinski</b>	Pfizer, Inc.

**Primary Source:** <http://ftc.gov/bc/workshops/hcbio/agenda/fobagenda.pdf>

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