



Federal Trade Commission

**THE COMPETITIVE IMPLICATIONS
OF GENERIC BIOLOGICS**

**Remarks of
Commissioner Pamela Jones Harbour**

**ABA Sections of Antitrust and Intellectual Property Law
Intellectual Property Antitrust:
Strategic Choices, Evolving Standards,
and Practical Solutions**

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I. INTRODUCTION

Good afternoon. Thank you for your kind introduction, and for inviting me to participate in this conference. It is my pleasure to join you today.

I have served as an FTC Commissioner for almost four years now. Throughout my term, I have devoted a great deal of attention to issues at the intersection of intellectual property and competition law. The Commission's unanimous *Rambus* liability decision,¹ issued last August under my authorship, is one particularly noteworthy example.

But I am not going to talk about standard-setting today. I will leave that discussion to tomorrow morning's panelists – other than to put in a shameless plug, before a captive audience, for my dissenting statement on remedy in *Rambus*. The statement is available on the Commission's website.²

When I accepted this invitation, I was determined to talk about something a little off the beaten path – something that would be thought-provoking for this highly skilled audience. I decided I would share what I have learned thus far about so-called “generic biologics” – also known as “follow-on” biologics, or FOBs. (As I will explain in a moment, the two terms are not necessarily interchangeable, but for now I will use them that way.) I believe you will be hearing even more about generic biologics in the future. And what you hear may have a lot of rhetoric

¹ In the matter of *Rambus Inc.*, FTC Dkt. No. 9302, Opinion of the Comm'n (Aug. 2, 2006), available at <http://www.ftc.gov/os/adjpro/d9302/060802commissionopinion.pdf>.

² In the matter of *Rambus Inc.*, FTC Dkt. No. 9302, Remedy Statement of Comm'r Pamela Jones Harbour, Concurring in Part and Dissenting in Part (Feb. 5, 2006), available at <http://www.ftc.gov/os/adjpro/d9302/070205harbourstmnt.pdf>.

attached to it, because different interest groups have strong – sometimes clashing – views on this topic.³

As an FTC Commissioner, I have two goals. I speak only for myself – not necessarily the Commission or any other Commissioners – but I will be up-front about my own agenda.

First, I want to ensure that the dialogue on generic biologics includes a principled and rigorous analysis of competition dynamics, especially from the perspective of consumers. I will sketch out a framework of key questions that should be considered. Even if you do not practice in the biotech sector, these big-picture questions are fascinating – especially because, ultimately, we and our loved ones will be affected as consumers of these drugs.

Second, I want to ensure that the Federal Trade Commission is an integral part of the dialogue on generic biologics. For years, the Commission has been intimately involved in shaping competition law and policy relating to generic drugs. The FTC’s expertise is unique and valuable. It should be tapped further, as generic biologics move to center stage in the drama of American healthcare.

³ Compare, e.g., Generic Pharmaceutical Association, *Biogenerics* (undated), available at http://www.gphaonline.org/AM/Template.cfm?Section=FDA_Science&TEMPLATE=/CM/HTMLDisplay.cfm&CONTENTID=1948 (“GPhA strongly supports . . . legislation that would establish the necessary, efficient, and effective abbreviated [approval] pathway for biogenerics Biogenerics would bring competition into the healthcare system, reduce costs and increase consumer access to affordable medicines.”); American Association of Retired Persons, News Release, *AARP Urges Congress to Act on Generic Biologics* (March 26, 2007), available at http://www.aarp.org/issues/advocacy/affordable_rx.html (“Safe, cost-effective generic biologics are a common sense alternative Science has progressed to the point where it is possible to create generic biologics and to do it safely.”); Barr Pharmaceuticals, Inc., Health Policy Issue Brief, *Generic Biologics – An Unmet Opportunity to Save Billions on American Healthcare* (undated), available at http://www.barrlabs.com/overview/government/BRL_pp-biologics.pdf (“[G]eneric competition for biotech pharmaceuticals has the potential to offer consumers dramatic and substantial savings, while also lowering America’s healthcare bill.”) with Biotechnology Industry Organization, News Release, *BIO Urges Congress to Prioritize Patient Safeway and Biomedical Innovation in Pathway for Follow-On Biologics* (May 2, 2007), available at http://bio.org/news/newsitem.asp?id=2007_0502_01 (“In order to ensure that new pioneer biotechnology products continue to reach patients and physicians, any pathway for the approval of follow-on biologics must protect patient safety and preserve incentives to innovate”); Pharmaceutical Research and Manufacturers of America, Press Release, *PhRMA Statement on Follow-On Biologics Legislation* (April 5, 2007), available at http://www.phrma.org/news_room/press_releases/phrma_statement_on_follow-on_biologics_legislation/ (“[W]e remain concerned that patient safety could be at significant risk if the current legislative follow-on biologics proposals move forward.”).

The Commission has a long history of working closely and cooperatively with the U.S. Department of Health and Human Services Food and Drug Administration (FDA), whose scientific expertise complements our competition expertise. Our agency also has an excellent relationship with legislators who focus on issues relating to drug costs. On behalf of consumers, I would like to see the Commission continue to foster all of these connections. Likewise, I hope that legislators and regulators will continue to seek the advice and knowledge of our talented FTC staff, as they try to solve the generic biologics puzzle.

II. BACKGROUND ON BIOLOGICS

Some background is necessary before I tee up the competition issues. I am going to begin exactly where I began, when I started to hear about issues relating to generic biologics. I asked the obvious question: what are biologics?

In simplest terms, biologics are drugs created from living cells, tissues, or organisms, through biologic processes. These drugs replicate natural biologic substances in our bodies, such as enzymes, antibodies, or hormones. Biologics are known as “large molecule” drugs, which means they typically are very complex in structure.

Many of today’s “miracle” drugs are biologics. These drugs are used to treat cancer, immune disorders, and metabolic diseases. They drastically reduce disabling symptoms, and sometimes even save lives.

Biologics require extremely sophisticated manufacturing techniques. Biologics manufacturers must program a living source to mass-produce a specific biological material. For example, scientists may use recombinant DNA technology to program instructions directly into

the DNA of a cell.⁴ The cell will produce the desired protein, which can be harvested and used as a therapeutic drug or a diagnostic product.

In contrast, traditional pharmaceutical drugs are “small molecule” compounds that are chemically synthesized, and usually consist of pure chemical substances. They are easier to manufacture, and they are also easier to analyze after they are manufactured.

A. The High Cost of Biologics

Not surprisingly, biologics are among the most expensive drug products.

- Sales of biologics were \$40.3 billion in 2006, which was about 15 percent of total U.S. prescription drug sales of nearly \$275 billion. The biologics market is growing much faster than the market for traditional pharmaceuticals. Sales of biologics increased 20 percent in 2006, compared to just over 8 percent growth for overall pharmaceutical sales.⁵
- According to figures from the Centers for Medicare and Medicaid Services (CMS), the top two anemia drugs, both biologics, accounted for 17 percent of all Medicare Part B carrier drug spending in 2005. Two other biologics – for rheumatoid arthritis and cancer – accounted for an additional 13 percent of all Medicare Part B carrier spending.
- CMS spends approximately \$2 billion per year on Epogen, a biologic for treating anemia. That is only one drug and one payor. (To put this in context, the FTC’s entire budget for FY 2007 is about a tenth of that, just over \$220 million.)
- Treatment with Avastin, a colon cancer drug, costs \$100,000 per year per patient.
- Treatment with Ceredase – a lifesaving drug used to treat Gaucher Disease, a rare genetic disorder – costs over \$300,000 per year per patient.⁶

⁴ Biologics may be produced by mammalian cells (frequently Chinese hamster ovarian cells), or from yeast or E. coli cells.

⁵ IMS Health Inc., Press Release, *IMS Reports U.S. Prescription Sales Jump 8.3 Percent in 2006, to \$274.9 Billion* (March 8, 2007), available at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_80415465,00.html.

⁶ *Safe and Affordable Biotech Drugs – The Need for a Generic Pathway: Hearing on H.R. 1038 Before the H. Comm. on Oversight and Gov’t Reform*, 110th Cong. (2007) [hereinafter House Oversight Hearing] (statement of Mary Nathan, Gaucher patient), available at

Biologics are expensive, in part, because they cost so much to develop and manufacture. But another major reason for their high cost is that, with very rare exceptions, there are no generic biologics available on the market in the United States.

III. WHY ARE THERE NO GENERIC BIOLOGICS?

So, that leads to the obvious next question: *why* are there no generic biologics in the United States?

There are a few different explanations. And to be honest, it is my perception that different constituencies spin these factors in different ways. But in attempting to untangle the issues and present them to you objectively, I have identified two interrelated categories of obstacles to market entry by generic biologics: scientific and regulatory.

A. The Science of Follow-On Biologics

On the scientific front, some argue that there can be no true “generic” version of a biologic drug.

In the realm of traditional pharmaceuticals, there is a basic assumption that a generic drug is both chemically and therapeutically equivalent to a pioneer or branded drug. I won’t say “identical” because it is possible that a generic drug might, for example, have different inactive ingredients. But with respect to a small-molecule pharmaceutical, it is relatively easy – for a chemist, at least – to compare a pioneer drug to a potential generic alternative, look at the chemical composition of the two drugs, and determine that they have the same active ingredient

at the same level of potency. It is also relatively easy to determine whether the generic drug enters the bloodstream and affects the human body in the same way as the pioneer drug.

When your doctor writes a prescription and does not check the box prohibiting generic substitution of a traditional pharmaceutical . . . and when the pharmacist fills your prescription with a generic alternative . . . and when you go home and take the generic drug every morning . . . everyone is relying on the same assumption: that the generic will be just as safe and effective as the branded version.

The same assumptions cannot necessarily be made when it comes to biologics. As the argument goes, it is impossible to exactly replicate a complex biological process, which is so dependent on specific manufacturing details. In some sense, the process *is* the product. And even slight changes in the manufacturing process – including minor changes in equipment or facilities – might affect the molecular composition of the biological product. The changes in the molecule might not be detectable by standard chemical or molecular biology characterization techniques. But these changes could profoundly alter the safety or efficacy profile of the drug.⁷ In particular, these changes may affect the immunogenicity profile of a biologic, meaning that they might alter the body’s immune response to the drug.⁸ In short, unless the manufacturing process is identical, some argue, one cannot guarantee that the output will be the same.

⁷ U.S. Food & Drug Admin., Center for Drug Evaluation & Research, *Frequently Asked Questions About Therapeutic Biological Products*, No. 9 (updated July 26, 2006), <http://www.fda.gov/cder/biologics/qa.htm>.

⁸ See, e.g., Xenia P. Kobylarz, *The Patent Killer*, IP LAW & BUS. (May 2007), available at <http://www.ipww.com/display.php/file=/texts/0507/barr> (Johnson & Johnson changed manufacturing process for an anemia drug; new formulation unexpectedly caused certain compounds to leach out of uncoated rubber stoppers used on drug vials, causing clumps to form in bloodstream and triggering an extreme form of anemia); House Oversight Hearing, supra note 6 (statement of Inger Mollerup, Vice President, Novo Nordisk A/S), available at <http://oversight.house.gov/documents/20070326122040-15085.pdf> (slight change in amino acid sequence in early version of fast-acting insulin analogue caused significantly increased incidence of tumor growth in rats during preclinical animal toxicological studies).

In addition, it may be difficult to identify the clinically active components of a complex, large-molecule biologic drug. For some of these drugs, scientists will tell you, “we know the drug works, but we really aren’t quite sure why.” That may make it tricky – if not impossible – to determine whether a follow-on drug is “bioequivalent” to a pioneer drug. At best, a follow-on biologic may be “biosimilar” to an existing biologic.

It is worth noting, however, that some biologics are less complex than others. And scientists seem to agree that, at least for some biologics, the technology does exist to identify safe and effective follow-ons, without having to completely replicate all of the clinical trials. I will return to this point later in my remarks.

B. Hatch-Waxman for Traditional Pharmaceuticals

_____ With that scientific primer in mind, let’s turn to the regulatory front, where it all comes down to one basic regulatory reality. The Hatch-Waxman pathway – which is commonly used by generic firms to obtain abbreviated approval of small-molecule drugs – cannot be used for most biologics.

I do not want to turn this into a speech about the Hatch-Waxman Act, because it has been the subject of much discussion at this conference and countless others over the years.⁹ But just in case anyone in this audience is unfamiliar with it, I will attempt to summarize Hatch-Waxman with very broad strokes.

When a drug company seeks FDA approval for a new, branded drug, it files a New Drug Application, or NDA. As part of the NDA process, the pioneer firm must conduct extensive

⁹ An excellent primer on the Hatch-Waxman regulatory scheme is included in Fed. Trade Comm’n, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002) [hereinafter *FTC Generic Drug Study*], at 3 *et seq.*, available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

human clinical trials, and submit all of those results to the FDA, to prove that the drug is safe and effective.

When a generic firm seeks approval of a generic alternative to an existing pharmaceutical drug, the generic firm does not need to start from scratch. Under the Hatch-Waxman regulatory scheme, the generic firm can submit an Abbreviated New Drug Application, or ANDA. The generic firm must establish that its drug is “pharmaceutically equivalent” – meaning that it uses the identical active ingredient, in the same amount and dosage form. The generic firm also must establish “bioequivalence” – which means the drug is absorbed into the bloodstream of healthy human volunteers at roughly the same rate and extent as the branded drug (within an 80 to 120 percent margin of equivalence).

If the generic firm can satisfy these requirements, the firm does not need to replicate all of the clinical studies that the branded firm submitted as part of its NDA. For example, the generic may not need to conduct two-year toxicity tests in animals, or lengthy Phase One, Two, and Three clinical tests to prove safety and efficacy. In effect, the generic firm gets to ride on the coattails of the branded firm, relying on the safety and efficacy data generated by the branded firm. This dramatically reduces the research and development costs for generic firms, which is a major reason why they are able to charge so much less for their generic products. In addition to speeding the availability of lower-cost alternatives, the ANDA process also avoids duplicative, unnecessary human testing, which potentially addresses ethical as well as financial challenges.

At the heart of Hatch-Waxman is a *quid pro quo* that balances the interests and incentives of branded and generic firms, especially with respect to research and development (R&D) and innovation. When the branded firm files an NDA, it must also list with the FDA all patents that cover the new drug. This listing of “Approved Drug Products with Therapeutic Equivalence

Evaluations” is known as the FDA Orange Book. When a generic firm files an ANDA that references an existing NDA, the generic firm must certify that any of the patents listed in the Orange Book pursuant to the original NDA are either invalid, or are not infringed, by the generic drug.

Hatch-Waxman provides certain incentives to the first ANDA filer, to encourage generic firms to challenge weak patents via patent infringement lawsuits. Notably, the first ANDA filer gets 180 days of marketing exclusivity once it successfully challenges the patents and its product is approved and marketed, meaning that no other generic can enter during that time.

Likewise, in order to preserve R&D incentives for the branded firms, Hatch-Waxman gives the branded firm a 30-month cushion after an ANDA is filed and patent litigation ensues. During that time, no generic entry is allowed.

C. No Regulatory Pathway for Follow-On Biologics

So there is my whirlwind summary of Hatch-Waxman. For our purposes today, the important thing to realize is: there is no comparable regulatory scheme for biologics.

Whole law review articles have been written on this topic, and there are many different interpretations of how the regulations play out, in terms of the scope of FDA authorization and the original legislative intent. If you are interested, I encourage you to consult these other sources for more details.¹⁰

¹⁰ See, e.g., Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD DRUG L.J. 77 (2007); Nawel Bailey & Nathaniel Lipkus, *Follow-On Biopharmaceuticals: A New Frontier in the Battle Between Brand and Generic*, ANTITRUST HEALTH CARE CHRONICLE, March 2007, Vol. 20, No. 4, at 11 (publication of the Health Care & Pharmaceuticals Committee, Antitrust Section, American Bar Association); David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD DRUG L.J. 143 (2005).

But in a nutshell, for historical reasons, the FDA approves biologics under a different set of regulations. While the Food, Drug, and Cosmetics Act applies to traditional pharmaceuticals, biologics also are subject to the Public Health Service Act. Biologics are approved pursuant to a Biologics Licensing Application, or BLA, instead of an NDA.

If a product has been approved as a “biologic” rather than a “drug” under FDA regulations – in other words, if it derives from a BLA instead of an NDA, which is the case for most biologics – any follow-on product is ineligible for approval under Hatch-Waxman. And currently, there is no Hatch-Waxman-like process that applies to BLAs.

D. A Few Other Observations on the Intersection of Science and Regulation

Now, to further complicate matters before I talk specifically about competition issues, let me make three observations on the interesting interplay between the science and regulation of biologics.

1. Existing Regulations Tolerate Manufacturing Changes

First, the approval of a BLA involves strict FDA oversight of the sourcing, manufacturing, and packaging process, to ensure that different lots of the same biologic are equally safe, pure, and effective. But, importantly, there is some degree of tolerance for variations among batches, as long as the lots are “consistently acceptable” and the manufacturing process is carefully monitored to assure predictable outcomes.¹¹

¹¹ A comparability “bridging study” often is used when manufacturing changes occur, but the product is still manufactured using the same (or very similar) master cell banks and the same (or very similar) upstream and downstream processes. For example, the location of manufacture may change, or a firm entering commercial production may scale up its production from a small bioreactor to a larger one. In order to establish comparability, the producer must be able to demonstrate that any changes in the manufacturing process will not adversely impact the drug’s quality, safety, and efficacy. See U.S. Dep’t of Health & Human Servs, Food & Drug Admin., Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research, *Guidance for Industry: Q5E*

Recall the “science” factors I discussed earlier, where I highlighted the “process is the product” argument against generic biologics. But others might argue that the existing BLA scheme itself demonstrates that it is possible to strike an appropriate balance between the high costs of biologics, the idiosyncrasies of biologics manufacture, and the safety of consumers. After all, even batches of the “same” biologic are not expected to be identical. To quote a policy piece by Barr Pharmaceuticals, one of the major generic firms:

The science to create affordable generic biotech drugs exists today. . . . It is being done every time a brand manufacturer changes a manufacturing process or location and uses comparability to ensure the biotech drug will provide the same safety and efficacy. . . . [B]iotech firms routinely justify process and site changes via comparability studies. For example, if an innovator biotech company seeks changes in processes supporting the manufacture of their products, or seeks to change the manufacturing location of a product, comparability is the process by which the amended product is judged to provide the same clinical effect and safety profile.¹²

Given this existing compromise with respect to branded biologics, the “process is the product” argument against generic biologics loses some force.

2. NDA vs. BLA Loophole

Second, for reasons I won’t get into today, some older biologics actually *were* approved under the traditional “drug” pathway, pursuant to NDAs. Insulin and human growth hormone are oft-cited examples. In fact, Omnitrope, a follow-on version of a human growth hormone, was approved under Hatch-Waxman in May 2006;¹³ the same drug previously had been approved as a

Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (June 2005), available at <http://www.fda.gov/cber/gdlns/ichcompbio.pdf>.

¹² Barr, Health Policy Issue Brief, *supra* note 3, at 2.

¹³ Omnitrope’s eventual approval was preceded by a long and complicated legal history. Sandoz’s 2003 application for the approval of Omnitrope languished at the FDA for years because the FDA claimed it did not have the authority to approve follow-on biologics. Sandoz eventually brought a declaratory judgment action in federal district court. The court agreed that the FDA needed to make a timely decision, and granted Sandoz’s motion

“biosimilar” in Europe.¹⁴ Follow-on insulin and human growth hormone products are in development, and some of them already have been marketed in other countries.¹⁵

Granted, these two types of drugs are relatively simple in structure, so it may be somewhat easier to analyze and approve follow-on products. But proponents of generic biologics argue that, given the current state of the science, it would be equally possible to analyze and characterize follow-ons of more complex biologics, without requiring full duplication of clinical trials. If true, there is no clear scientific reason to allow generic entry under NDAs but categorically prohibit it under BLAs.

for summary judgment. *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006). See also U.S. Dep’t of Health & Human Servs, Food & Drug Admin., Center for Drug Evaluation & Research, *Omnitrope (somatropin [rDNA origin]) Questions and Answers* (May 30, 2006), <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>:

[Question] Does today’s approval of Omnitrope create a new pathway for follow-on versions of all protein products? [Answer] No. The approval of Omnitrope in a 505(b)(2) application does not establish a pathway for approval of follow-on products for biological products licensed under section 351 of the Public Health Service Act, nor does it mean that more complex and/or less well understood proteins approved as drugs under the Food, Drug, and Cosmetic Act could be approved as follow-on products.

But see Generic Pharmaceutical Association, Press Release, *GPhA Hails Omnitrope Approval As Significant First Step in Opening Door to Biopharmaceutical Savings for U.S. Consumers, Says Decision Demonstrates that Pathway Exists for Approvals* (May 31, 2006), available at http://www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=2535 (quoting Kathleen Jaeger, GPhA President and Chief Executive Officer):

The approval of this product represents a significant first step toward opening the door for billions of dollars in potential savings on biopharmaceutical products for American consumers It demonstrates that generic companies can develop safe and effective biopharmaceutical products. It demonstrates that FDA already has the authority to approve such products. And it brings our nation one step closer to the day when generic versions of expensive biopharmaceuticals will be readily available, as they already are in Europe and around the world, to help dramatically lower America’s health care costs.

¹⁴ European Medicines Agency, Press Release, *European Medicines Agency adopts first positive opinion for a similar biological medicinal product* (Jan. 27, 2006), available at <http://www.emea.europa.eu/pdfs/human/press/pr/3179706en.pdf>; Sandoz International Industries, Media Release, *Sandoz Receives European Commission Marketing Authorization for Omnitrope®* (April 18, 2006), available at http://www.sandoz.com/site/en/company/media/news/pool/omnitrope_approval.pdf.

¹⁵ Narinder S. Banait, *Follow-on Biological Products – Legal Issues* (Fenwick & West LLP 2005), available at <http://www.fenwick.com/docstore/publications/IP/follow-on.pdf>.

3. Patent Landscape for Biologics

Third, I've managed to speak all this time and I still haven't talked about the patent landscape for biologics – which is probably horrifying to the patent lawyers in the room. Surely, patent protection must be a relevant factor in the debate over generic biologics? Well, it is and it isn't.

Of course, biologics typically are covered by multiple patents. This includes not only patents on the products, but also patents on many of the basic research tools used to develop potential biologic drug products. Moreover, a firm's proprietary manufacturing process may be covered by trade secrets, which goes back to the “process is the product” argument. And the data generated during clinical trials may also be proprietary. In order to preserve R&D incentives, it is critical to protect the intellectual property (IP) of pioneer firms. The Commission has long recognized this fundamental tenet.¹⁶

But the truth is, some biologics already have lost patent protection, or are likely to lose patent protection in the near future.¹⁷ For these products, generic entry is being blocked not by

¹⁶ See especially U.S. Dep't of Justice & Fed. Trade Comm'n, Antitrust Guidelines for the Licensing of Intellectual Property (April 6, 1995), available at <http://www.ftc.gov/bc/0558.pdf>; Fed. Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* (Oct. 2003), available at <http://www.ftc.gov/os/2003/10/innovationrpt.pdf>; U.S. Dep't of Justice & Fed. Trade Comm'n, *Antitrust Enforcement and Intellectual Property Rights: Promoting Innovation and Competition* (April 2007), available at <http://www.ftc.gov/reports/innovation/P040101PromotingInnovationandCompetitionrpt0704.pdf>.

¹⁷ See, e.g., Steve Miller, MD & Jonah Houts, *Potential Savings of Biogenerics In the United States* (Feb. 2007), available at <http://www.express-scripts.com/ourcompany/news/outcomesresearch/onlinepublications/study/potentialSavingsBiogenericsUS.pdf> (calculating total estimated savings of \$71 billion over a ten-year period if the FDA develops a pathway for approval of follow-on biologics, based on patent expiration predictions for biologics in four major therapeutic categories); but see Biotechnology Industry Organization, News Release, *Express Scripts and PCMA Follow-On Biologics Studies Are Based on Flawed Assumptions That Undermine Their Credibility* (Feb. 22, 2007), available at http://bio.org/news/newsitem.asp?id=2007_0222_04 (“Assumptions about patent expirations that are inconsistent with credible analyst reports seriously call into question more than \$40 billion of the alleged savings cited by the Express Scripts study”).

IP, but primarily by the lack of an approval pathway. In other words, for many biologics, patents may not be an obstacle to generic entry.

IV. GUIDANCE FROM A COMPETITION PERSPECTIVE

With all of that background in mind, how should competition law deal with issues relating to generic biologics? I see at least a few areas where competition policy might inform the debate.

A. What's Best For Consumers?

As an FTC Commissioner – and a state antitrust enforcer before that – I am always guided by one fundamental principle: do what is best for consumers. In the realm of biologics, it is easy to focus on the spiraling costs of these high-tech miracle drugs, and to conclude that more competition and cheaper generic alternatives would benefit consumers. Certainly, it is tempting to believe that more competition and lower prices are always desirable. As an antitrust lawyer, that would be my first instinct as well.

1. Safety

But jumping to this conclusion too quickly might be short-sighted for several reasons, the most obvious of which is patient safety. The Hatch-Waxman abbreviated approval process for generic pharmaceuticals is premised on the ability to identify truly equivalent drugs, and thereby assure their safety when substituted for branded drugs. But as I discussed earlier, the tradeoff may be different with biologics. Sometimes, it may not be possible to assure that a follow-on biologic meets a safe level of equivalence, without at least some additional clinical studies. Yes,

these studies may raise the cost and delay the entry of generic biologics. But if safety is a major concern – if a drug could cure or kill you depending on how “equivalent” it really is – a delay, and a higher but quality-adjusted price, may be acceptable.

I urge the FDA to take the lead in establishing whether – or, more likely, under what circumstances, according to what sliding scale – the science exists or needs to be developed to support the approval of generic biologics with some form of abbreviated testing. If the science is there or can be developed, then by all means let’s not hide behind science as an excuse. Let’s move the ball forward and find a way to facilitate market entry of safe and effective generic biologics. But first, someone – probably the FDA – needs to objectively determine where the science really is, so that policymakers can rely on facts, instead of rhetoric and position papers from various interest groups.

2. Short- vs. Long-Term Effects on Innovation

Jumping to conclusions about lower-priced generic biologics poses another risk as well: the risk that short-term gains could be offset by longer-term harm to competition and consumers. Specifically, any regime for approval of generic biologics must strike an appropriate balance between promoting generic entry in the short run, and preserving incentives to innovate in the long run.

As I mentioned earlier, the Hatch-Waxman scheme was designed to balance the desire for lower-cost generics with the IP rights of pioneer firms, to ensure that branded firms would still have adequate incentives to engage in costly R&D activities. It was also designed to create incentives for aggressive R&D by generic firms, via the promise of market exclusivity for the first ANDA filer upon successful challenge of patents listed in the Orange Book. But it would be

incorrect to assume that Hatch-Waxman can simply be imported from the pharmaceutical realm to biologics. There are too many critical differences.

In particular, pharmaceutical drugs usually are covered by a relatively small number of patents, owned by a small number of firms. Biologics, in contrast, may be covered by a much greater number of patents – including research tool patents – owned by multiple entities. Patents on large-molecule biologics also tend to be far more complex than patents for small-molecule drugs.

3. Gaming the Hatch-Waxman System

These differences open up the possibility of “gaming” a Hatch-Waxman-like system in ways that would harm consumers. In the realm of biologics – with more patents, more patent owners, and a lot more dollars at stake – there likely would be even greater incentives and opportunities to game the system.

For example, I would be very skeptical of a follow-on biologic approval pathway that included an Orange Book-like system of patent listings. Each Orange Book listing represents a new hurdle for would-be entrants. With respect to biologics – where patents are far more numerous and complex – it might be even easier, and more tempting, to exploit Orange Book listings. A biologics manufacturer might make small tweaks to its manufacturing process, generate new patents, and list them in a “biologic Orange Book” at the last minute – or make other questionable Orange Book listings that would thwart follow-on entry plans.¹⁸

¹⁸ The Commission has, in the past, challenged improper Orange Book listings. *See, e.g.*, Bristol-Myers Squibb Co., 135 F.T.C. 444 (2003) (consent order), *available at* <http://www.ftc.gov/os/decisions/docs/Volume135.pdf>; Biovail Corp., 134 F.T.C. 407 (2002) (consent order), *available at* <http://www.ftc.gov/os/decisions/docs/Volume134.pdf>.

I am also concerned about importing the problem of “exclusion payments” from pharmaceuticals to biologics, but on an even more massive scale. The Commission has been especially vocal in its opposition to exclusion payments, which are an unintended consequence of the Hatch-Waxman 180-day exclusivity provision. Under the guise of settling patent litigation, a branded firm can effectively block generic entry by paying the first ANDA filer to stay off the market. The branded drug maintains its monopoly, and the branded firm and the first filer split the monopoly profits – at consumers’ expense.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 imposed a requirement that certain patent settlement agreements between branded and generic firms be filed with the FTC and the Department of Justice, to provide the agencies with greater visibility into these potentially anticompetitive practices.¹⁹ The Commission pursued one exclusion payment case, the *Schering* case, all the way to the Supreme Court.²⁰ And when *certiorari* was denied in that case – and, not coincidentally, the number of patent settlement filings skyrocketed – we began working even more aggressively with legislators to close some of the Hatch-Waxman loopholes relating to the 180-day exclusivity provision.

I don’t want to give you the wrong impression. I am a firm believer in the benefits of generic competition, and I applaud the efforts of policymakers to extend generic competition to biologics. But I think it is important not to make critical policy decisions based on potentially

¹⁹ Fed. Trade Comm’n, *Medicare Prescription Drug and Improvement Act Requires Drug Companies to File Certain Agreements with the Federal Trade Commission and U.S. Department of Justice* (Jan. 2004), available at <http://www.ftc.gov/os/2004/01/040106pharmrules.pdf> (“Section 1112 of Subtitle B . . . of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 . . . requires that brand name drug manufacturers and generic drug applicants file certain agreements with the Federal Trade Commission and the Assistant Attorney General . . . within 10 business days of execution of the agreement. This requirement covers agreements executed on or after January 7, 2004.”).

²⁰ In the Matter of Schering-Plough Corp. *et al.*, FTC Dkt. No. 9297, available at <http://www.ftc.gov/os/adjpro/d9297/index.shtm>.

flawed assumptions about the incentives of generic firms. Generic firms exist, primarily, to make money for their shareholders. They do not necessarily exist to look out for the interests of consumers. It would be wrong to assume that what is best for generic firms is always best for consumers. As we have seen in the exclusion payment context, sometimes what is best for generic firms is actually *harmful* to consumers. We must not forget that someone needs to be looking out specifically for consumers.

Going back to my innovation point, in the realm of biologics, the Orange Book and 180-day marketing exclusivity *quid pro quo* is not needed. Given the extremely high price at which biologics are sold, and the relatively small number of firms capable of manufacturing follow-on biologics, the promise of market exclusivity is not needed to entice R&D investment. The incentives to innovate are already high. All that is missing is a regulatory pathway for the approval of follow-on biologics.

B. Vigor of Generic Competition

One other area where competition policy might inform the debate is in thinking about the likely structure of biologics markets, if and when a follow-on approval pathway is created, and how this structure might influence competitive dynamics.

Realistically, only a few of the biggest generic firms will be able to afford the huge investments needed to manufacture generic biologics. Some have argued that entry by follow-on biologics may not meaningfully bring prices down if there are not enough generic entrants, which might reduce the expected savings to the government and other payors.²¹ The Commission's

²¹ See, e.g., Duke University Fuqua School of Business, News Release, *Generic Biologic Drugs Unlikely to Offer Significant Savings* (May 2, 2007), available at <http://www.fuqua.duke.edu/news/biologics-0507.html>; Henry G. Grabowski *et al.*, *Entry and competition in generic biologics*, 28 *MANAGERIAL & DECISIONAL ECON.* 1 (2007), available at

own report on generic drug competition agreed that the price effects are greatest when there are multiple generic competitors.²²

But when you are talking about billion-dollar drugs, even small savings can be significant. A 50 percent discount on a small-molecule drug that costs \$20 is \$10.²³ But even a five percent discount on a biologic that costs \$20,000 per year is \$1000. That's a lot of money, in real dollar terms.

An analysis of market structure also must consider the role of drug substitution laws in encouraging generic competition. With respect to traditional pharmaceuticals, as I alluded to earlier, pharmacists in most states can substitute a generic version for a branded drug, without consulting with the doctor who wrote the original prescription. For many payors, automatic substitution is a huge element in obtaining cost savings from generics. But automatic substitution is far less likely to take hold in the realm of high-tech and expensive biologics, where treatment decisions are made on a case-by-case basis, and there are so many therapeutic variables in play. Rather, physicians probably would have to write prescriptions for specific follow-on biologics. Their willingness to do so – and the willingness and ability of insurers to

<http://faculty.fuqua.duke.edu/~dbr1/research/Biogenerics.pdf>; House Oversight Hearing, *supra* note 6 (statement of Henry G. Grabowski, Ph.D.), available at <http://oversight.house.gov/documents/20070416132526.pdf>.

²² FTC Generic Drug Study, *supra* note 9, at 9; see also David Reiffen and Michael R. Ward, *Generic Drug Industry Dynamics*, Fed. Trade Comm'n Bureau of Econ. Working Paper No. 248 (Feb. 2002), available at <http://www.ftc.gov/be/workpapers/industrydynamicsreiffenwp.pdf>.

²³ See, e.g., FTC Generic Drug Study, *supra* note 9, at 9, citing Congressional Budget Office, *A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998) at 28, available at <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> (“The study found that, for drugs that are available in both generic and brand-name versions, the average price of a generic prescription was approximately half of the average price of a brand-name prescription [based on retail pharmacy data from 1993 and 1994].”). See also National Association of Chain Drug Stores, *Industry Facts-At-A-Glance: Pharmaceutical Pricing*, <http://www.nacds.org/wmspage.cfm?parm1=507#pharmpricing> (average brand-name prescription cost \$111.02 in 2006, compared to \$32.23 for average generic prescription, reflecting average savings of nearly 71%).

channel patients toward lower-priced alternatives – will dramatically affect the cost savings that generic biologics might bring about.²⁴

V. NEXT STEPS

So, where do we go from here? Scientists have been discussing generic biologics for quite some time. Now, the academic literature on the law and policy of generic biologics is beginning to grow. And often, a flurry of ideas is a good predictor of action in the near future.

A. Congressional Interest

Congress clearly is interested in these issues. Various bills have been introduced in the House and the Senate to create an abbreviated approval pathway for biologics.²⁵ As recently as March 2007, the House Committee on Oversight and Government Reform (chaired by Representative Henry Waxman, of Hatch-Waxman fame) held a “Hearing on Safe and Affordable Biotech Drugs – The Need for a Generic Pathway.”²⁶ Not surprisingly, the speakers at that hearing were overwhelmingly in favor of the concept of creating a regulatory scheme to

²⁴ As one commentator has noted,

Do not expect to hear your pharmacist say, Oops, I almost forgot to mention that I'm giving you the generic version of that monoclonal antibody your doctor prescribed. . . . Even if the FDA is not excessively cautious in permitting [follow-on biologics] to enter the market, there is the matter of what doctors and patients will do. Compared to payers and academic thought leaders, doctors have always been the toughest sell for generic drugs. When choosing between a branded pioneer biologic and a quasi-generic of uncertain bioequivalence, doctors have been exceptionally reluctant to switch.

John E. Calfee, *Facing Reality on Follow-on Biologics*, HEALTH POLICY OUTLOOK (newsletter of the American Enterprise Institute for Public Policy) (April 24, 2007), available at http://www.aei.org/publications/pubID.26010/pub_detail.asp.

²⁵ Access to Life-Saving Medicine Act, H.R. 1038 & S. 623, 110th Cong. (2007); Affordable Biologics for Consumers Act, S. 1505, 110th Cong. (2007); Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. (2007).

²⁶ Complete hearing materials are available at <http://oversight.house.gov/story.asp?ID=1223>.

facilitate market entry of generic biologics.²⁷ Testimony by an FDA official at that hearing was more cautious, but she indicated that the agency would be issuing a series of “guidance documents” regarding follow-on protein products.²⁸ It seems inevitable that legislation ultimately will emerge from Congress, although it unclear what form that legislation will take.

B. Role for the FTC

As the debate continues, I hope and expect that the FTC will play an important role. Our agency has been closely involved in monitoring the competitive effects of Hatch-Waxman over the years. Through advocacy as well as aggressive enforcement,²⁹ we have fought to maintain competition in markets for generic drugs, and to close unintended but dangerous Hatch-Waxman loopholes that have denied consumers the full benefits of generic competition. In recent months,

²⁷ The speakers included representatives from the FDA, large and small biotechnology firms, the academic and scientific communities, AARP, patient groups, health care benefits providers, and government entities that purchase large quantities of biopharmaceuticals on behalf of insured patients.

²⁸ House Oversight Hearing, *supra* note 6 (statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, FDA), *available at* <http://oversight.house.gov/documents/20070326104056-22106.pdf>.

²⁹ In addition to the *Schering* litigation, *see supra* note 20, the Commission also has pursued enforcement actions against mergers and other conduct that impacted competition in generic drug markets. *See, e.g.*, Warner Chilcott Corporation and Barr Pharmaceuticals., Civil Action No. 1:05-CV-2179-CKK (D.D.C.) (complaint filed Nov. 7, 2005; amended complaint filed Dec. 2, 2005; final order against Warner Chilcott issued Oct. 24, 2006), *available at* <http://www.ftc.gov/os/caselist/0410034/0410034.htm>; Perrigo Company and Alpharma Inc., Civil Action No. 1:04CV01397 (RMC) (D.D.C.), (complaint filed August 17, 2004; final orders issued August 25, 2004), *available at* <http://www.ftc.gov/os/caselist/0210197/0210197.shtm>; Actavis Group hf. & Abrika Pharmaceuticals, Inc., C-4190 (consent order issued May 22, 2007), *available at* <http://www.ftc.gov/os/caselist/0710063/index.shtm>; Hospira, Inc. & Mayne Pharma Ltd., C-4182 (consent order issued March 23, 2007), *available at* <http://www.ftc.gov/os/caselist/0710002/index.htm>; Watson Pharmaceuticals, Inc. & Andrx Corp., C-4172 (consent order issued December 6, 2006), *available at* <http://www.ftc.gov/os/caselist/0610139/index.htm>; Barr Pharmaceuticals, Inc., C-4171 (consent order issued December 8, 2006), *available at* <http://www.ftc.gov/os/caselist/0610217/0610217.htm>; Teva Pharmaceutical Industries Ltd. & IVAX Corp., C-4155 (consent order issued March 2, 2006), *available at* <http://www.ftc.gov/os/caselist/0510214/0510214.htm>; Novartis AG, 140 F.T.C. 480 (2005) (consent order), *available at* <http://www.ftc.gov/os/decisions/docs/Volume140.pdf>. *See generally* Fed. Trade Comm’n, Bureau of Competition, Healthcare Services & Products Division, *Overview of FTC Antitrust Actions in Pharmaceutical Services and Products* (April 2007), *available at* <http://www.ftc.gov/bc/0608rxupdate.pdf> (full listing of all Commission actions in the pharmaceutical industry).

FTC officials and staff have been particularly active in supporting legislation to end anticompetitive exclusion payments from branded firms to generics.³⁰

The FTC has developed tremendous expertise in analyzing the competitive dynamics of generic pharmaceuticals. This expertise should be brought to bear on biologics, as current legislative proposals evolve. In addition to providing informal advice, it might be worthwhile for Commission staff to conduct a formal, disciplined study of the likely competitive effects of creating a Hatch-Waxman-like scheme for follow-on biologics. Of course, the Commission's resources are limited. But as we have seen in the past, if Congress orders us to conduct a study, it tends to happen³¹ – so we'll see what Congress might ask of us in the future.

C. European Perspective

I also expect that we can learn from our counterparts in Europe, where a pathway has existed since 2004 for abbreviated approval of “biosimilars.” Of course, we need to consider how the European Medicines Agency, Europe's equivalent of the FDA, has balanced safety versus costs – and whether the United States is prepared to strike the same balance. But given

³⁰ See especially Fed. Trade Comm'n, *Protecting Consumer Access to Generic Drugs: The Benefits of a Legislative Solution to Anticompetitive Patent Settlements in the Pharmaceutical Industry*, Prepared Statement before the Subcomm. on Commerce, Trade, and Consumer Protection, Comm. on Energy and Commerce, U.S. House of Reps. (May 2, 2007), available at http://www.ftc.gov/os/testimony/P859910%20Protecting_Consume_%20Access_testimony.pdf.

³¹ See, e.g., Energy Policy Act of 2005, Pub. L. No. 109-58 § 1809, 119 Stat. 594 (2005) (requiring the Commission to “conduct an investigation to determine if the price of gasoline is being artificially manipulated by reducing refinery capacity or by any other form of market manipulation or price gouging practices.”); Science, State, Justice, Commerce, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-108 § 632, 119 Stat. 2290 (2005) (appropriations legislation directed the Commission to conduct an investigation into nationwide gasoline prices and possible price gouging in the aftermath of Hurricane Katrina); Fed. Trade Comm'n, *FTC Investigation of Gasoline Price Manipulation and Post-Katrina Gasoline Price Increases*, Prepared Statement before the Comm. on Commerce, Science, and Transp., U.S. Senate (May 23, 2006), available at <http://www.ftc.gov/os/testimony/0510243CommissionTestimonyConcerningGasolinePrices05232006Senate.pdf> (presenting Commission's findings in the two mandated investigations).

the global dimensions of the pharmaceutical and biotech industries – and, importantly, the global nature of the science underlying drug innovations – I expect we might derive some useful insights if we look abroad.

VI. CONCLUSION

To conclude, biologics are the wave of the future, and issues relating to generic biologics are going to become even hotter as more biologics enter the market. While these drugs often work miracles, they come at a huge cost, to individuals as well as to society as a whole. The availability of generic biologics is likely to lower prices and expand the benefits of biologics to a greater number of consumers. But policymakers should tread carefully, to ensure they fully understand the likely competitive implications and long-term consequences of their decisions. And in any event, the FTC should be a part of that process.

Thank you for your time today.