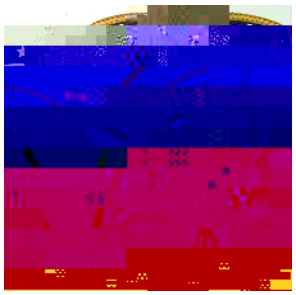

Federal Trade Commission

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 d3 my authorship, is t000 TD(. I wi)Tj27

[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.

[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_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 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 fr

[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*

[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

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

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[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 "Appr

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,tics 4600 0.0000 TD(o-cattch-Wax41.0400 0.0000 TD(icsman. -likj68.0500 0.0000 TD(tioocess wi38

[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*

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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 Policrl0 0.00 d400 0.0B600 0.6.2000 (rr, He)Tjief1.00000 0.00000 0.00000 1.00000 0.0000 0.0000 cm0.0

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 P

[16] *See especially*

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 abbrevi0 595 1 4tsET1.t a TDet TDc4mf 0.If t in est.

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]

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[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.

[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/

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 actu

[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 biologicals*, 28 MANAGERIAL & DECISIONAL ECON. 1 (2007), *available at*

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.

[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

[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 manipula

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.