Testimony of

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1. INTRODUCTION

Mr. Chairman, members of the committee, thank you for the opportunity to participate in today's hearing on the subject of follow-on biologics. I am Dr. Lester M. Crawford, Acting Commissioner, Food and Drug Administration (FDA or the Agency). I am honored to lead an agency whose mission is to protect the public health by assuring the safety and efficacy of our nation's human and veterinary drugs, human biological products, medical devices, human and animal food supply, cosmetics, and radiation emitting products.

2. EXECUTIVE SUMMARY

The enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) has been an unqualified success. Each year consumers save billions of dollars because lower cost generic drugs are on the market. In addition to approving generic drugs, FDA is examining other mechanisms to lower the cost of drug development and find ways to make the drug approval process faster, more certain and more affordable without compromising the thoroughness of drug review.

In the same way that the generic drug program under the Federal Food, Drug, and Cosmetic (FD&C) Act has yielded important public health benefits for the American public, there may be an opportunity for Congress to establish a similar program for biologics regulated under the Public Health Services (PHS) Act. Because there are many unanswered scientific, legal and policy questions about follow-on versions of biologics products approved under section 351 of the Public Health Service (PHS) Act that must be explored,, FDA plans to promote public dialogue on these questions. We hope to address the challenge by determining whether, scientific and technical issues posed by such products, we could approve such products, as well as to clarify about the associated legal issues. Ultimately, the decision to proceed with a program for follow-on biologics regulated under section 351 rests with Congress; however, for biologic products regulated as drugs under section 505 of the Food, Drug, and Cosmetic (FD&C) Act, the Agency believes it can move forward with their consideration.

Perhaps in so doing, we can help lay the groundwork for future consideration of legislative options.

3. GREATER ACCESS TO MORE ENERIC DRUGS - AFFORDABLE DRUGS

FDA and Congress share a great concern for senior citizens and other patients who have difficulty paying for prescription drugs. That is why the Administration worked with Congress to

enact the new Medicare prescription drug law. And it is also why FDA has made it a priority to establish and expand programs that promote access to innovative treatments to help Americans live healthier lives and assure that Americans have access to medications and treatments that they can afford.

FDA has taken a number of significant steps to promote greater access to affordable prescription medications, including unprecedented steps to lower drug costs by helping to speed the development and approval of low-cost generic drugs. Generic drugs typically cost 50 to 70 percent less than their brand-name counterparts. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. The savings are even greater when the use of generics by hospitals is considered.

A. Hatch-Waxman

The Hatch-Waxman Amendments govern the generic drug approval process for human drugs approved under section 505 of the FD&C Act. These provisions give 180 days of marketing exclusivity to certain generic drug applicants. The 180-day generic drug exclusivity provision is one component of the complex patent listing and certification process, which also provides for a 30-month stay on generic drug approvals while certain patent infringement issues are litigated.

The Hatch-Waxman Amendments were intended to balance two important public policy goals. First, Congress wanted to ensure that brand-name (also known as innovator) drug manufacturers would have meaningful incentives for research and development through patent protection and a period of marketing exclusivity to enable them to recoup their investments in the development of valuable new drugs. Second, Congress sought to ensure that, once the statutory patent protection and marketing exclusivity for these new drugs expired, consumers would benefit from the rapid availability of lower priced generic versions of innovator drugs.

Since its enactment in 1984, Hatch-Waxman has governed the generic drug approval process. In general, the law has been working well. Since 1984, over 10,000 generic drugs have entered the market, and generics now account for close to 50 percent of prescriptions filled.

B. Recent Legislation in Response to Concerns

Over the past few years, Congress and the public focused attention on two key provisions of Hatch-Waxman. These grantthe law that allow 180 days of marketing exclusivity for to certain generic drug applicants and provide a 30-month stay on generic approvals when there is patent infringement litigation. On June 18, 2003, FDA published its final rule intended to speed access to and increase the availability of generic drugs by limiting the use of 30-month stays by brand-name drug sponsors and by clarifying the types of patents that must and must not be submitted to FDA for listing in the Orange Book.

The goal of FDA"s rule was to improve access to generic drugs and lower prescription drug costs for millions of Americans. The changes will save Americans over $35 billion in drug costs over the next 10 years and will also provide billions in savings for the Medicare and Medicaid programs. Elements of this rule were incorporated into the Medicare prescription drug lawlegislation last year and, with FDA's urginalong withg, Congress included additional

mechanisms to enhance generic competition. President Bush signed the Medicare Modernization Act into law on December 8, 2003 and FDA is aggressively working to implement these important reforms.

C. Other FDA Efforts to Lower Drug Costs

FDA's objective is to enhance the ability of innovators, generic drug manufacturersfirms and the Agency to achieve the goals embodied in Hatch-Waxman. While Tthe Medicare Modernization Act amendmentsprescription drug law will enhanceimprove the Agency's efforts for taking additional steps implementation of the law, this is only one part of FDA's efforts to reduce drug costs by encouraging innovation and speeding up the drug development and approval process, while maintaining FDA's high standards for safety and effectiveness. Reforms in the generic approval process will generally shave months off the time to availability of generic drugs across-the- board. Similarly, new pathways for approving inhaled and topical generic drugs will potentially affect many products. This broad improvement in the availability of new drugs and generic drugs will have a positive impact on all patients.
, not just those affected by previous imperfections in the operation of Hatch-Waxman.

D. Resources for Generic Drug Review

In addition, lFor fiscal year 2004, Last year the Administration supported and Congress enacted an increase of $8 million for FDA's generic drug program, the largest infusion of resources into this program since its inception. This increase in the generic drug budget enables FDA to hire additional expert staff to review generic drug applications more quickly and initiate targeted research to expand the range of generic drugs available to consumers. Improvements in the efficiency of review procedures have led to significant reductions in approval times for generic drugs since 2002 and will save consumers billions more by reducing the time for developing generic drugs and making them available. The Agency is now approving generic drugs at an average rate of one per day.

4. OTHER FDA INITIATIVES FOR AFFORDABLE DRUGS

In addition to our important responsibilities regarding generic drugs, the Agency has also taken steps to help improve the development process to help lower the cost of developing new drugs.

A. Lowering the Cost of Drug Development

FDA is continuing to improve the methods by which assistance and advice is provided to sponsors regarding what we believe are the best approaches to develop new therapies and maximize the prospects for swift FDA approval. These ongoing efforts are designed to provide sponsors with the best possible information and thus increase the efficiency of the development process. FDA has identified several priority disease areas, such as cancer, diabetes, and obesity, and new technologies including gene therapy, pharmacogenomics and novel drug delivery systems that are good candidates for efforts to clarify regulatory pathways and clinical endpoints.

B. Advancing the Critical Path

On March 16, 2004, FDA issued a major report on medical product development. Known as the Critical Path Report, this document identifies the problems and potential solutions to the daunting task of ensuring that the unprecedented breakthroughs in medical science are demonstrated to be safe and effective for patients as quickly and inexpensively as possible. The report carefully examines the critical path of medical product development -- the crucial steps that determine whether and how quickly a medical discovery becomes a reliable medical treatment for patients. It also describes the unique opportunities for FDA to collaborate with academic researchers, product developers, patient groups, and other stakeholders to make the critical path more predictable, and less costly.

FDA will strive to turn the process of bringing these technologies to patients from a costly and time-consuming art form to a well-understood science. Our reviewers have a unique vantage point to understand the scientific challenges that cause delays and failures in product testing and manufacture. The enormous investment in biomedical science has yielded many promising technologies, ranging from engineered tissues to new kinds of biologics to genomics-based treatments, and we can help guide these technologies through the development pipeline and into the hands of the medical community.

5. THE IMPORTANCE OF INNOVATION

Medical innovation is a complex process, but one that can bring great value to patients. To realize the full benefits of medical innovation it is important to adopt policies that protect incentives to develop new drugs and medical devices.

Achieving this goal requires a delicate effort to strike a proper balance. Promoting innovation requires the right mix of incentives, safeguards, and effective regulation to secure maximum benefit from safe and effective new medical technologies, while assuring mechanisms for broad and equitable access to these new treatments.. We will continue to realize the full benefits of medical innovation if we are thoughtful about achieving this balance. As Acting Commissioner of Food and Drugs, I am working to implement policies, initiatives, and regulatory improvements that reflect these important goals in order to promote increased access to high quality, high value, safe and effective medical products.

6. PROTEINS REGULATED AS DRUGS ORvs BIOLOGICAL PRODUCTS

As you may know, FDA has different approval mechanisms and different governing statutes for drugs and most biological products (although many biological products are also drugs, as that term is broadly defined in the Federal Food, Drug, and Cosmetic (FD&C) Act). FDA has different statutory approval mechanisms and different governing statutes for drugs and most biological products. I say "most" biological products because many biological products are also drugs, as that term is broadly defined in the FD&C Act. The FD&C Act defines drugs drugs by their intended use, as ""(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.. . and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals"" ([FD&C Act, sec. 201(g)(1))]. A biological product is defined, in relevant part, under the PHS Act, as ""any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, or blood component or derivative, allergenic product, or analogous

product product . . . applicable to the prevention, treatment or cure of a diseases or conditioninjuries of human beings." " ([PHSPHS Act, sec 351(i))].

In the past Traditionally, some many natural source proteins have beenwere regulated as drugs, includuinge.g. insulin, hyaluouronidase, menotrophins, natural hormones such as insulin, and human growth hormones, while other and many natural source proteins, such as blood factors, arewere regulated as biological products., e.g. blood factors. In the late 1970s and early 1980s, recombinant proteins and monoclonal antibodies began to be developed. These products were regulated by the Center for Drug Evaluation and Research (CDER) under the FD&C Act as drugs when they were hormones, such as insulin and human growth hormones, and by the Center for Biologics Evaluation and Research (CBER) under the PHS Act for cytokines or blood factors, such as factor 8 for the treatment of hemopheilia. In 1993, CDER and CBER agreed to move all recombinantr- proteins and monoclonal antibodiesmoAb to CBER except hormones, such as insulin and human growth hormones, which remained regulated by CDER under the FD&C Act.. In 2003, therapeutic products regulated by CBER were transferred to CDER, with no change to the applicable approval authority. Therefore, Ccurrently, some "biotech" proteins are licensedapproved under the PHS Act and some are approved under the FD&C Act.

7.Process and Standards for Review of Generic Drugs

A generic drug contains the same active ingredient as an innovator or brand name product, and must be both bioequivalent to the brand name drug and have the same dosage form, strength, route of administration, labeling, and conditions of use. Health professionals and consumers can be assured that FDA approved generic drugs have met the same rigid standards as the innovator drug. Although generic drugs contain the same active ingredient as their branded counterparts, they are typically sold at substantial discounts from the branded price.
Drug companies must submit an abbreviated new drug application (ANDA) for approval to market a generic product. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness

Health professionals and consumers can be assured that FDA approved generic drugs have met the same rigid standards as the innovator drug. To gain FDA approval, a generic drug must:
?Contain the same active ingredients as the innovator drug (inactive ingredients may vary).
? Have the same strength, dosage form, and route of administration.
? Have the same conditions of use.
?Be bioequivalent.
?Be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products.

78. STATUTORY LEGAL EGAL FRAMEWORK FOR DRUG APPROVAL

RAMEWORK
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As I previously mentioned, FDA approves new drugs, as distinguished from biological products, under approval mechanisms found in section 505 of the FD&C Act, and . FDA licenses most biological products under sSection 351 of the PHS Act. Full new drug applications (NDAs) under section 505 of the FD&C Act and bBiologics lLicense aApplications (BLAs) under the PHS Act require submission of complete reports of clinical and animal data to support approval. For drugsproducts approved under the FD&C Act, manufacturers can apply to FDA under section 505(j) of the FD&C Act for approval of to sell generic versions of the brand products after the patent and other exclusivity periods expire. This process is known as the abbreviated new drug application (ANDA) process. Section 505(b)(2) also provides for approval of NDAs supported by literature or by FDA"s earlier finding that a drug is safe and effective.

A. Approval of Generic Versions of Drugs Approved under the FD&C Act

The ANDA process in section 505(j) was established through the 1984 Hatch-Waxman Amendments. This is an abbreviated approval mechanism for generic versions of drugs approved under section 505 of the FD&C Act. Under these statutory standards, a generic drug generally must contain the same active ingredient as an innovator product, it must be bio-equivalent to the innovator drug, and must have the same dosage form, strength, route of administration, labeling, and conditions of use. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. By establishing that the drug product described in the ANDA is the same as the innovator drug product approved in the NDA, the ANDA applicant can rely on the Aagency"s finding of safety and effectiveness for the drug. Although generic drugs are essentially the same as their branded counterparts, they are typically sold at substantial discounts from the branded price.

Health professionals and consumers can be assured that FDA approved generic drugs have met the same rigid standards of quality, purity, and identity as the innovator drug. In addition, generic drugs must be manufactured under the same strict standards of FDA"s good manufacturing practice regulations required for innovator products.

In addition, the FD&C Act also contains an alternative mechanism through which an NDA sponsor can obtain approval of new drug products. This so-called 505(b)(2) mechanism permits a sponsor to rely on literature - or on the Aagency"s finding of safety and effectiveness for an approved product - for approval of a drug product that differs from an approved innovator product (and thus cannot be a generic) or that requires additional human studies for approval.

Both the ANDA and 505(b)(2) approval processes incorporate consideration of the innovator"s intellectual property rights into the drug approval process. The patents listed with FDA by the innovator NDA holder at the time of NDA approval must be acknowledged by the ANDA or 505(b)(2) applicant, and approval will be delayed until patent disputes are resolved and statutory marketing exclusivity has expired.

B. Approval of Follow-on Versions of Biological Products Approved under the PHS Act

The FD&C Act providesThe ANDA process permits g the ANDA and 505(b)(2) abbreviated approval pathwayseneric companies for drugs approved under section 505to reference

information in an innovator company's new drug application (NDA). of that Act. However, the PHS Act has no similar provision. That is, i.e., unlike section 505 of the FD&C Act, there is no provision under the PHS Act for an abbreviated applicationbiologics license application that would permit approval of a "generic"" or ""follow-on"" biologic" based on the Aagency"s earlier dataapproval of from another manufacturer's application.

The approval of generic or follow-on protein and peptideAs mentioned, tThere are a limited number of protein products regulated as new drugs under section 505 of the FD&C Act. These include hormones such as insulin and human growth hormones. Each of these products was approved or licensed based on its own independent data, under section 505(b)(1) of the FD&C Act. The question that they present, however, is whether Can the Agency can approve "follow-on" versions of these 505-approved proteins and other biologic products that may be regulated under section 505 of the FD&C Act, rather than being licensed under section 351 of the PHS Act?

The question products has both scientific and a legal dimensions. First, as a scientific matter, FDA believes that for some biologic products (primarily relatively simple peptide or protein products regulated under section 505 of the FD&C Act), science has progressed sufficiently that we are able to can assess the degree of similarity or identity between the innovator and a follow - on product. The principle underlying such a determination here is that the greater the degree of similarity or identity between two proteins, the greater the confidence that their clinical performance will be similar or the same. From a legal perspective, for products approved under section 505 of the FD&C Act, we also believe there is legalexisting authority to allow us to approve applications for such products under section 505(b)(2) of the FD&C Act, relying using non-public data from the innovatoron the .earlier approval of the innovator product. In contrast, regardless of the state of the science of protein characterization, we do not believe such we have authority exists for to approve a "follow- on" biologics applicationbiologics application under section 351 of the PHS Act that relies on based on non-pubthe prior approval of the biological product or onlic data submitted by another from sponsorthe innovator.

9.8. NEXT STEPSTHE POTENTIAL FOR FOLLOW-ON PROTEINS

In recent years - and with increasing frequency, - questions about "generic," or "follow-on," or "me too"proteins biologics have arisen in response to scientific advances, impending patent expirations, and the ability to better characterize and understand biological products. When we use the term "follow on protein," the Agency is referring to a protein product with the same amino acid sequence and similar structure that is intended for the same use as an existing product.

Manyost drugs are small molecules regulated under section 505 of the FD&C Act are small molecules. For these drugs, iIt has beenis possible to show scientifically that another product has the same active ingredient as the innovator product. On the other hand, because protein drug products are large, complex molecules, derived from biological sources, generally it has not been possible to assess relative sameness with a high degree of confidence. However, the science of characterization has progressed to the point where it is becoming possible to make such assessments for some products, and we expect that science will continue to progress.

Acknowledging Recognizing scientific and legal limitations in this area, yet also recognizing the public health need to move forward to assist industry and make more products available to the public, the Agency is exploring the concept of follow-on biologics. FDA intends to conduct a public process to examine the scientific, legal, and related policy issues regardinglating to follow-on biologics. This process will ensure that scientific considerations and issues related to Agency approval authority under section 351 of the PHS Act are fully examined and that all interested parties have an opportunity for input.

FDA recognizes that before a program to approve generic versions of small molecule drugs was formally established, Congress took action in 1984 by passing the Hatch-Waxman amendments. These amendments provided both new incentives to ensure continued pharmaceutical innovation and an abbreviated approval process for competitor products. Because we believe there are significant questions about the scope of the Agency's existing authority to approve follow-on biologics where an innovator product is licensed under section 351, a similar legislative approach to approval of follow-on biologics where an innovator product is licensed under section 351 could be considered. of the PHS Act, and because these questions deserve full exploration, we also plan to commence a process to seek broad public comment on legal and related policy issues related to follow-on biologics.

9.10. CONCLUSION

FDA believes that follow-on proteins, like the advent of generic drugs, may hold the potential for greater access to therapies and meaningful savings for consumers. We acknowledge that approvals lications for potentialof follow-on versions of more complex products are likely proteins approved under the PHS Act are still years away, and would require resolution of that there are serious scientific, legal, and policy issues. to be explored. Furthermore, we recognize that the limitations inherent in the authorities related to the PHS Act differ from the authorities available to consider some biologic products regulated as drugs under the FD&C Act. Yet we also believe that it is in the interest of the public health to provide meaningful opportunities for thoughtful public discourse on this subject as the science progresses.the time has come to commence a thoughtful public discourse on this topic. Today"s hearing is an important part of that discussion and I thank Chairman Hatch for holding it..