THE POTENTIAL NEED FOR MEASUREMENT STANDARDS TO FACILITATE THE RESEARCH AND DEVELOPMENT OF BIOLOGIC DRUGS

HEARING

BEFORE THE

SUBCOMMITTEE ON TECHNOLOGY AND INNOVATION

COMMITTEE ON SCIENCE AND TECHNOLOGY

HOUSE OF REPRESENTATIVES

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September 24, 2009

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THE POTENTIAL NEED FOR MEASUREMENT STANDARDS TO FACILITATE THE RESEARCH AND DEVELOPMENT OF BIOLOGIC DRUGS

THURSDAY, SEPTEMBER 24, 2009

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON TECHNOLOGY AND INNOVATION,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, DC.

The Subcommittee met, pursuant to call, at 10:11 a.m., in Room 2318 of the Rayburn House Office Building, Hon. David Wu [Chairman of the Subcommittee] presiding.

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HEARING CHARTER

SUBCOMMITTEE ON TECHNOLOGY AND INNOVATION
COMMITTEE ON SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

The Potential Need for Measurement Standards to Facilitate the Research and Development of Biologic Drugs

THURSDAY, SEPTEMBER 24, 2009
10:00 A.M.–12:00 P.M.
2318 RAYBURN HOUSE OFFICE BUILDING

I. Purpose

On September 24, 2009, the Subcommittee on Technology and Innovation will hold a hearing to discuss measurement science, standards and technology that need to be developed in order to (a) facilitate the discovery and development of biologics,[1] including biosimilars;[2] (b) reduce manufacturing costs for biologics and improve the ability to monitor quality during the manufacturing process; (c) provide tools to shorten the amount of time needed for the research, development and regulatory approval of biologics; and (d) ensure that patients receive life saving medicines that are both safe and effective.

II. Witnesses

Dr. Anthony Mire-Sluis is the Executive Director of Global Product Quality and Quality Compliance at Amgen, Inc.

Dr. Patrick VJJ Vink is the Senior Vice President and Global Head of Biologics at Mylan GmbH.

Steven Kozlowski, M.D., is the Director of the Office of Biotechnology Products and the Office of Pharmaceutical Science at the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration.

Willie May, Ph.D., is the Director of the Chemical Science and Technology Laboratory at the National Institute of Standards and Technology.

III. Background

The use of biologics to treat complex diseases such as cancer, diabetes, and multiple sclerosis is a novel approach to modern medicine that offers new hope for once incurable and life threatening diseases.[3] But the lack of scientific knowledge about biologics presents risks to patient safety as their use may result in severe and potentially life-threatening adverse reactions. As an example, between 1998 and 2004, nearly 200 patients taking Eprex, a genetically engineered version of erythropoietin, or EPO, contracted a disease called pure red cell aplasia that resulted in several of those patients becoming chronically dependent on blood transfusions.[4]

If proper and accurate measurement standards, methods and tools had been available, the Eprex incident may have been avoided. Biotechnology companies, the Food

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[1] The terms "biologics" and "biologic drugs" refer to a class of medicinal products that are created by a biological process, as opposed to being chemically manufactured, or medicinal products that include molecules created by a biological process. Examples include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

[2] The terms "biosimilars" and "follow-on biologics" (FOBs) are used interchangeably to describe biologic drugs that are similar versions of approved biologic drugs and may be considered for expedited regulatory approval.

[3] See, e.g., Medicines in Development, Biotechnology, 2006 Report; available at *http://www.phrma.org/files/Biotech%202006.pdf*

[4] See Bennett, Charles L., et. al., Pure Red-Cell Aplasia and Epoetin Therapy, *N. Engl. J. Med.*, 351;1403–1408 (September 30, 2004), *www.nejm.org*; McKoy, June M., et. al., Epoetin-associated pure red cell aplasia: past, present, and future considerations, *Transfusion*, Vol. 48 (August 2008), 1754–1762.

and Drug Administration (FDA) and academia have suggested that proper measurement standards and reference materials may reduce the need for clinical trials and provide a scientific basis in support of a regulatory pathway for the expedited approval of biosimilars. This would result in lower costs both for new biologic drugs[5] and biosimilars.[6]

As an example, if there were a standard and universally accepted method to look at the three-dimensional structure of a protein, any variation in that structure could be readily recognized and a biotechnology company or the FDA could determine what tests may be needed to show whether the variation impacted the quality of a biologic drug based on that protein. As another example, standard reference methods and materials that indicate a biological molecule's potential to interact with other biological molecules[7] or other substances in a way that could be harmful to patients would help researchers and the FDA determine whether that particular molecule may be harmful. In fact, the FDA has expressed a need for the development of methods, measurements and protein characterization tools to help them better assess the "sameness" of two biological molecules, as well as examine factors which may indicate the potential for a biologic drug to interact with other materials in a way that can cause an immune response in a patient.[8] Development of these standard methods, measurements and tools will allow biotech companies and the FDA to be more flexible in developing and refining the manufacturing processes for biologics.

IV. Witness Questions

The witnesses were asked to provide their views on how research, development and the regulatory approval process for biologic drugs could be improved through the development of standard reference methods and materials. In particular, the following questions were asked of each witness:

- Is there a need for measurements, reference materials, reference standards, standard processes, and validation procedures to improve the research, development or regulatory approval of biologics?
- If developed, how would these measurements, reference materials, reference standards, standard processes, and validation procedures: (a) reduce manufacturing costs or improve safety monitoring during the manufacturing process for biologics; and/or (b) reduce the need for or improve the accuracy of preclinical and clinical trials for biologics and biosimilars?
- What are the current scientific challenges to assessing the "sameness" of two biological molecules produced by different processes, or to comparing different batches of biologics produced by the same process? What measurements, reference materials, reference standards, standard processes, and validation procedures can be developed to address these challenges and how would they benefit the biotech industry and patients?

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[5] Although estimates vary, on average the research and development costs for a new biologic drug are believed to be about $1.2–$1.7 billion and it is estimated that it takes about eight to ten years of pre-clinical and clinical testing to obtain federal regulatory approval. See, e.g., DiMasi, Joseph A., et. al., The price of new innovation: new estimates of drug development costs, *J. Health Econ.* 22(2003) 151–185; Drug Development Costs Hit $1.7 Billion, *DrugResearcher.com* (December 8, 2003), *http://www.drugresearcher.com/Research-management/Drug-development-costs-hit-1.7-billion*

[6] According to the Congressional Budget Office, the Federal Government could save between $9 and $12 billion in Medicare payments over the next ten years with the expedited approval of biosimilars. *Budget Options*, Vol. 1: Health Care, Congress of the United States, Congressional Budget Office (December, 2008), 126–128; *Report to the Congress: Improving Incentives in the Medicare Program*, MedPac (June, 2009), 107.

[7] These interactions are called "aggregation," which is the process by which one or more proteins may "clump" together. If proteins that make up a biologic drug show a tendency to aggregate, this increases the likelihood of an immunogenic response in a patient that receives the drug.

[8] Testimony of Janet Woodcock, *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway,* Hearing before the Committee on Oversight and Government Reform, House of Representatives, 110th Congress, 1st Session, Ser. No. 110–43 (March 26, 2007), 19–55.

Chairman WU. The hearing will come to order.

Good morning. I would like to welcome everyone to this subcommittee's hearing on metrology, the measurement needs to support the development of biologics and biosimilars.

While I am very, very aware that other policy issues related to biologics and biosimilars are being considered by Congress, today we are here to focus on the role that we can play in helping develop the underlying science needed to support the growing biologics industry in general.

As I have studied the challenges of developing biological drugs, I realized that some of the issues facing researchers may be addressed through the same paradigm used for traditional pharmacologic drug development but in other arenas the measurement tools to completely characterize relevant pharmacological products do not exist for biologics today.

I have learned as a Member of this subcommittee and I have frequently said that if you can't measure it, it doesn't really exist for technologic or economic purposes. It could be an important item of faith but it is not an item of economics or technology. I do believe that this is the crux of the inconclusive nature of the biologics debate, this difficulty in characterization and measurement, which is why this subcommittee has convened this hearing, and this is—at least at this point—I view this as the beginning of a series of hearings that we will hold on this and related biologics topics.

This is not a new area of inquiry for the Science and Technology Committee. This committee was the first in Congress to hold hearings on the science and potential of other growing scientific fields, such as recombinant DNA, cloning, genome mapping and genetic testing. The Committee's emphasis has always been focused on meeting the metrology needs that allow these new technologies to move forward. I would like to think that the Science and Technology Committee was successful in realizing that goal in a number of other arenas.

In that line, today's hearing will focus on the metrology needs of the biologics industry, and this will be the first in a series of hearings surrounding potentially personalized medicine and genetic diagnostics.

One additional issue I want to address today is the interaction between the industry and the Federal Government to date. I welcome the suggestions of our industry witnesses on how the relationship between NIST [National Institute of Standards and Technology] and industry might be enhanced to ensure that NIST can fully anticipate the industry's metrology needs. The thrust of these questions will not be to criticize, but to learn how a better working relationship might be created.

I want to thank our witnesses for appearing before the Subcommittee and I look forward to your comments and suggestions.

Now I would like to recognize my colleague, Representative Smith, for his opening statement.

[The prepared statement of Chairman Wu follows:]

PREPARED STATEMENT OF CHAIRMAN DAVID WU

I want to welcome everyone to this subcommittee's hearing on the metrology—or measurement science—needs to support the development of biologics and biosimilars.

While I am aware that other policy issues related to biologics and biosimilars are being considered by Congress, today we are here to focus on the role of the Federal Government in helping develop the underlying science needed to support the growing biologics industry.

As I studied the challenges of developing biologic drugs, I realized some of the issues facing researchers may be addressed through the same paradigm used for traditional pharmaceutical drug development, where measurement tools to completely characterize relevant pharmacological products exist. At this point, methods to fully characterize the complex molecules used in biologics have not yet been developed.

I have learned as a Member of this subcommittee that if you can't measure it, it doesn't exist. I believe this is the crux of the inconclusive nature of the biologics debate, which is why the Subcommittee has convened this hearing.

This is not a new area of inquiry for the Science and Technology Committee. The S&T Committee was the first in Congress to hold hearings on the science and potential of other growing scientific fields, such as recombinant DNA, cloning, genome mapping, and genetic testing. The Committee's emphasis has always been focused on meeting the metrology needs that allow these new technologies to move forward. Given the state of these fields today, I would like to think the S&T Committee was successful in realizing that goal.

Along the same line, today's hearing will focus on the metrology needs of the biologics industry. This is the first in a series of hearings the Subcommittee will hold on the metrology issues surrounding personalized medicine and genetic diagnostic testing.

One additional issue I want to address today is the interaction between industry and the Federal Government to date. I welcome the suggestions of our industry witnesses on how the relationship between NIST and industry might be enhanced to ensure that NIST can fully anticipating industry metrology needs. The thrust of these questions is not to criticize, but to learn how a good working relationship might be made better.

I thank our witnesses for appearing before the Subcommittee and I look forward to their comments and suggestions.

Mr. SMITH. Thank you, Mr. Chairman, for calling this hearing today on the very important emerging issue of biologic drugs and the associated standards and measurement science necessary to facilitate their continued safe and effective development.

On this committee, we regularly review and consider the impact science and technology and related policies have on our lives. Arguably, in no other area has this impact been so direct and profound as in medical science where dramatic technological advances have lengthened and improved countless lives here in America and throughout the world.

At the heart of these advances are the continuous revolutionary innovations of the pharmaceutical industry. We have almost come to take new lifesaving drugs for granted, expecting the arrival of new medications to continue quickly without full appreciation of the complicated and sensitive development system.

Central to this system, of course, are strong intellectual property protections without which there would not be incentives to enable the risk taking and investment of capital necessary to foster new drugs throughout the long scientific development and regulatory approval process. This is especially important with respect to biologics where the enormous and unique potential to combat major diseases is hindered by the lack of a regulatory pathway for managing intellectual property.

To this end, I am pleased to be a sponsor along with Chairman Wu of the *Pathway for Biosimilars Act,* which would provide the intellectual property protections and regulatory clarity necessary for ensuring and accelerating continued advances in biologics.

However, we are here this morning to focus on a separate potentially limiting factor to biologic drug development, the need for measurement science and standards development to enable and leverage further advances in biologics. The FDA and industry stakeholders have identified significant measurement science needs to support the regulatory approval and manufacturing processes associated with biopharmaceuticals, and we know NIST has world-class measurement science capabilities well suited to this task.

While there appears to be a good opportunity to leverage NIST's capabilities to meet these needs, the details of what exactly needs to be done and what the appropriate roles and responsibilities of NIST, FDA, industry and other stakeholders should be must be carefully considered. These are complicated questions surrounding an incredibly complex issue. That is of course why we are here today, and I certainly hope and expect this hearing provides us a better understanding to this end.

I want to welcome the witnesses here today. Thank you for your time out of busy schedules, and I look forward to a productive discussion.

[The prepared statement of Mr. Smith follows:]

PREPARED STATEMENT OF REPRESENTATIVE ADRIAN SMITH

Thank you, Mr. Chairman, for calling this hearing today on the very important emerging issue of biologic drugs, and the associated standards and measurement science necessary to facilitate their continued safe and effective development.

On this committee we regularly review and consider the impact science and technology and related policies have on our lives. Arguably, in no other area has this impact been so direct and profound as in medical science, where dramatic technological advances have lengthened and improved countless lives here in America and throughout the world.

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Central to this system, of course, are strong intellectual property protections, without which there would not be incentives to enable the risk-taking and investment of capital necessary to foster new drugs through the long scientific development and regulatory approval process. This is especially important with respect to biologics, where the enormous and unique potential to combat major diseases is hindered by the lack of a regulatory pathway for managing intellectual property.

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I want to welcome the witnesses here today, and I look forward to a productive discussion.

Chairman WU. Thank you very much.

If there are any other Members who wish to submit additional opening statements, your statements will be added to the record at this point.

[The prepared statement of Mr. Mitchell follows:]

PREPARED STATEMENT OF REPRESENTATIVE HARRY E. MITCHELL

Thank you, Mr. Chairman.

I believe that it is critical to establish a system to bring low-cost, generic forms of biologic medicines to the market. A pathway for "follow-on" biologics is important for treating various medical conditions, including illnesses for which no other treatments are currently available.

Today we will discuss the measurement science, standards, and technology needed in order to facilitate the discovery and development of biologics, including biosimilars.

We will also examine how to reduce manufacturing costs for biologics, how to shorten the amount of time needed for the research, development, and regulatory approval of biologics, and how to ensure that biologics are both safe and effective.

I look forward to hearing from our witnesses.

I yield back.

Chairman Wu. I would like to introduce our witnesses. Dr. Anthony Mire-Sluis is the Executive Director of Global Product Quality and Quality Compliance at Amgen. Dr. Patrick Vink is the Senior Vice President and Global Head of Biologics at Mylan GmbH. Dr. Steven Kozlowski is the Director of the Office of Biotechnology Products in the Office of Pharmaceutical Science at the Center for Drug Evaluation and Research at the United States Food and Drug Administration. We are just going to call you czar of something. And our final witness is Dr. Willie May, who is the Director of the Chemical Science and Technology Laboratory at the National Institute of Standards and Technology. You will each have five minutes for your spoken testimony. Your written testimony will be included in the record in their entirety, and when you complete all of your testimony, we will begin with questions and each Member will have five minutes to question the panel. Dr. Mire-Sluis, please begin.

STATEMENT OF DR. ANTHONY MIRE-SLUIS, EXECUTIVE DIRECTOR, GLOBAL PRODUCT QUALITY, AMGEN INC.

Dr. MIRE-SLUIS. Chairman Wu, Ranking Member Smith and Members of the Subcommittee, I would like to thank you for the opportunity to testify to you today. I have devoted much of my career as a scientific researcher and regulator to the question of how best to standardize and improve methods for biotechnology medicinal products, so I am particularly grateful for the change to weigh in on this topic.

There is a clear and pressing need for standards and methods to better understand biotechnology medicines and their manufacturing processes. First, although we need standards, they should be the best standards, not just any standards. We also need to understand that even the best standards can and must evolve as science evolves. And finally, while having the best standards possible is necessary, it is not sufficient to assure safety and efficacy. Randomized clinical trials will be needed in order to understand biotechnology medicines the best that we can.

First, let us look at the impact of standards on patient safety. One place where it is very critical to have the best and most modern standards is when detecting and measuring whether and how

a patient's immune system is reacting to a biological product, that is immunogenicity testing. Immunogenicity happens when your body attacks the medicine that it has been given. Consequences can be that the drug does not work, or even worse, can result in severe side effects. In testing immunogenicity, every company uses different tests and internal standards which have different capabilities. Because of this, we cannot compare the results that these tests produce. Standardization would allow scientists and clinicians to accurately and consistently measure the immune response against biotechnology products, essentially allowing us to speak the same language.

Second, let us look at the impact that standards could have on testing biotechnology products themselves. It is essential that we understand the structure of our biological products and its impact on safety and efficacy and having the very best standard methods and reference materials available will help us to achieve this. They could also lead to reduced costs by minimizing wasted time and effort and could facilitate greater efficiencies of the FDA [Food and Drug Administration].

But measurement standards alone cannot ensure the continued health of the biotech pipeline. It is essential that we preserve the incentives that drive innovative research and development and that we have a strong science-based FDA. Companies must invest on average $1.25 billion to develop and test a biological product and only seven percent of biotech medicines that enter development ever reach the market. That is why strong protection of intellectual property, both patents and data, must remain the cornerstone of this research-intensive innovation-driven industry. In addition, maintaining the FDA as a world-class science-driven regulatory agency is essential to public health and safety. Only vigilant government oversight can sustain confidence in the safety and effectiveness of biotechnology products taken by millions of patients. Federal appropriations for FDA have increased in recent years. However, more needs to be done to support the agency's ability to recruit and retain the best and brightest scientists and medical reviewers, modernize the agency's information technology systems and enhance FDA's scientific capacity. We commend the Science and Technology Committee and the Subcommittee for your roles in passing the COMPETES Act, which has provided a firm foundation for American scientific innovation.

Over the past three decades, biotechnology products have revolutionized the war against chronic and life-threatening disease. The biotechnology industry, the FDA and, most of all, patients are counting on policy-makers to continue to foster biotechnology as our best hope against the devastating diseases that face us today.

So thank you for inviting me to testify today and I will be pleased to answer any questions you may have.

[The prepared statement of Dr. Mire-Sluis follows:]

PREPARED STATEMENT OF ANTHONY MIRE-SLUIS

Chairman Wu, Ranking Member Smith and Members of the Subcommittee, thank you for the opportunity to testify today. My name is Anthony Mire-Sluis and I am the Executive Director of Global Product Quality at Amgen, one of the world's leading health care biotechnology companies. We are headquartered in Thousand Oaks, California and have a significant presence in North America, Asia, and Europe, with

research, manufacturing, distribution and sales facilities worldwide. Amgen has more than 17,000 employees.

Amgen's mission is to serve patients. We discover, develop, manufacture and deliver innovative human therapeutics. A biotechnology pioneer since 1980, Amgen was one of the first companies to realize the new science's promise by bringing safe and effective medicines from lab, to manufacturing plant, to patient. Amgen therapeutics have changed the practice of medicine, helping millions of people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, and other serious illnesses. With a deep and broad pipeline of potential new medicines, Amgen remains committed to advancing science to dramatically improve people's lives.

A Perspective on the Importance of Biotechnology Medicines

Biotechnology medicines are the new frontier in the fight against illness. The first approved medicine manufactured by Amgen—Epogen®—revolutionized treatment for patients on dialysis. Kidney disease hinders the production of red blood cells, causing severe and chronic anemia in patients. Just 25 years ago, these patients would have to receive regular blood transfusions, yet with the FDA approval of Epogen®, patients simply received an injection when they went for dialysis and their bodies were able to produce red blood cells on their own. This effectively eliminated the time-consuming and risky burden of transfusions.

This is just one example of the way biotechnology is revolutionizing the war against disease. Since the science of biotechnology was first utilized to make medicines, more than 200 biologics have been approved, including Amgen therapeutics, and these products have changed the practice of medicine, helping over 325 million people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, hemophilia, multiple sclerosis, and other serious illnesses.

Enormous investments in biotechnology have made possible the industry's medical breakthroughs, including:

- new cancer medicines that take specific aim at tumor cells;
- "clot-buster" medicines that dissolve clots that cause heart attacks and strokes, thus dramatically reducing disability and death from these health episodes. When patients are treated a short time following a stroke, they are at least 30 percent more likely to have minimal or no disability three months after the stroke,[1] which was the third leading cause of death in the U.S. and the leading cause of adult disability in 2004;[2]
- a medicine that can help inhibit the progression of joint damage and dramatically improve the health and well-being of patients suffering from rheumatoid arthritis and juvenile rheumatoid arthritis; and
- medicines that can alter the debilitating course of multiple sclerosis.

Biotechnology holds the promise of other breakthrough solutions for many devastating diseases and conditions for which there is currently inadequate treatment or no treatment. There are scientific breakthroughs taking place every day that will eventually have a dramatic effect on our ability to treat and cure patients . . . from therapies that may one day replace damaged tissue and organs, to cures for sickle cell anemia and congenital blindness.

At present, more than 630 biotechnology medicines are in development,[3] including:

- 254 for cancer and related conditions
- 162 for infectious diseases
- 59 for autoimmune disorders
- 25 for cardiovascular disease
- 19 for diabetes and related conditions

These innovative treatments include:

- monoclonal antibodies to treat asthma, Crohn's disease, and lupus
- therapeutic vaccines for AIDS
- recombinant proteins to treat autoimmune disorders

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[1] MEDTAP International, Inc., *The Value of Investment in Health Care* (Bethesda, MD: 2004) at p. 12.

[2] *Id.* at p. 10.

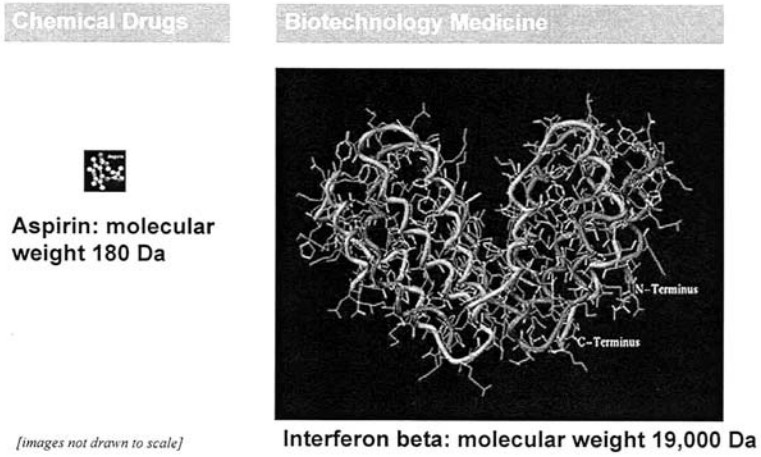
[3] PhRMA, "Medicines in Development: Biotechnology" (2008), at p. 1, available at *http://www.phrma.org/images/110308%20biotech%202008.pdf* (last visited Sept. 21, 2009).

Yet with all of the promise that biotechnology holds for modern medicine, there are a number of very difficult hurdles that must be overcome to bring that promise to fruition for patients. A recent peer-reviewed study in the Journal of Managerial and Decision Economics estimated the total capitalized cost per approved biopharmaceutical to be $1.241 billion.[4] Time is also a challenge for developers of biopharmaceuticals: the Tufts Center for the Study of Drug Development found that the a biotech medicine takes 97.7 months—more than eight years—to progress through clinical development and FDA review.[5] And biotech drug development is not for the feint of heart. Only seven percent of biotechnology medicines that enter the development stage ever reach the market.[6]

The importance of biotechnology medicines to the health of patients in the U.S. and throughout the world is clear. We have some specific comments in response to the questions you have raised about methods and standards that are used to understand the structure, function and safety of biotechnology medicines.

The Need for Improved Methods and Standards for Characterizing Biotechnology Medicines

Biotechnology medicines are complex molecules that require as thorough as possible an understanding of their structure and function to ensure their safety and efficacy. In comparison to standard chemical drugs, biotechnology medicines (proteins) are hundreds of times larger and more complicated. They are a chain of building blocks (amino acids) that are often folded in many ways and can have sugars attached to them that make them even more complex.



Because biotechnology medicines are usually made using living cells, each protein molecule can be slightly different, resulting in a product that includes a mix of many different forms of a single protein. Due to this potential variability, it is critical for biotechnology companies to utilize the very best methods[7] to understand

[4] DiMasi, Joseph A. and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial & Decision Economics*, vol. 28, issue 4–5, pp. 469–479 (2007), at p. 475, available at *http://www.manhattan-institute.org/projectfda/wiley_interscience_cost_of_biopharm.pdf* (last visited Sept. 19, 2009).

[5] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product Is $1.2 Billion" (Nov. 9, 2006), available at *http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69* (last visited Sept. 19, 2009).

[6] PharmaProjects, "Biotech Marches On Despite Low Success Rates and Faltering Investment" (June 10, 2002), available at *http://www.pjbpubs.com/uploads/downloads/pharmaprojects/100602.doc* (last visited Sept. 19, 2009). As PharmaProjects points out, "[o]nly anticancer drugs, with a success rate of 4.6%, represent a more risky prospect." *Id.*

[7] These methods (often termed 'assays') are laboratory procedures using machines or devices that allow scientists to look at different parts of the protein—its structure (physicochemical assays) and how it works (biological assays). For example, one can develop an assay that indicates whether a protein exists as a single chain or as two or more chains stuck together, or even more.

their medicines and accurately identify which parts of the protein are most important, in order to ensure optimal product safety and efficacy.

One safety concern with biotechnology medicines—immunogenicity—occurs when the body does not recognize the protein being administered, triggering the immune system to produce antibodies, which are special proteins that bind to the offending protein in an attempt to neutralize it and clear it from the body. Depending on the nature of the protein administered, immunogenicity can cause the medicine to be ineffectual, or could result in adverse reactions ranging from mild to life-threatening. Because of the potential for immunogenicity, it is essential for patient safety that scientists and clinicians are able to properly, accurately, and consistently measure antibodies that develop in patients against biotechnology medicines.

It has been shown that subtle or even undetectable changes in the structural properties of a biotechnology medicine can have an impact on its safety, efficacy or immunogenicity. Therefore, the laboratory-based analytical methods used to understand the structural characteristics of biological medicines play a critical role in the product development process.

The earlier on in development a company can develop sound and rigorous measurement methods, the earlier it can alter the product or the process as necessary to maximize the chance of success with a new biologic—ideally, before expensive clinical studies are started and patients given a medicine that may not work as expected. Having standard methods and reference materials available as soon as product development begins should give companies a head start in creating a successful product. Furthermore, development costs may be minimized if manufacturers don't have to 'reinvent the wheel' of method development and validation for each product. In addition, better understanding of the product allows for development of more robust manufacturing processes that in themselves lead to reduced manufacturing failures, reduced wasted materials and rework, and cost containment.

The availability of standard methods, and of reference standards, may also ease the burden on regulatory reviewers in verifying that the methods used by product sponsors were appropriately developed and validated and routinely run. This would reduce the need for continuous, in-depth evaluation of methods from product to product and from company to company. In fact, the pharmacopoeias[8] represent such a precedent, in that they have already developed some standard method protocols ("monographs") that are widely used in drug development and regulatory review, freeing reviewers from the need to spend unnecessary time verifying method development/performance.

As described earlier, from the patient's perspective, one area of testing that would most directly benefit from standardization is detecting and measuring whether and how a patient's immune system is reacting in response to administration of a biologic medicine—that is, *immunogenicity testing.* This testing can only be carried out in clinical studies because, simply put, this is the only way to really understand what is happening inside the patient.

Biopharmaceutical developers use a number of different assays to detect and measure immunogenicity. Each such assay is developed in parallel to the medicinal product and is specific to that particular product. Additionally, each such assay utilizes internally-produced, custom-made materials to make it work. Because these assays and methods are unique to each company and to each product, though, they are not amenable to being standardized, and reference materials are not easily

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This is important to know because the protein that is safe and efficacious could be the single chain, whereas two or more chains stuck together in the medicine might not have the same ability to work, or may even raise safety concerns.

Important things to understand about an assay include, for example, how well it identifies its target(s) at the right level (sensitivity), how well it provides the same result if the same sample is tested several times (reproducibility), and the extent to which different laboratories are able to carry out the assay and achieve consistent results.

"Validation" refers to the way that scientists ensure that they can understand how well an assay works once it has been developed. This may involve running an assay several times with different samples for which the results are known, and then assessing the results achieved in the real-world setting. If the expected results are achieved, scientists can be confident that the assay can be used again and again and will provide consistently reliable results.

[8] For example, the United States Pharmacopeia (see *http://www.usp.org/aboutUSP/*), a non-profit, non-governmental organization that serves as an official public standards-setting authority for prescription and OTC medicines and other health care products manufactured or sold in the U.S.; and the European Pharmacopoeia Commission (see *http://www.edqm.eu/en/Work-ProgrammeStatus-607.html*), which promulgates European reference standards and is currently working to advance a "Biological Standardisation Programme" (see *http://www.edqm.eu/site/BSP_Background_Missions-60.html*). (Sites last visited 9/19/2009).

available. Because of this, understanding exactly how sensitive or accurate these methods are can be very challenging.

It takes a very substantial amount of work for a biotechnology company to produce good immunogenicity assays that will ensure that any signs of an immune response in patients are detected as early as possible after administration of a biologic medicine. The future availability of high-quality standard methods, validation techniques, and reference standards will reduce the chance that immunogenicity assays are not able to detect the antibodies that could expose patients to risks to their health. The more sensitive the method, the more likely it is that an immune response can be detected and stopped before it has a chance to harm the patient.

To date, scientists have not been able to determine exactly what can trigger the body to recognize a protein product as "foreign" and try to stop the immune response and clear it from the body. Because of this, clinical studies must be conducted, in order to determine what will happen when a biologic medicine is administered to patients. Scientists have been working tirelessly to develop ways to predict patients' responses, in order to prevent the occurrence of adverse events in clinical studies. Much work remains to be done. Developing better ways to predict immunogenicity will be key to the biotech industry's ability to create protein-based medicines that do not cause unwanted side effects in patients, both during the pre-approval clinical studies required to establish safety and efficacy, and in studies conducted after product approval.

It is clear that the development of standard methods, validation procedures, and reference materials for the variety of methods described (i.e., to understand the structure of the protein product, how it functions, whether and how it causes immune responses, and the like) will be of direct benefit to patients as well as to the biotechnology industry. But how they will be created and developed must be carefully considered. If researchers working in federal agencies such as NIST, government regulators, and industry scientists work together in this effort, it is much more likely that the outcomes will be successful—for government, for industry, and ultimately for the benefit of patients.

Science, Regulation, and Intellectual Property—Needs Beyond Measurements

As discussed, the development of good assays to understand the structure, function, safety and efficacy of biotechnology medicines is important, but it is also crucial to biotechnology and to U.S. leadership in biotechnology innovation that we focus on the three-legged stool that serves as the public policy foundation on which the biotechnology industry stands.

First, it is essential to support the scientific component of biotechnology. The U.S. Government has an important role to play in ensuring that our students receive rigorous scientific education and training in order to cultivate the next generation of scientists. It is also important that Congress make a renewed commitment to supporting the basic research that will fuel future scientific discoveries. These foundational components benefit our society as a whole by creating the capacity for scientific initiative. These scientific contributions of government are absolutely necessary—but they are not sufficient to foster a robust biotechnology industry.

We must also maintain and fully support a robust, science-based regulatory system to ensure that patients and their physicians can be confident that the biomedical innovations available to them are safe and effective.

Finally, we must put in place strong intellectual property protections that encourage the public and private investment needed to advance scientific innovation.

The Science & Technology Committee has been a leader on many of these foundational necessities of biotechnology. The Committee—under Chairman Gordon's leadership—has demonstrated that it understands the need to put in place all three "legs" to provide a firm foundation for scientific innovation. We commend your work to date and ask that you facilitate U.S. biotechnology—the future of medicine *and* an economic engine of the U.S. innovation economy—by continuing your efforts to support robust science and regulation.

Fostering Science, Technology, Engineering & Mathematics ("STEM") Education

The Members of the House Science & Technology Committee clearly understand the important role that education plays in the future of our innovation economy, and have led Congressional efforts to improve science, math and technology education

in the U.S. The House's Innovation Agenda[9] has also supported this new emphasis on science, technology, engineering, and mathematics ("STEM") education.

In 2007 Congress, with the key involvement of the Science & Technology Committee, passed the *America COMPETES Act*.[10] This landmark bipartisan legislation was enacted in response to concerns identified by the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine in the 2007 report, *"Rising Above the Gathering Storm: Energizing and Employing America for a Brighter Economic Future."*[11] The *America COMPETES Act* included many provisions related to enhancing mathematics, science and technology education and workforce development in the United States, including:[12]

- Investing in 25,000 new teachers through professional development, summer training institutes, graduate education assistance, and scholarships;
- Creating grant programs to allow prospective teachers to earn undergraduate degrees in mathematics, science, engineering, technology, and critical foreign languages, in conjunction with teaching certifications;
- Establishing new math-focused programs for elementary and secondary schools, particularly high-needs schools; and
- Working with the business community and academia, creating public-private partnerships in mathematics education and training.

Amgen shares Congress' and the Committee's concern and interest in educating the next generation of American scientists. Amgen invests millions in programs to advance science education, from the local elementary school to the world's top universities.[13] To date, the Amgen Foundation[14] has committed more than $45 million in science education funding to non-profit organizations throughout the United States, Puerto Rico, and Europe.[15] Our signature programs in advancing science education include the Amgen Scholars Program,[16] the New Science Teacher Acad-

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[9] "In 2005, House Democrats, working with leaders from the academic, high-technology, biotech, venture capital, and telecommunications sectors, as well as with students and young entrepreneurs, launched the Innovation Agenda, a Commitment to Competitiveness." "The Innovation Agenda: Creating a New Generation of Innovators," available at *http://speaker.house.gov/issues?id=0016* (last visited 9/10/2009).

[10] The *America COMPETES Act* ("*America Creating Opportunities to Meaningfully Promote Excellence in Technology, Education, and Science Act*"), Pub. Law 110–69 (121 Stat. 572, Aug. 9, 2007), available at *http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ069.110.pdf* (last visited 9/10/2009).

[11] The National Academies, Committee on Prospering in the Global Economy of the 21st Century, *"Rising Above the Gathering Storm: Energizing and Employing America for a Brighter Economic Future"* (Washington, D.C.: The National Academies Press, 2007), available at *http://books.nap.edu/openbook.php?record_id=11463&page=R1* (last visited 9/10/2009). The Committee was charged by the National Academies to respond to a request by Senators Lamar Alexander and Jeff Bingaman of the Senate Committee on Energy and Natural Resources, with endorsement by Representatives Sherwood Boehlert and Bart Gordon of the House Committee on Science (now the House Committee on Science & Technology), to address the following questions: "What are the top 10 actions, in priority order, that federal policy-makers could take to enhance the science and technology enterprise so that the U.S. can successfully compete, prosper, and be secure in the global community of the 21st century? What strategy, with several concrete steps, could be used to implement each of those actions?"

[12] "The Innovation Agenda: Creating a New Generation of Innovators," available at *http://speaker.house.gov/issues?id=0016* (last visited 9/10/2009).

[13] For example, the Amgen-Bruce Wallace Biotechnology Lab Program (named in memory of one of Amgen's first staff members) provides high school students with flexible hands-on, inquiry-based experience with some of the same materials, tools, and techniques used by professional scientists. The three-week program, funded by the Amgen Foundation, allows teachers to introduce recombinant DNA technology, a fundamental of biotechnology, into their science curriculum and provides all needed equipment, supplies, and reagents at no cost to the teacher or school. Miletich, Joseph P., "Needed—One Giant Leap for Science Education" (Sept. 2, 2009), available at *http://www.genengnews.com/blog/item.aspx?id=548* (last visited 9/10/2009).

[14] The Amgen Foundation, established in 1991, seeks to advance science education, improve quality of care and access for patients, and support resources that create sound communities where Amgen staff members live and work. Amgen Inc., "Inspiring the Scientists of Tomorrow," brochure available at *www.amgen.com*

[15] Amgen Inc., "Inspiring the Scientists of Tomorrow," brochure available at *www.amgen.com*

[16] The Amgen Scholars Program, launched in 2007, is a $27.5 million, eight-year program that provides undergraduate students with the opportunity to engage in hands-on scientific research at some of the world's top universities. The initiative is designed to advance science education by inspiring college students to pursue graduate training and, ultimately, research and scientific careers. Amgen Inc., "Inspiring the Scientists of Tomorrow," brochure available at *www.amgen.com*

emy (co-founded with the National Science Teachers Association), and the Amgen-Bruce Wallace Biotechnology Lab Program.[17]

Continuing America's Biotechnology Leadership Through Strong Intellectual Property Protection

Strong protection of intellectual property—both patents and data—is the cornerstone of any research-intensive, innovation-driven industry. Failure to ensure adequate intellectual property protection will undermine investment in biotech innovation. Without it, venture capital that is the lifeblood of startup companies will divert resources to investments with more certain returns, regardless of their social value.

Investment decisions by more mature biotech companies that are self-funding are necessarily driven by the possibility of recovering the cost of bringing a product to market because this funds the next discovery. Without adequate intellectual property protection, research and development will be greatly diminished. This is a very expensive proposition for patients waiting for cures.

We know that incentives to invest can be successful. For example, Congress has put in place incentives to encourage orphan drug development. Moreover, partnerships with American universities in high-risk early-stage research are extremely important and can only flourish with a strong intellectual property base.

The respect for intellectual property in America is one of the reasons that we, as a country, lead the world in biotechnology innovation. The biotech medicines industry not only helps patients, it is also a major economic and job-producing asset for the U.S. at a time when concern about losing jobs to low-wage countries is growing.

The U.S. leads the world in biotechnology research and development. In 2006, the U.S. biotech industry invested in R&D nearly four times what the next largest market invested.[18] Moreover, in 2003, the U.S. biotechnology industry spent more than $14 billion on research and development, more than double the amount of biotech industry R&D spending in Germany, France, Canada, Denmark, Switzerland, Italy, Australia, Israel, and Korea combined.[19]

Employment figures also reflect the U.S.'s dominance in biotech R&D: the Organization for Economic Cooperation and Development (OECD) estimates that the U.S. biotech sector employed approximately 50 percent more people than the U.K., Germany, France, Canada, Denmark, Switzerland, Israel, Spain, Sweden and Belgium combined.[20]

U.S. leadership in this industry is second to none, but we must be mindful that virtually every industrialized country in the world has on its economic agenda the development of a biotech sector to take over the U.S. lead in high-skilled, high-paying biotech jobs. In order to maintain U.S. leadership in biotechnology, supportive government infrastructure and strong intellectual property protections are essential.

Science-Based, Transparent Regulation

It is also critical to scientific and biomedical innovation that America has—in the FDA—a world-class, science-driven regulatory agency. Ensuring a strong system of regulation is an absolute necessity to get vital medicines to patients, because doctors and patients must have confidence in the safety and effectiveness of biomedical discoveries.

A strong, well-funded FDA is essential to the health and safety of the American public. This agency carries the important charge of helping to assure the safety, ef-

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[17] "The Amgen-Bruce Wallace Biotechnology Lab Program is an educational outreach program that provides equipment, curriculum assistance and supplies to high schools and colleges. This molecular biology curriculum is designed to introduce, with extensive teacher support, the excitement of scientific discovery to students. Each year, over 10,000 students and faculty participate in this laboratory experience and have the opportunity to explore the steps involved in creating biotechnology therapeutics. The reach of this program has been extraordinary with over 100,000 students exposed to the fundamentals of biotechnology across multiple states." See "About the Amgen-Bruce Wallace Biotechnology Lab Program," available at *http://bwbiotechprogram.com/aboutus.php* (last visited 9/15/2009).

[18] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007," at p. 7, available at *http://www.ey.com/Global/assets.nsf/International/Industry_Biotechnology_Beyond_Borders_2007_Full/$file/BeyondBorders2007.pdf* (last visited 9/15 2009).

[19] Van Beuzekom, Brigitte and Anthony Arundel, "OECD Biotechnology Statistics—2006," at p. 41, available at *http://www.oecd.org/dataoecd/51/59/36760212.pdf* (last visited 9/15/2009).

[20] Employment figures also reflect the U.S.'s dominance in biotech R+D: the Organization for Economic Co-operation and Development estimates that the U.S. biotech sector employed about 73,000 people in 2003—compared to 46,000 biotech employees in the U.K., Germany, France, Canada, Denmark, Switzerland, Israel, Spain, Sweden and Belgium *combined*. These employment numbers are significantly lower than other estimates, as noted above. Van Beuzekom, Brigitte and Anthony Arundel, "OECD Biotechnology Statistics—2006," at p. 21, available at *http://www.oecd.org/dataoecd/51/59/36760212.pdf* (last visited 9/15/2009).

fectiveness and availability of medicines taken by millions. While federal appropriations for the FDA have increased over the last several years, more needs to be done to support the Agency's critical work. Additional federal funding is critical to FDA's ability to recruit and retain the best and brightest scientists and medical reviewers, modernize the agency's information technology systems, and restore FDA's scientific capacity.

The House and Senate each have approved legislation[21] that would provide more than $2.5 billion in appropriated funding for FDA salaries and expenses in fiscal year 2010. This represents an increase of nearly $299 million in discretionary funding over FY 2009, the fourth straight increase in FDA appropriations since 2006, and the highest level of FDA appropriations ever proposed to be enacted. We encourage Congress to pass legislation providing this historic level of funding for FDA, the world's standard-bearer for sound, science-based regulation.

We have been greatly encouraged not only by the recent increase in resources that Congress has provided to the FDA but also in the public comments by Commissioner Hamburg since her confirmation. We encourage this committee to support Commissioner Hamburg's efforts to maintain and improve the science base of the Agency and to establish Regulatory Science as a discipline as well-regarded as basic research in the years to come. Without a strong foundation of science in regulation, life-saving therapies will be unnecessarily delayed.

Additionally, we wish to thank Commissioner Hamburg for her emphasis on transparency in the regulatory process, communicating risk-benefit to the public, and fostering scientific exchange. All of these efforts will go a long way toward advancing biomedical therapies in the years to come. Amgen takes this opportunity to applaud these efforts and specifically to voice our firm commitment to open scientific exchange with FDA scientists.

Conclusion

We thank the Subcommittee and the Science & Technology Committee as a whole for your work to date, and we urge you to continue as the Committee of "good ideas and consensus" in fostering innovation in science and biotechnology and maintaining America's role as the global leader in biomedical discovery, R&D, and regulation.

We encourage the Committee and Congress to continue to strengthen the three essential components of biomedical innovation:

- Education in mathematics, science and technology—and basic scientific research;
- Strong intellectual property protection; and
- A robust, science-based regulatory system.

Amgen and other biotechnology innovators, the FDA, and—most of all—patients, are counting on you as policy makers to continue to support and foster biotechnology as our best hope for addressing the most devastating diseases facing us today.

BIOGRAPHY FOR ANTHONY MIRE-SLUIS

Anthony Mire-Sluis, Ph.D., is currently Executive Director of Global Product Quality and Quality Compliance at Amgen. In this role, he is responsible for the scientific assurance of product quality for Amgen's biotechnology products and leads the company's corporate quality compliance organization, ensuring compliance to regulatory and Good Manufacturing Practice (GMP) requirements.

Prior to joining Amgen, Dr. Mire-Sluis served as Principal Advisor of Regulatory Science and Review in the Office of Pharmaceutical Sciences at the U.S. Food & Drug Administration's (FDA) Center for Drug Evaluation & Research (CDER) and as head of Analytical Sciences and Standards in the Office of the Director at the FDA's Center for Biologics Evaluation & Research (CBER). While at the FDA, he worked on a variety of regulatory issues, including regulatory review best practices, guidance on biosimilar characterization, biotechnology product comparability and stability and published on the topic of methodology to assess immunogenicity.

Dr. Mire-Sluis trained in Genetics and Biometry at University College, London University in the United Kingdom and has a Ph.D. in Cell Biology and Biochemistry from the Royal Free Hospital in London.

[21] See H.R. 2997, *"Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act,* 2010," available at *http://thomas.loc.gov/cgi-bin/query/z?c111:H.R.2997* (last visited Sept. 21, 2009).

Dr. Mire-Sluis began his career as the head of the Cytokine Group in the Division of Immunobiology at the National Institute for Biological Standards and Control, a United Kingdom regulatory authority and World Health Organization (WHO) laboratory. He specialized in the development of assays for the characterization and quantitation of biological products and for the creation of WHO International Standards for Cytokines and Immunological Sera.

Dr. Mire-Sluis joined the biopharmaceutical industry when he became Director of BioAnalytical Sciences at Genentech. He also served in the industry as Executive Director of Analytical Sciences at CancerVax Corporation in San Diego, Calif.

Dr. Mire-Sluis is an expert for The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). He is on the editorial boards of the *Journal of Immunological Methods* and the journal, *Biopharmaceuticals,* and has over 100 scientific references in journals and textbooks.

Chairman WU. Thank you very much.

Dr. Vink, please proceed.

STATEMENT OF DR. PATRICK VINK, SENIOR VICE PRESIDENT AND GLOBAL HEAD OF BIOLOGICS, MYLAN INC.

Dr. VINK. Good morning. Thank you, Chairman Wu, Ranking Member Smith and the Members of the Subcommittee on Technology and Innovation. My name is Patrick Vink and I am the Head of Global Biologics at Mylan. I am privileged today to testify before the Subcommittee on behalf of Mylan, which for over almost half a century has established a solid reputation of manufacturing high-quality, affordable pharmaceuticals. Mylan is the largest U.S.-based generic-pharmaceutical manufacturer with one out of every 13 prescriptions dispensed in the United States, brand name or generic, being a Mylan product.

Today, Mr. Chairman, on the 25th anniversary of Hatch-Waxman, we face a situation comparable to that of 1984 when perpetual monopolies enjoyed by biologics under the PHS [Public Health Service] Act ended. Unlike Europe, the United States lacks a biosimilar pathway. A viable biosimilar pathway does not require a competitor to re-establish *de novo* the safety and efficacy of a legacy molecule. Instead, a biosimilar's pathway recognizes how much is already known about legacy biologics and enables both regulators and competing biologics manufacturers to appropriately rely upon the prior knowledge and regulatory conclusion flowing from the data. Specifically, this information is the safety and efficacy of the underlying molecule itself. It is that demonstration of comparability, Mr. Chairman, where biologic reference standards could play a crucial role. Comparability is an established scientific and regulatory principle that the branded biopharma industry itself developed with FDA in 1996 to alleviate regulatory burden on the branded industry when they changed the manufacturing process for biologics. An example of this is the product Avonex, which paved the way for biosimilars and in many important respects effectively constituted the first biosimilar because its approval dispelled the age-old paradigm of the product is the process and established a new biologics regulatory paradigm premised on comparability. As a result of subsequent regulatory developments, comparability was adopted globally as the same standard for all biologics and yet every time a brand biologic manufacturer has implemented the manufacturing change, the change has result in a change in its biologic. The evolutionary process of this com-

parability creep among branded biologics means there are a number of brand biologics on the market today that may have drifted significantly or to a minor extent away from the original versions of those biologics initially approved by the FDA across the entire lineage of a brand biologic. There is therefore a continuum of substitutability determinations that have maintained the market acceptance and enhanced the abundant market success of so many high-priced biologics in the U.S. market today. It is time to recognize the implications of the regulatory history, accept the scientific conclusions and regulatory confidency supports and proceed to apply all logical inferences across the regulatory framework for all biologics going forward.

This is where reference biologic standards come in. With the availability of appropriate reference standards, it should be readily ascertainable just how much a branded biologic has drifted between its original approval and FDA's approval of its most recent manufacturing change. Originally approved biologics and the most recent changed biologics enable a fair and readily adoptable set of parameters. These essentially could serve as the regulatory goal posts for approval of a generic biologic. Thus, to be approved, a competing biologic manufacturing would need to demonstrate comparability within that range. From Mylan's perspective, a viable approach for this subcommittee is to appropriately incentivize reference standards by creatively linking them in a straightforward manner to existing and future incentives benefiting brand biologics so as to provide a return to American taxpayers, the U.S. health care system and patients in need of these biologics. Specifically, we believe reference standards should be linked directly to these incentives including any exclusivity, if any.

While Mylan, like other key stakeholders, is very troubled by the excessive exclusivity that is currently contemplated, we have identified a constructive way to leverage exclusivity if there needs to be any. This can be accomplished by simply conditioning a brand biologic company's receipt of exclusivity on the brand's voluntary provision of a reference monograph and reference standard materials consisting of supplies of active ingredient and the various iterations of finished products approved by the FDA as comparable. The monograph would be published as the reference materials are evaluated and sold on a not-for-profit basis to companies and researchers for analytical testing purposes. NIST certainly would be an appropriate repository for such reference standard materials. NIST could apply its in-house expertise and develop new analytical tools for regulators and biologic developers and characterizing those reference standards will be without developing new standards or guidance which would become quite problematic at the regulatory interface with FDA. Authorizing NIST to implement such a system could put the United States back in a leadership position and enable the United States to begin catching up with Europe and other countries that are now many years ahead in terms of enabling patients access to generic biologics. The state-of-the-art analytical methods now available to biologics competitors like Mylan, the operation of a reference standard system would further enhance the global nature of comparability and contribute to a single universal set of tools by which FDA could assess comparability

going forward. Such a system would benefit all biologics stakeholders. The approach is suitable and appropriate, I am convinced about it, readily implementable and can enhance both the quality and efficiency of all biologics while enhancing patients' access to biologics that can help save lives.

In closing, Mr. Chairman, I again want to thank you and the Subcommittee on behalf of Mylan for this opportunity to present our perspective on the critical importance of establishing a biologics reference standard system as Mylan has proposed. Towards that end, Mr. Chairman, Mylan looks forward to working with the Subcommittee to implement this approach, and I welcome the opportunity to address your questions.

[The prepared statement of Dr. Vink follows:]

PREPARED STATEMENT OF PATRICK VINK

Good morning. Thank you, Chairman Wu, Ranking Member Smith, and Members of the Committee on Science and Technology's Subcommittee on Technology and Innovation. My name is Patrick Vink, and I am the head of Global Biologics at Mylan Inc. (Mylan).

For nearly 50 years, Mylan has built a legacy of manufacturing high-quality, affordable pharmaceuticals. We are the largest U.S.-based generic pharmaceutical manufacturer and the third largest generics and specialty pharmaceutical company in the world. One out of every 13 prescriptions dispensed in the U.S.—brand name or generic—is a Mylan product. Additionally, Mylan has consistently been recognized by the U.S. Food and Drug Administration (FDA) and by the pharmacy community for excellence in quality and service.

Mylan's proven track record of U.S. and global leadership led me to join the Company to lead its biologics business, having spent 20 years in the pharmaceutical industry, including the past decade managing various businesses across the breadth of the biopharmaceutical industry. If the Subcommittee will indulge me, I would appreciate the opportunity to review briefly that biologics' experience and how directly relevant it is to the issues at hand during today's hearing.

After obtaining my academic degree as a medical doctor and holding different positions in the Pharmaceutical industry, I was appointed Vice President of International Sales at Biogen Idec in 2001, where I managed the commercial activities of a product that not only paved the pathway for biosimilars but that in many respects effectively constituted the first biosimilar itself: Avonex® (interferon beta 1a). As has been well documented in court filings and public policy debates, Biogen "broke the mold" by eliminating the age-old paradigm of "the product is the process," thereby forever changing the biologics world. In the process, Biogen validated a scientific and regulatory science principle that is the basis for all biologics today, including biosimilars: comparability (to which I will return in a moment). Based on that limited filing, FDA determined that Biogen had demonstrated comparability of two biosimilar products from a different cell-line, a different manufacturing facility with a different manufacturing process-based solely on analytics—without a single comparative clinical trial, let alone a head-to-head clinical trial—all the very same "differences" that many opponents of biosimilars point to today as purported rationales for continued regulatory blocks on FDA's approval of true biosimilars. In 2002 I became Global Head of Biopharmaceuticals for Sandoz, part of the Novartis Group of companies, where I managed all facets of the business, including the R&D and regulatory initiatives culminating in approval of the first biosimilar in Europe, Omnitrope® (somatropin), which became the first recombinant follow-on product to a previously-approved recombinant drug approved by FDA. As in the past, while working now with Mylan, I have been extensively involved on an ongoing basis in policy discussions and legal/regulatory dialogue around implementation of biosimilars legislation in Europe and the U.S. and development of biosimilars guidelines in Canada and Japan.

In a very short period of time, Mylan has built a robust biologics business implementing a sound strategy that has positioned Mylan as a future leader in the field.

Mylan's success in biologics will build on Mylan's proven track record in developing generic versions of synthetically-manufactured complex drugs that are regulated by FDA under the *Federal Food, Drug, and Cosmetics Act* (FD&C Act).

Instead, it is biologics—like erythropoietins, beta-interferons, anti-TNFs, monoclonal antibodies, and other biologics—FDA regulates under the *Public Health*

Service Act (PHS Act) that make today's critically-important hearing so relevant and the Subcommittee's consideration of biologics standards so timely. The regulatory history and U.S. marketing experience of these and so many other PHS Act biologics point to the very significant role that could be played by the appropriate implementation of biologics' standards in enabling biologics' R&D across the biopharma spectrum. As I will outline, with a viable biologics' standards system in place, claims about biosimilars having "differences" could be rapidly resolved from the outset on technical scientific grounds, quite separate from the demonstration that such claims lack merit as a legal/regulatory matter. That legal conclusion about these and comparable arguments—all of which build on the disingenuous theme that biosimilars are "only similar" but not "the same"—could be buttressed by biologics' standards that establish the inherent scientific flaws underlying such blockades to generic biologics access.[1] As has been demonstrated repeatedly, the purported "differences" in generic biologics are, in reality, no more significant and typically are much less significant than the "differences" that FDA so readily accepted when approving Avonex based on its finding of analytical comparability. Similarly, an appropriately-implemented system of biologics' standards would bring an immediate halt to scare tactics—such as those that have been used for years here on Capitol Hill to block viable generic biologics legislation and that continue to be vocalized through heavy investments across Europe to impede competition as more and more biosimilars enter the European market. Such irresponsible fear-mongering has been the strategic lynchpin of those who have expressly and/or implicitly opposed constructive solutions to marketplace entry of competing biosimilar products under the PHS Act. This subcommittee can help bring those specious claims to a halt.

It is with this background in mind that I would like to take this opportunity to outline for the Subcommittee in more concrete terms how such an appropriate biologics' standards system can be viably established—including through the use of creative incentives—and to address the precise role of such standards at the regulatory interface of FDA's evaluation of all biologics, both branded originator biologics as well as biosimilars that compete against those biologics. As I trust will become apparent, this is a true win:win opportunity for all stakeholders if collectively we have the courage to seize the opportunity.

As has been well-established over many decades of experience with chemical drugs, reference standards play a critical role for all stakeholders. At their core, reference standards provide a transparent and global "toolkit," if you will, that enables regulators, manufacturers, researchers, and others to know whether a product is what it purports to be. For chemical drugs, in the U.S., that process has been and continues to be managed exceedingly well by the U.S. Pharmacopeia (USP). USP develops and publishes drug monographs that specify various tests, measurements, and methodologies for analyzing products, and USP sells on a not-for-profit basis actual drug ingredient reference standards for use in analytical testing. This system has significantly advanced the pharmaceutical sciences, enhanced drug development across the biopharma industry, and facilitated the work of federal and State enforcement officials who can readily test whether products meet established USP specifications. It also has substantially added to patient confidence in the high quality of medicines across the spectrum that are labeled "USP," from over-the-counter products to prescription drugs.

A comparable process does not exist today for biologics, of course, which is precisely why this hearing has been convened. Both I and others could delineate for the Committee at some length the actual and supposed reasons for the absence of such a system, but that will not significantly advance its establishment. From my perspective, based on my global experience across the biopharma industry, I note that a key driver to date has been the inability to compel the establishment of reference standards due to Constitutional and other legal considerations that could arise from compulsory mandates requiring biologics manufacturers to publish monographs and make actual reference biologic standards available. Today, however, it is apparent to me and to Mylan that this barrier no longer exists, not because those legal issues have been resolved, but simply because those issues can be avoided through the use of some creative but also very straightforward incentives.

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[1] It is worthwhile in this regard to consider the comparable gamesmanship that has been underway for some time with synthetically-manufactured drugs, which is mired in a Citizen Petition proceedings at FDA that seeks to indefinitely delay approval of applications. Such Petitions are indicative of what the biosimilars industry is likely to confront in the years ahead in seeking FDA approval for biosimilar that would compete with marketed PHS Act biologics. Reference standards could ensure that such gaming of an otherwise-legitimate public petitioning process is no longer incentivized.

As Members of the Subcommittee undoubtedly are aware, your colleagues on the Energy and Commerce Committee reported a bill as part of health care reform that includes various provisions on biosimilars (many of which, in Mylan's view, build very effective and time-consuming blockades to FDA review and approval of biosimilars under the guise of enabling competition—a subject beyond the scope of this hearing).

In addition, that Committee-reported bill grants a new, and globally unprecedented, 12-year non-patent data exclusivity period to all currently-marketed biologics as well as to all future biologics.[2] As currently drafted, that 12-year exclusivity provision is simply a direct grant to the biotech industry without any give-back in return by the industry to American taxpayers and patients in need of access to biologics. While Mylan, like many of our allies in the generics industry, finds that 12-year exclusivity period to be highly problematic—particularly in the context of legislation replete with a myriad of roadblocks to biosimilars such as those in the Committee-reported bill—I have been re-evaluating the role of that exclusivity in the context of this hearing. In doing so, I would suggest that perhaps there is a constructive manner in which to both consider and leverage that generous exclusivity, even if it ends up being, as we would cage, much shorter than 12 years, such that it provides a meaningful return to U.S. taxpayers as well as the breadth of the biopharmaceutical industry. This could be accomplished simply by conditioning a brand biotech company's receipt and exercise of exclusivity on the company's voluntary provision of a reference monograph as well as reference standard materials (both active ingredient and the various iterations of finished product) to a centralized Federal Government repository, which could evaluate the materials and also sell them on a not-for-profit basis to other companies and researchers for their testing purposes.

One appropriate repository for such reference standard materials could be NIST, which, as such a repository, could apply its in-house expertise to enhance existing and develop new analytical tools for regulators and biologics developers in characterizing those reference standards and comparable biologics. In that role, NIST also could readily publish the manufacturer-provided monographs that would be a precondition of receiving exclusivity. Enabling NIST to implement such a system could allow the U.S. to regain some of the important leadership in biologics and biosimilar regulation that it has lost to Europe and other parts of the world, who are now many years ahead of the U.S. While there is a great deal of lost time to be made up, taking this significant step could bring the U.S. a long way forward in the global regulatory community. Importantly, this system does not envision NIST undertaking the de novo development of new standards and monographs or the like, as such a step could be confounding not only to industry in developing biologics but also become quite problematic at the regulatory interface with FDA. To the extent there is guidance or standards to be implemented, that authority should remain with FDA as it continues its over 100-year-old role as the regulator of biologics.

There are many legislative precedents for a "carrot" approach such as the one I am proposing here. Perhaps the most readily-translatable one involves highway funding and the 55 mph speed limit. Years ago, Congress conditioned states' receipt of Federal highway funds on implementation of State laws imposing a 55 mph speed limit. After much Congressional debate and Supreme Court argumentation about states' rights and related Constitutional issues, the Supreme Court confirmed the appropriateness of the legislative approach because it was non-compulsory, and such "voluntary" contingencies on the receipt of federal largess became engrained in the legislative process. The biopharma industry is quite familiar with the reverse process, having engrained the PDUFA process on FDA, with review timelines conditioned on the payment of user fees. In many respects, the approach I have outlined here would simply establish some degree of reciprocity from the industry.

There is no reason that such an approach could not be implemented here, and I would be happy to share some initial concepts for such a system with the Subcommittee if that would be helpful. More to the point, there are compelling rationales for adopting such an approach in the context of biologics reference standards, because it would immediately overcome the anticipated onslaught of objections and demands for "public participatory processes" that could quickly mire down this sub-

[2] In implementing its biosimilars framework, Europe simultaneously implemented a new 8+2+1 data exclusivity regime. While that EU exclusivity can total up to 11 years, its implementation was dramatically different than that which is proposed for the 12-year biologics exclusivity in the U.S. Specifically, the EU exclusivity applied prospectively only to *future* products, *not* to existing products, and it only went into effect for the first time for products first approved several years after the pharmaceuticals legislation was adopted in Europe. Furthermore, extensive price control systems within the EU make that situation very different from the U.S.

committee's initiatives in the same type of never-ending procedural hurdles that have kept biosimilars off the U.S. market for 10 years despite Biogen's establishment of the technical and regulatory pathway for biosimilars through its and FDA's ratification of comparability in 1996.

Importantly, it is likely to be that comparability context in which the greatest value of biologics' standards will be realized.

Ever since FDA's adoption of the comparability standard in 1996 (guidance attached) and the courts' ratification of that comparability standard in Biogen's defense of its Avonex approval in 1997 (judicial opinion attached), its ensuing history—including the International Conference on Harmonization's adoption of the comparability standard on a global basis in 2005 (guidance attached), and Europe's adoption of it as the basis of its biosimilars framework (guideline attached)—has resulted in its establishment and global recognition as the "sameness" standard for all biologics. And yet, there is no universally-accepted set of analytical tools by which comparability is judged. Instead, each biologics manufacturer adopts and applies its own tools and methodologies and pre-clears them with FDA as the bases for their individual comparability protocol. That said, the current state-of-the-art methods and technologies for characterizing biologics and assessing comparability are significantly improved in comparison to those used initially (and still maintained today for some biologics) when the first biologics were approved. We are nowadays able to establish comparability between biologics from different manufacturer and confirm this with abbreviated clinical trials. Further improvement of these characterization tools will further help in avoiding unnecessary clinical trials.

The adoption of even more sophisticated analytical methods and consistent reference standards, particularly utilizing an approach such as the one I have outlined here, would further enhance the universal nature of comparability and could enable a single, universal set of tools by which FDA could assess comparability going forward. Such a system would benefit all biologics stakeholders, originators and biosimilar manufacturers alike. In the pre-approval phase, this system could enhance batch-to-batch consistency and enable greater certainty before initiating human clinical trials. Post-approval, such a system would establish a consistent approach to comparability assessments and create a level playing field for all companies manufacturing biologics and seeking to demonstrate comparability—whether on an intercompany or an intracompany basis. Notably, Europe began applying comparability across companies on an intracompany basis in 2003, which has benefited all stakeholders tremendously.

The impact of biologics' reference standards would perhaps be felt most directly, and most pro-competitively, in this latter context involving biosimilars to PHS Act. This is because of the past utilization of comparability by the branded manufacturers of such products. Over the years, the Amgen's, the Genzyme's, and the Genentech's of the world have run dozens and dozens of comparability protocols for their marketed, and still-exclusive, biologics. While there is no centralized repository of accessible data on the nature and extent of the manufacturing changes implemented by branded biologics manufacturers in connection with those comparability protocols, one can readily anticipate based upon professional meeting presentations and publications in the scientific literature that such manufacturing changes have run the one gamut—from a piping modification, to a manufacturing process change, from a building change on the same campus to a cross-country or international facility change, from an inactive ingredient change to a change in cell line. These and many other manufacturing changes have been approved by FDA, and each time FDA has determined—as it did 10 years ago with Avonex—that the "changed" biologic is comparable to the pre-changed biologic, thereby enabling both biologics to be on the market and freely interchanged with one another as supplies of the pre-change biologic are depleted and supplies of the changed biologic come on-line. For many biologics, this cycle has occurred on multiple occasions with the "same" biologic. In the process, as a result of the cumulative effective of the full set of manufacturing changes that have been implemented by the branded manufacturer and approved by FDA, the currently marketed product has evolved quite significantly from the one FDA approved originally. And yet, all the way through, with each iteration of change, FDA has found comparability, creating a situation in which the currently-marketed product has to be considered comparable with the original one and thus fully interchangeable regardless of the nature or extent of the evolution.

In short, while FDA has at various points addressed concerns about comparability "drift" between biosimilar products and the branded biologic to which comparability has been established, there is a longstanding history of Agency acceptance and indeed ratification of that "drift" for branded biologics themselves. Scientifically, in the absence of data to the contrary, neither should be a concern, as reflected by FDA's continual approval of numerous manufacturing changes for any individual

biologic. Instead, we should collectively recognize the implications of that regulatory history over the past decade, accept the apparent scientific conclusions it supports, and proceed to make it an established part of the regulatory framework for biologics going forward.

This is where reference standards can play a critical role. With the availability of reference standards as I have outlined here, it could readily be determined just how much a branded biologic has "drifted" in terms of its specifications between the date of its original licensure and the most recent manufacturing change approved by FDA. Those specifications could then readily be adopted as the regulatory "goal posts" that would need to be met by any other sponsor seeking approval to market a comparable biologic. We therefore support the current initiatives the National Institute for Science and Technology wants to undertake.

The approach I am advocating is suitable and appropriate, readily implementable, and can enhance both the quality and efficiency of biologics' R&D while enhancing patients' access to the biologics that can help save lives. It is for this reason, among many others, that as a physician with my industry background, I am very comfortable with the option of biosimilars being dispensed to patients, and adoption of this reference standards system would only reinforce that comfort level.

Towards those ends, Mr. Chairman, I again want to thank you and the Subcommittee on behalf of Mylan for this opportunity to present our Company's perspective on these critically-important issues. I look forward to addressing any questions that you and your colleagues on the Subcommittee might have.

Guidance for Industry

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2005
ICH

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Contains Nonbinding Recommendations

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Guidance for Industry[1]

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1) [2]

A. Objectives of the Guidance (1.1)

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guidance is intended to assist manufacturers of biotechnological/biological products in the collection of relevant technical information that serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety, and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical, or clinical strategy. The main emphasis of the document is on quality aspects.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2004.

Contains Nonbinding Recommendations

B. Background (1.2)

Manufacturers[3] of biotechnological/biological products frequently make changes to manufacturing processes[4] of products[5] both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact[6] the safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate.

While ICH documents have not specifically addressed considerations for demonstrating comparability between prechange and postchange product, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes (see section IV (4.0) References). This document builds upon the previous ICH guidances and provides additional direction regarding approaches to:

- Comparing postchange product to prechange product following manufacturing process changes; and
- Assessing the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy of the product.

C. Scope (1.3)

The principles adopted and explained in this document[7] apply to:

- Proteins and polypeptides, their derivatives, and products of which they are components, e.g., conjugates. These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be

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[3] For convenience, when the term *manufacturer* is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).

[4] For convenience, when the term *manufacturing process(es)* is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.

[5] For convenience, when the term *product* is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.

[6] Improvement of product quality is always desirable and encouraged. If the results of the comparability exercise indicate an improved quality suggesting a significant benefit in efficacy and/or safety, the pre- and postchange product may not be comparable. However, this result could be considered acceptable. The manufacturer is advised to consult the appropriate regional regulatory authority.

[7] This document applies to situations in which all three of the bulleted conditions are present.

highly purified and characterized using an appropriate set of analytical procedures;

- Products where manufacturing process changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of prechange and postchange product; and
- Products where manufacturing process changes are made in development or for which a marketing authorization has been granted.

The principles outlined in this document might also apply to other product types, such as proteins and polypeptides isolated from tissues and body fluids. Manufacturers are advised to consult with the appropriate regional regulatory authority to determine applicability.

D. General Principles (1.4)

The goal of the comparability exercise is to ensure the quality, safety, and efficacy of drug product produced by a changed manufacturing process through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the prechange and postchange product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the postchange product are not warranted. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and postchange product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

To identify the impact of a manufacturing process change, a careful evaluation of all foreseeable consequences for the product should be performed. In consideration of this evaluation, appropriate criteria to define highly similar postchange product can be established. Generally, quality data on the pre- and postchange product are generated, and a comparison is performed that integrates and evaluates all data collected, e.g., routine batch analyses, in-process control, process validation and/or evaluation data, characterization and stability, if appropriate. The comparison of the results to the predefined criteria should allow an objective assessment of whether or not the pre- and postchange product are comparable.

Following the evaluation of the quality attributes, the manufacturer could be faced with one of several outcomes, including:

- Based on appropriate comparison of relevant quality attributes, pre- and postchange product are highly similar and considered comparable, i.e., no adverse impact on safety or efficacy profiles is foreseen.

- Although the pre- and postchange product appear highly similar, the analytical procedures used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider employing additional testing (e.g., further characterization) or nonclinical and/or clinical studies to reach a definitive conclusion.
- Although the pre- and postchange product appear highly similar, some differences have been observed in the quality attributes of the prechange and postchange product; but it can be justified that no adverse impact on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and postchange product can be considered comparable.
- Although the pre- and postchange product appear highly similar, some differences have been identified in the comparison of quality attributes and a possible adverse impact on safety and efficacy profiles cannot be excluded. In such situations, the generation and analysis of additional data on quality attributes are unlikely to assist in determining whether pre- and postchange product are comparable. The manufacturer should consider performing nonclinical and/or clinical studies.
- Differences in the quality attributes are so significant that it is determined that the products are not highly similar and are therefore not comparable. This outcome is not within the scope of this document and is not discussed further.

II. GUIDANCE (2)

A. Considerations for the Comparability Exercise (2.1)

The goal of the comparability exercise is to ascertain that pre- and postchange drug product are comparable in terms of quality, safety, and efficacy. To meet this goal, the product should be evaluated at the process step most appropriate to detect a change in the quality attributes. This may entail evaluating the product at multiple stages of manufacture. For example, even though all process changes occurred in the manufacture of the drug substance, in cases where the drug product could be impacted by the change, it might be appropriate to collect data on both the drug substance and the drug product to support the determination of comparability. Comparability can often be deduced from quality studies alone (limited or comprehensive analysis, as appropriate), but might sometimes need to be supported by comparability bridging studies. The extent of the studies necessary to demonstrate comparability will depend on:

- The production step where the changes are introduced;
- The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product-related substances);
- The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and
- The relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience.

When considering the comparability of products, the manufacturer should evaluate, for example:

- Relevant physicochemical and biological characterization data regarding quality attributes;
- Results from analysis of relevant samples from the appropriate stages of the manufacturing process (e.g., intermediate, drug substance, and drug product);
- The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;
- Batches used for demonstration of manufacturing consistency;
- Historical data that provide insight into potential "drift" of quality attributes with respect to safety and efficacy, following either a single or a series of manufacturing process changes. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.

In addition to evaluating the data, manufacturers should also consider:

- Critical control points in the manufacturing process that affect product characteristics, e.g., the impact of the process change on the quality of in-process materials, as well as the ability of downstream steps to accommodate material from a changed cell culture process;
- Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the postchange process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
- Nonclinical or clinical characteristics of the drug product and its therapeutic indications (see section II.E (2.5) of this guidance.

B. Quality Considerations (2.2)

1. Analytical Techniques (2.2.1)

The battery of tests for the comparability exercise should be carefully selected and optimized to maximize the potential for detecting relevant differences in the quality attributes of the product that might result from the proposed manufacturing process change. To address the full range of physicochemical properties or biological activities, it might be appropriate to apply more than one analytical procedure to evaluate the same quality attribute (e.g., molecular weight, impurities, secondary/tertiary structures). In such cases, each method should employ different physicochemical or biological principles to collect data for the same parameter to maximize the possibility that differences in the product caused by a change in the manufacturing process might be detected.

It can be difficult to ensure that the chosen set of analytical procedures for the prechange product will be able to detect modifications of the product due to (1) the limitations of the assays (e.g., precision, specificity, and detection limit) and (2) the complexity of some products due to molecular heterogeneity. Consequently, the manufacturer should determine:

- Whether or not existing tests remain appropriate for their intended use or should be modified. For example, when the manufacturing process change gives rise to a different impurity profile in the host cell proteins, manufacturers should confirm that the test used to quantitate these impurities is still suitable for its intended purpose. It might be appropriate to modify the existing test to detect the new impurities;
- The need to add new tests as a result of changes in quality attributes that the existing methods are not capable of measuring. That is, when specific changes in quality attributes are expected as a result of a process change (e.g., following addition of a new raw material or modification of a chromatographic purification step), it might be appropriate to develop new analytical procedures, i.e., to employ additional analytical techniques above and beyond those used previously for characterization or routine testing.

The measurement of quality attributes in characterization studies does not necessarily entail the use of validated assays, but the assays should be scientifically sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidances (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

2. *Characterization (2.2.2)*

Characterization of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.

When a manufacturing process change has been made that has the potential to have an impact on quality attributes, a complete or limited (but rationalized) repetition of the characterization activity conducted for the market application is generally warranted to directly compare the prechange and postchange product. However, additional characterization might be indicated in some cases. For example, when process changes result in a product characterization profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials (e.g., reference materials, marketed batches), the significance of these alterations should be evaluated. Results of comprehensive characterization of the material used in pivotal clinical trials could provide a useful point of reference for subsequent comparability exercises.

Each of the following criteria should be considered as a key point in the conduct of the comparability exercise:

- **Physicochemical Properties**

The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered. Following a manufacturing process change, manufacturers should attempt to determine that higher order structure (secondary, tertiary, and quaternary structure) is maintained in the product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay (see biological activity below) could indicate a correct conformational structure.

- **Biological Activity**

Biological assay results can serve multiple purposes in the confirmation of product quality attributes that are useful for characterization and batch analysis, and, in some cases, could serve as a link to clinical activity. The manufacturer should consider the limitations of biological assays, such as high variability, that might prevent detection of differences that occur as a result of a manufacturing process change.

In cases where the biological assay also serves as a complement to physicochemical analysis (e.g., as a surrogate assay for higher order structure), the use of a relevant biological assay with appropriate precision and accuracy might provide a suitable approach to confirm that change in specific higher order structure has not occurred following manufacturing process changes. Where physicochemical or biological assays are not considered adequate to confirm that the higher order structure is maintained, it might be appropriate to conduct a nonclinical or clinical study.

When changes are made to a product with multiple biological activities, manufacturers should consider performing a set of relevant functional assays designed to evaluate the range of activities. For example, certain proteins possess multiple functional domains that express enzymatic and receptor mediated activities. In such situations, manufacturers should consider evaluating all relevant functional activities.

Where one or more of the multiple activities are not sufficiently correlated with clinical safety or efficacy or if the mechanism of action is not understood, the manufacturer should justify that nonclinical or clinical activity is not compromised in the postchange product.

- **Immunochemical Properties**

When immunochemical properties are part of the characterization (e.g., for antibodies or antibody-based products), the manufacturer should confirm that postchange product is comparable in terms of the specific properties.

- **Purity, Impurities, and Contaminants**

The combination of analytical procedures selected should provide data to evaluate whether a change in purity profile has occurred in terms of the desired product.

If differences are observed in the purity and impurity profiles of the postchange product relative to the prechange product, the differences should be evaluated to assess their potential impact on safety and efficacy. Where the change results in the appearance of new impurities, the new impurities should be identified and characterized when possible. Depending on the impurity type and amount, it might be appropriate to conduct nonclinical or clinical studies to confirm that there is no adverse impact on safety or efficacy of the drug product.

Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product. New contaminants should be evaluated to assess their potential impact on the quality, safety and efficacy of the product.

3. Specifications (2.2.3)

The tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterize it. The manufacturer should confirm that the specifications after the process change are appropriate to ensure product quality. Results within the established acceptance criteria, but outside historical manufacturing control trends, might suggest product differences that warrant additional study or analysis. Modification, elimination, or addition of a test (i.e., in the specification) might be indicated where data suggest that the previous test is no longer relevant for routine batch analysis of the postchange product. For example, the elimination of bovine serum from the cell culture process would remove the need for related analyses. However, a widening of the acceptance criteria is generally not considered appropriate unless justified. In some cases, additional tests and acceptance criteria on the relative amount of specific new impurities might be appropriate if the impurity profile is different following the manufacturing process changes. When evaluating both the test methods and acceptance criteria for the postchange product, it is important to consider the general principles for setting specifications as defined in Q6B, i.e., the impact of the changes on the validated manufacturing process, characterization studies, batch analysis data, stability data, and nonclinical and clinical experience.

4. Stability (2.2.4)

For certain manufacturing process changes, even slight modifications of the production procedures might cause changes in the stability of the postchange product. Any change with the potential to alter protein structure or purity and impurity profiles should be evaluated for its impact on stability, since proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents. Furthermore, stability studies might be able to detect subtle differences that are not readily

detectable by the characterization studies. For example, the presence of trace amounts of a protease might only be detected by product degradation that occurs over an extended time period; or, in some cases, divalent ions leached from the container closure system might change the stability profile because of the activation of trace proteases not detected in stability studies of the prechange product. Therefore, real-time/real temperature stability studies on the product potentially affected by the change should be initiated, as appropriate.

Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of prechange and postchange product. The results thus obtained might show product differences that warrant additional evaluation and also identify conditions indicating that additional controls should be employed in the manufacturing process and during storage to eliminate these unexpected differences. Appropriate studies should be considered to confirm that suitable storage conditions and controls are selected.

ICH Q5C and Q1A(R) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.

C. Manufacturing Process Considerations (2.3)

A well-defined manufacturing process with its associated process controls ensures that acceptable product is produced on a consistent basis. Approaches to determining the impact of any process change will vary with respect to the specific process, the product, the extent of the manufacturer's knowledge of and experience with the process, and development data generated. The manufacturer should confirm that the process controls in the modified process provide at least similar or more effective control of the product quality, compared to those of the original process.

A careful consideration of potential effects of the planned change on steps downstream and quality parameters related to these steps is extremely important (e.g., for acceptance criteria, in-process specification, in-process tests, in-process hold times, operating limits, and validation/evaluation, if appropriate). This analysis will help identify which tests should be performed during the comparability exercise, which in-process or batch release acceptance criteria or analytical procedures should be reevaluated, and which steps should not be impacted by the proposed change. For example, analysis of intermediates might suggest potential differences that should be evaluated to determine the suitability of existing tests to detect these differences in the product. The rationale for excluding parts of the process from this consideration should be justified.

While the process will change and the associated controls might be redefined, the manufacturer should confirm that prechange and postchange product are comparable. To support the comparison, it is often useful to demonstrate, for example, that specific intermediates are comparable or that the modified process has the capability to provide appropriate levels of removal for process- and product-related impurities, including those newly introduced by the process change. To support process changes for approved products, data from commercial-scale batches are generally indicated.

The process assessment should consider such factors as the criticality of the process step and proposed change, the location of the change and potential for effects on other process steps, and

the type and extent of change. Information that can aid this assessment is generally available from several sources. The sources can include knowledge from process development studies, small scale evaluation/validation studies, experience with earlier process changes, experience with equipment in similar operations, changes in similar manufacturing processes with similar products, and literature. Although information from external sources is useful to some extent, it is within the context of the specific manufacturing process and specific product that the change should be assessed.

When changes are made to a process, the manufacturer should demonstrate that the associated process controls, including any new ones, provide assurance that the modified process will also be capable of providing comparable product. The modified process steps should be reevaluated and/or revalidated, as appropriate. The in-process controls, including critical control points and in-process testing, should ensure that the postchange process is well controlled and maintains the quality of the product. Typically, reevaluation/revalidation activities for a simple change might be limited to the affected process step if there is no evidence to indicate that there is an impact on the performance of subsequent (downstream) process steps or on the quality of the intermediates resulting from the subsequent steps. When the change considered affects more than a single step, more extensive analysis of the change and resultant validation might be appropriate.

Demonstration of state of control with the modified/changed manufacturing process might include, but is not limited to, such items as:

- Establishment of modified specifications for raw, source and starting materials, and reagents;
- Appropriate bioburden and/or viral safety testing of the postchange cell banks and cells at the limit of in vitro cell age for production;
- Adventitious agent clearance;
- Removal of product- or process-related impurities, such as residual host cell DNA and proteins; and
- Maintenance of the purity level.

For approved products, an appropriate number of postchange batches should be analyzed to demonstrate consistent performance of the process.

To support the analysis of the changes and the control strategy, the manufacturer should prepare a description of the change that summarizes the prechange and the postchange manufacturing process and that clearly highlights modifications of the process and changes in controls in a side-by-side format.

D. Demonstration of Comparability During Development (2.4)

During product development, it is expected that multiple changes in the manufacturing process will occur that could impact drug product quality, safety, and efficacy. Comparability exercises are generally performed to demonstrate that nonclinical and clinical data generated with prechange product are applicable to postchange product in order to facilitate further development and, ultimately, to support the marketing authorization. Comparability studies conducted for

products in development are influenced by factors such as the stage of product development, the availability of validated analytical procedures, and the extent of product and process knowledge, which are limited at times due to the available experience that the manufacturer has with the process.

Where changes are introduced in development before nonclinical studies, the issue of assessing comparability is not generally raised because the manufacturer subsequently conducts nonclinical and clinical studies using the postchange product as part of the development process. During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should utilize available information and will generally become more comprehensive. Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorization, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product. Some outcomes of the comparability studies on quality attributes can lead to additional nonclinical or clinical studies.

In order for a comparability exercise to occur during development, appropriate assessment tools should be used. Analytical procedures used during development might not be validated, but should always be scientifically sound and provide results that are reliable and reproducible. Due to the limitations of the analytical tools in early clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability; therefore, bridging nonclinical and/or clinical studies, as appropriate, might be needed.

E. Nonclinical and Clinical Considerations (2.5)

1. Factors To Be Considered in Planning Nonclinical and Clinical Studies (2.5.1)

Determinations of product comparability can be based solely on quality considerations (see section 2.2) if the manufacturer can provide assurance of comparability through analytical studies as suggested in this document. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis in consideration of various factors, which include among others:

Quality findings

- Drug product — The type, nature, and extent of differences between the postchange product and the prechange product with respect to quality attributes including product-related substances, the impurity profile, stability, and excipients.
  For example, new impurities could warrant toxicological studies for qualification;
- Results of the evaluation/validation studies on the new process including the results of relevant in-process tests;
- Availability, capabilities, and limitations of tests used for any comparability studies.

The nature and the level of knowledge of the product

- Product complexity, including heterogeneity and higher order structure — Physicochemical and in vitro biological assays might not be able to detect all differences in structure and/or function;
- Structure-activity relationship and strength of the association of quality attributes with safety and efficacy;
- Relationship between the therapeutic protein and endogenous proteins and the consequences for immunogenicity;
- Mode(s) of action (unknown vs. known, single vs. multiple active sites).

Existing nonclinical and clinical data relevant to the product, aspects of product use, and product class

- Therapeutic indications/target patient groups — The impact of possible differences can vary between patient groups, e.g., risk for unintended immunogenicity. It may be appropriate to consider the consequences separately for each indication;
- Posology, e.g., dosing regimen, route of administration — The risk of certain possible consequences of a difference, such as immunogenicity, could be higher with chronic administration as compared to short-term administration; subcutaneous administration might induce immunogenicity more often than intravenous administration;
- The therapeutic window/dose-response curve — The impact of a certain change could be different for products that have a wide therapeutic window as compared to those with a more narrow window. The safety or efficacy of products with a steep or a bell-shaped dose-response curve can be affected by minor changes in pharmacokinetics or receptor-binding;
- Previous experience, e.g., immunogenicity, safety — The experience with the original product or with other products in the same class can be relevant, especially with regard to rare adverse effects, e.g., knowledge about the consequences of immunogenicity;
- Pharmacokinetic (PK)/pharmacodynamic (PD) relation, distribution, clearance.

2. *Type of Studies (2.5.2)*

The nonclinical and clinical studies referred to in this document might include, depending on the situation, PK studies, PD studies, PK/PD studies, clinical efficacy studies, specific safety studies, immunogenicity studies, and pharmacovigilance studies. The purpose of these studies is to enable comparison of pre- and postchange product. Where appropriate, these studies should be direct comparative studies.

Contains Nonbinding Recommendations

GLOSSARY (3)

Comparability Bridging Study: A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process.

Comparable: A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

Comparability Exercise: The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.

Quality Attribute: A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency, and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes.

REFERENCES (4)

Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (Q5A).

Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (Q5B).

Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C).

Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (Q5D).

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B).

Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Q7A).

Text on Validation of Analytical Procedures (Q2A).

Validation of Analytical Procedures: Methodology (Q2B).

Common Technical Document for the Registration of Pharmaceuticals for Human Use (M4Q).

Stability Testing of New Drug Substances and Products (Q1AR).

Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6).

Statistical Principles for Clinical Trials (E9).

Choice of Control Group and Related Issues in Clinical Trials (E10).

BERLEX LABORATORIES, INC., Plaintiff, v. FOOD AND DRUG ADMINISTRATION, et al., Defendants.
Civil Action No. 96-0971 (JR)

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

942 F. Supp. 19; 1996 U.S. Dist. LEXIS 15169

October 7, 1996, Decided
October 7, 1996, FILED

DISPOSITION: [1]** Plaintiff's motion for summary judgment [# 48] DENIED. Defendants' motions to dismiss [# 36, # 39] treated as motions for summary judgment GRANTED and case DISMISSED.

CASE SUMMARY

PROCEDURAL POSTURE: Plaintiff drug manufacturer filed a motion for summary judgment in its action against defendant United States Food and Drug Administration (**FDA**) and intervenor competitor drug manufacturer (competitor). The drug manufacturer sought a judgment declaring that the **FDA's** approval of the competitor's interferon beta product was unlawful and an order rescinding its approval. The **FDA** and the competitor filed cross-motions for summary judgment.

OVERVIEW: The drug manufacture was given market exclusivity of its drug under the Orphan Drug Act (Act), 21 U.S.C.S. §§ 360aa-360dd. When the **FDA** approved the competitor's similar drug, the drug manufacturer sought recission of its action. The competitor intervened and all parties filed motions for summary judgment. The court on review granted the cross-motions of the **FDA** and the competitor. Giving deference to the **FDA's** interpretation of its regulations, the court held that the **FDA** had an adequate basis upon which to consider the competitor's drug "clinically superior" to the drug manufacturer's version when it relied exclusively on a single side effect. Accordingly, it did not act arbitrarily in nullifying the drug manufacturer's orphan drug protection. The drug manufacturer had standing to complain under the Public Health Service Act (PHSA), 42 U.S.C.S. § 262, of the approval. The record contained ample support for **FDA's comparability** determination and for its finding that the competitor's drug was "safe, pure and potent" as required by the PHSA. As the **FDA's comparability** guidance document was interpretive and not legislative, its issuance did not require notice-and-comment rulemaking.

OUTCOME: The court denied the drug manufacturer's motion for summary judgment in its action to rescind the **FDA's** approval of a similar drug manufactured by a competitor. The court granted the cross-motions for summary judgment by the **FDA** and the competitor that the **FDA's** actions were not arbitrary, capricious, or unlawful.

CORE TERMS: clinical, regulation, comparability, comparable, clinically, interferon, biological, beta, manufacturer, notice-and-comment, site, Orphan Drug Act, rulemaking, injection, potency, purity, summary judgment, necrosis, interpretive, exclusivity, joint venture, memorandum, issuance, regulations provide, economic interest, new drug, orphan, manufacture, scientific, challenger

LexisNexis(R) Headnotes • Hide Headnotes

Administrative Law > Informal Agency Actions

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

HN1 The Orphan Drug Act, 21 U.S.C.S. §§ 360aa-360dd, permits Food and Drug Administration (**FDA**) approval of a drug that treats the same condition as did an original orphan drug if the **FDA** determines that the two drugs are not the same. A new drug is not considered the same as a previously approved drug if the new drug is "clinically superior." 21 C.F.R. § 316.3(b)(13)(ii). A new drug is "clinically superior" if it offers greater safety in a substantial portion of the target populations. 21 C.F.R. § 316.3(b)(3)(ii). More Like This Headnote

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

HN2 21 U.S.C.S. § 360bb(2) provides that "orphan drugs" are drugs that treat diseases 1) affecting fewer than 200,000 persons or 2) affecting more than 200,000 person for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States. More Like This Headnote

Administrative Law > Informal Agency Actions

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

HN3 Under Food and Drug Administration (**FDA**) regulations, an example of "greater safety" in a substantial portion of a target population is the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. 21 C.F.R. § 316.3(b)(3)(ii). Even a small demonstrated diminution in adverse reactions is sufficient to allow a finding of clinical superiority of a new drug over an original orphan drug. More Like This Headnote

Administrative Law > Judicial Review > Reviewability > Preclusion

Administrative Law > Agency Rulemaking > Rule Application & Interpretation

HN4 The court gives deference to the Food and Drug Administration's (**FDA**) interpretation of its regulations. The **FDA's** application of an interpretation in a specific case is upheld if the agency has based its decision upon relevant factors that have evidentiary support. More Like This Headnote

Administrative Law > Judicial Review > Standing

HN5 Prudential standing to challenge an agency decision exists if the challenger is within the zone of interest to be protected or regulated by the statute. A plaintiff has no right to bring suit against an agency, however, if the plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit. More Like This Headnote

Administrative Law > Judicial Review > Standing

HN6 A plaintiff who has a competitive interest in confining a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect. More Like This Headnote

2

Administrative Law > Judicial Review > Standing

HN7 The manufacturer of a "pioneer" drug has standing to sue the Food and Drug Administration (**FDA**) under the Public Health Service Act, 42 U.S.C.S. § 262, for its alleged failure to enforce safety and efficacy standards against a competitor. The interests of the plaintiff and the **FDA** are "systematically aligned" in such a way as to promote the principal safety objective of the statute and the manufacturer is thus a "suitable challenger" for standing purposes. The pioneer drug manufacturer is well-positioned to monitor the **FDA** regulations implementing statutorily mandated requirements when it is their pioneer drug the generic manufacturer seeks to copy. The economic interest of such a plaintiff provides an incentive for the plaintiff to advocate the overriding necessity of ensuring public access to safe commercial drugs. More Like This Headnote

Administrative Law > Agency Rulemaking > Formal Rulemaking

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

Administrative Law > Agency Rulemaking > Rule Application & Interpretation

HN8 42 U.S.C.S. § 262(d)(1) of the Public Health Service Act, 42 U.S.C.S. § 262, authorizes the Food and Drug Administration (**FDA**) to license biological products that meet standards designed to insure the continued safety, purity, and potency of such products. The **FDA's** regulations require applicants for licenses to submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency. 21 C.F.R. § 601.2(a). While no quantitative or measurable "standards" for safety, purity or potency exist, the regulations set out definitions of those terms that guide **FDA's** case-by-case determinations. 21 C.F.R. § 600.3. More Like This Headnote

Administrative Law > Judicial Review > Reviewability > Preclusion

Administrative Law > Agency Rulemaking > Rule Application & Interpretation

HN9 The Food and Drug Administration's (**FDA**) policies and its interpretation of its own regulations are paid special deference because of the breadth of Congress' delegation of authority to **FDA and because of FDA's** scientific expertise. More Like This Headnote

Administrative Law > Agency Rulemaking > Informal Rulemaking

HN10 The Administrative Procedure Act requires notice-and-comment rulemaking when an agency issues new "legislative" or "substantive" rules that establish binding norms having the force of law. 5 U.S.C.S. § 553. "Interpretive" rules, however, are expressly excused from the notice-and-comment requirements. 5 U.S.C.S. § 553(b)(3)(A). An interpretive rule is one issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers. A rule is legislative, rather than interpretive, if any one of the following four questions is answered in the affirmative: (1) whether in the absence of the rule there would not be an adequate legislative basis for agency action to confer benefits or ensure the performance of duties; (2) whether the agency has published the rule in the Code of Federal Regulations; (3) whether the agency has explicitly invoked its general legislative authority: or (4) whether the rule effectively amends a prior legislative rule. More Like This Headnote

COUNSEL: James R. Phelps, Robert A. Dormer, A. Wes Siegner, Jr., Hyman, Phelps & McNamara, P.C., Washington, DC. Drake Cutini, Office of Consumer Litigation, U.S. Department of Justice, Washington, DC, Counsel for Defendants.

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Counsel for Intervenors: Meredith Manning, U.S. Food and Drug Administration, Rockville, MD.

JUDGES: James Robertson, United States District Judge

OPINION: **[*21]** MEMORANDUM OPINION

Plaintiff Berlex Laboratories, Inc. ("Berlex") manufactures Betaseron, a biological drug classified as an interferon beta product. n1 On July 23, 1993, the Food and Drug Administration approved Betaseron for the treatment of multiple sclerosis. Because it was the first interferon [**2] beta product approved for the treatment of MS, Betaseron was also given market exclusivity for seven years under the Orphan Drug Act. 21 U.S.C. §§ 360aa-360dd.

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n1 Interferons are a family of proteins in the human body that inhibit the replication of a wide spectrum of viruses and are important in the functioning of the body's immune system. The interferon beta products discussed in this opinion are produced by modifying and recombining portions of deoxyribonucleic acid (DNA) molecules and inserting the altered molecules into other cells.

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Intervenor-defendant Biogen, Inc. developed an interferon beta product similar to Betaseron. On May 17, 1996, the FDA approved Biogen's product, known as Avonex, for manufacture and sale in the United States for the treatment of MS.

In this action, Berlex seeks a judgment declaring that FDA's approval of Biogen's Avonex was unlawful and an order rescinding that approval. Berlex's claims are that FDA 1) unlawfully nullified Betaseron's Orphan Drug protection upon an arbitrary [**3] and capricious finding that Avonex is "clinically superior" to Betaseron; 2) violated the Public Health Service Act, 42 U.S.C. § 262, and regulations issued thereunder by approving [*22] Avonex without requiring the completion of full clinical trials; and 3) failed to conduct required notice-and-comment rulemaking before issuing a "comparability guidance document" that was important to the approval of Avonex.

Biogen has intervened as a defendant. Cross-motions for summary judgment were argued on September 5, 1996. This memorandum sets forth the reasons for the accompanying order granting the motions of FDA and Biogen and denying the motion of Berlex.

BACKGROUND

FDA's approval of Avonex on May 17, 1996, marked the first time FDA had approved a biological product for manufacture and sale without requiring the completion of full clinical trials on that actual product. In approving Avonex, FDA allowed Biogen to rely on the results of a clinical study of another company's interferon beta product, known as BG9015, after concluding that BG9015 was "comparable" to Avonex.

BG9015 was manufactured in Laupheim, Germany, by a joint venture owned half by Biogen and half by Rentschler Technology. [**4] This joint venture commissioned Dr. Lawrence Jacobs to do a clinical study of BG9015 in the United States beginning in 1990. In 1993, while the clinical trial was going on, the joint venture failed and went into receivership. Production of BG9015 ceased, but researchers had enough BG9015 to complete the clinical trials, which ended in 1994. AR 2, 157-58.

As early as 1991, Biogen had begun separately producing interferon beta products similar to BG9015 at a manufacturing site in Cambridge, Massachusetts. After the Biogen-Rentschler joint venture failed, Biogen sought FDA approval of a new interferon beta, known as BG9216. Rather than conduct new clinical trials of BG9216, Biogen sought to rely on the Jacobs study and sought to demonstrate to FDA that BG9216 and BG9015 were comparable. The FDA concluded that BG9216 and BG9015 were not comparable, however, and declined to consider data from the Jacobs study in connection with the application of BG9216. AR 2.

Biogen then developed the interferon beta cell line that ultimately became Avonex and submitted it for FDA approval. Although FDA had invariably required full-scale clinical trials for new biological drugs in the past, Biogen again [**5] sought to rely on the results of the Jacobs study conducted on BG9015, asserting that Avonex was comparable to BG9015. This time FDA agreed. After extensive biological, biochemical, and biophysical analyses, as well as pharmacokinetic studies in humans, FDA concluded that BG9015 and Avonex were "comparable" -- that they were "biochemically and functionally equivalent" -- and permitted the Jacobs study to be used in place of a separate clinical trial of Avonex itself. AR 2-10, 55-57.

Before Avonex could be approved for sale in the face of Betaseron's exclusivity under the Orphan Drug Act, FDA also had to make a finding that Avonex was "different" from Betaseron. FDA made that finding, basing its conclusion on the substantially less frequent occurrence of the death of skin tissue in the injection area, or injection site necrosis, associated with Avonex. n2 AR 29. FDA also noted that four percent of Avonex patients experience injection site reactions, such as swelling, redness or tenderness, compared to 85 percent of Betaseron patients. On the basis of those comparisons, FDA found Avonex "clinically superior" to Betaseron and therefore "different" for Orphan Drug Act purposes.

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n2 Injection site necrosis sometimes requires surgical drainage or skin grafting for proper treatment. Concerns about injection site necrosis from Betaseron prompted a clinical report published in the New England Journal of Medicine. AR 502.

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On May 17, 1996, FDA approved Avonex "for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations." AR 1.

Approximately three weeks before FDA approved Avonex, it issued and published in the Federal Register a "guidance document." This document stated that FDA regulations permit the approval of biological products on the basis of "clinical data generated from a [*23] precursor product, made prior to a manufacturing change" so long as the manufacturer "can demonstrate that the precursor product is comparable to the manufactured product." FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products ("Comparability Guidance Document"), 3. FDA did not cite or refer to the "comparability guidance document" as a basis for its approval of Avonex. The principles and language embodied in the guidance document, however, were present in the document that announced FDA's approval of Avonex.

ANALYSIS

As a preliminary matter, it should be noted that this decision proceeds from an examination not only of the pleadings, [**7] but also of the administrative record. Defendants' motions have been treated as motions for summary judgment. Marshall County Health Care Auth. v. Shalala, 300 U.S. App. D.C. 263, 988 F.2d 1221, 1226 n.5 (D.C. Cir. 1993). Affidavits submitted by Berlex have not been considered, nor are they deemed to be part of the record of this case. See Camp v. Pitts, 411 U.S. 138, 142-43, 36 L. Ed. 2d 106, 93 S. Ct. 1241 (1973).

1. Elimination of Berlex's market exclusivity

Congress passed the Orphan Drug Act in 1983 to encourage the development of drugs for the treatment of rare diseases. n3 21 U.S.C. §§ 360aa-360dd. The Act provides seven-year market exclusivity for orphan drugs and precludes the grant of FDA approval to other manufacturers of the same drug intended for treatment of the same disease. 21 U.S.C. § 360cc. HN1The statute does permit FDA approval of a drug that treats the same condition as did the original orphan drug if FDA determines that the two drugs are not the same. FDA's implementing regulations provide that a new drug will not be considered the same as a previously approved drug if the new drug is "clinically superior." 21 C.F.R. § 316.3(b)(13)(ii). [**8] The regulations provide further that a new drug is "clinically superior" if it offers "greater safety in a substantial portion of the target populations . . . ." 21 C.F.R. § 316.3(b)(3)(ii). Applying those regulations to Avonex and relying primarily upon the disparity in the incidence of injection site necrosis caused by Betaseron (5%) and Avonex (0%), FDA concluded that Avonex was safer than Betaseron and therefore a "different" drug. AR 29, 502-03.

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n3 HN2"Orphan drugs" are drugs that treat diseases 1) affecting fewer than 200,000 persons or 2) affecting more than 200,000 person for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States. 21 U.S.C. § 360bb(2).

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Berlex challenges FDA's decision that Avonex is "clinically superior" to Betaseron. Berlex argues that it was arbitrary and capricious for FDA to rely exclusively on a single side effect when making that determination and contends that FDA should instead have compared [**9] the "overall safety profiles" of Avonex and Betaseron.

The Orphan Drug Act is silent as to the nature of the analysis FDA must undertake when deciding whether one drug is clinically superior to another. HN3 The regulations provide as an example of "greater safety" the elimination of "an ingredient or contaminant that is associated with relatively frequent adverse effects." 21 C.F.R. § 316.3(b)(3)(ii). FDA has interpreted its regulations to mean that even "a small demonstrated . . . diminution in adverse reactions may be sufficient to allow a finding of clinical superiority." 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992). HN4 That interpretation is entitled to the court's deference. Lyng v. Payne, 476 U.S. 926, 939, 90 L. Ed. 2d 921, 106 S. Ct. 2333 (1986).

FDA's application of that interpretation in a specific case must be upheld if the agency based its decision upon relevant factors that have evidentiary support. Ritter Transportation, Inc. v. ICC, 221 U.S. App. D.C. 312, 684 F.2d 86, 88 (D.C. Cir. 1982), cert. denied, 460 U.S. 1022, 75 L. Ed. 2d 494, 103 S. Ct. 1272 (1983). The substantial disparity between Avonex and Betaseron with regard to injection site necrosis was surely [**10] a factor relevant to safety, and Berlex does not challenge the sufficiency of [*24] the record evidence on that point. FDA had an adequate basis upon which to consider Avonex "clinically superior" to Betaseron, and its decision that Avonex is "different" for purposes of the Orphan Drug Act will not be disturbed.

2. Approval of Avonex without separate clinical trials

Berlex next asserts that FDA's approval of Avonex without requiring Biogen to conduct its own clinical trials contravened the Public Health Service Act ("PHSA") and FDA regulations issued thereunder. Biogen and FDA acknowledge FDA's past insistence upon clinical trials of each drug being considered for approval, but they contend that no statute or regulation requires it and submit that the use of data on "comparable" drugs is within FDA's discretion. In addition, Biogen argues that Berlex lacks standing to complain under the PHSA of the approval of a competitor's drug. The standing question, of course, must be addressed first.

a. Standing

HN5 Prudential standing to challenge an agency decision exists if the challenger is within the "zone of interest to be protected or regulated by the statute . . . ." Association [**11] of Data Processing Serv. Orgs. v. Camp, 397 U.S. 150, 153, 25 L. Ed. 2d 184, 90 S. Ct. 827 (1970). A plaintiff has no right to bring suit against an agency, however, "if the plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit." Clarke v. Securities Indus. Ass'n, 479 U.S. 388, 399, 93 L. Ed. 2d 757, 107 S. Ct. 750 (1987). There is no evidence suggesting that Congress created the PHSA to protect Berlex's economic interest in particular, or competition among drug manufacturers in general. Berlex's standing thus depends on whether its interests "coincide with the protected interests" of the PHSA in such a way that Berlex is a "suitable challenger" of FDA's decision. Hazardous Waste Treatment Council v. Thomas, 280 U.S. App. D.C. 296, 885 F.2d 918, 922-23 (D.C. Cir. 1989).

The present action is obviously driven by Berlex's economic interest in maintaining Betaseron's market position. That motivation, however, does not deprive Berlex of standing.

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As the Court of Appeals recently concluded, HN6"a plaintiff who has a competitive interest in confining [**12] a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect." First Nat'l Bank & Trust v. Nat'l Credit Union, 300 U.S. App. D.C. 314, 988 F.2d 1272, 1277 (D.C. Cir. 1993).

The question that must be resolved is whether the objectives of the PHSA are more likely to be frustrated or promoted by Berlex's claim. Scheduled Airlines Traffic Offices, Inc. v. Department of Defense, 87 F.3d 1356, 1359 (D.C. Cir. 1996) (citations omitted); First Nat'l Bank & Trust, 988 F.2d at 1275 (quoting Clarke, 479 U.S. at 397 n.12). Here, Berlex alleges that FDA has failed to comply with a statute that is focused on the safety and efficacy of new drugs.

On facts remarkably similar to those of the present case, the Third Circuit recently confirmed a drug manufacturer's standing to challenge FDA approval of a competing drug. Schering Corp. v. FDA, 866 F. Supp. 821 (D.N.J. 1994), aff'd, 51 F.3d 390 (3d Cir.), cert. denied, 133 L. Ed. 2d 195, 116 S. Ct. 274 (1995). The district court in that case held that HN7the manufacturer [**13] of a "pioneer" drug had standing to sue the FDA for its alleged failure to enforce safety and efficacy standards against a competitor. The court reasoned that the interests of the plaintiff and the FDA were "systematically aligned" in such a way as to promote the principal safety objective of the statute and that the manufacturer was thus a "suitable challenger" for standing purposes. Id. at 825. The Third Circuit affirmed, observing that the pioneer drug manufacturer was "well-positioned to monitor the FDA regulations implementing statutorily mandated requirements . . . when it is their pioneer drug the generic manufacturer seeks to copy." Schering Corp. v. FDA, 51 F.3d 390, 396 (3rd Cir. 1995). The court, in particular, emphasized [*25] that the economic interest of the plaintiff provided an incentive for the plaintiff to advocate the "overriding necessity of ensuring public access to safe commercial drugs." Id.

Berlex's interests are aligned sufficiently with those of the intended beneficiaries of the PHSA. As a manufacturer of a similar product that was recently approved, Berlex has both the expertise and the incentive to monitor FDA's actions. Berlex's challenge, whatever [**14] its merits, has required the FDA to justify its acknowledged departure from past drug approval procedures and to explain its conclusions that reliance on clinical tests of a "comparable" product will not compromise the statutory requirement of "safety, purity, and potency." 42 U.S.C. § 262(d)(1). Berlex has standing to bring this claim under the PHSA.

b. FDA approval process

HN8The PHSA authorizes FDA to license biological products that "meet standards designed to insure the continued safety, purity, and potency of such products . . . ." 42 U.S.C. § 262(d)(1). FDA's regulations require applicants for licenses to "submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency . . . ." 21 C.F.R. § 601.2(a). No quantitative or measurable "standards" for safety, purity or potency exist. The regulations do, however, set out definitions of those terms that guide FDA's case-by-case determinations. 21 C.F.R. § 600.3. n4

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n4 For example, the regulations define "safety" as "the relative freedom from harmful effect

to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." 21 C.F.R. § 600.3(p).

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Neither the PHSA itself nor FDA's regulations issued under the PHSA provide that the clinical study offered to demonstrate the safety, purity and potency of a new biological product shall have been conducted on that very product. The absence of a specific provision on this point raises the now-standard question of whether the agency's view of what is "appropriate in the context of this particular program is a reasonable one." Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 845, 81 L. Ed. 2d 694, 104 S. Ct. 2778 (1984). HN9[↑]FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise. Lyng v. Payne, 476 U.S. 926, 939, 90 L. Ed. 2d 921, 106 S. Ct. 2333 (1986); see Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 216 (D.D.C. 1996).

FDA's decision in this case to allow Biogen to rely on the clinical trials of BG9015 was based upon a reasonable interpretation of the PHSA and FDA regulations. FDA conceded that it had never before approved a new biological drug on the basis of a clinical study of a "comparable" [**16] drug, but FDA demonstrated by reference to public documents that the principle of comparability was not unknown and that, in fact, it had been previously applied in other situations. FDA argues that its extension of the comparability principle in this case reflects a reasonable interpretation of the statutory grant of its regulatory authority, particularly given the rapidly changing scientific and technological context in which FDA regulates biological products. The record contains ample support for FDA's comparability determination and for its finding that Avonex is "safe, pure and potent" as required by the statute. This court may not substitute its own judgment for that of the FDA, an agency created by Congress to address difficult scientific issues such as the one at the center of this claim.

3. Comparability Guidance Document

Berlex's third claim focuses on FDA's issuance, on April 25, 1996, of the "guidance document" that explained FDA's position on comparability. Berlex had predicted (accurately) that the guidance document would prove to be the harbinger of FDA's decision on May 17, 1996, to approve [*26] Biogen's license applications for Avonex. n5 Berlex's argument [**17] now is that the guidance document was unlawfully issued without the notice-and-comment rulemaking required by the APA.

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n5 The original complaint in this action, filed on April 26, 1996, sought to enjoin FDA from approving Avonex. Plaintiff's application for a temporary restraining order was denied on April 30, 1996.

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The guidance document, which lays out FDA's policy for accepting clinical trials completed

on "comparable" products, was published three weeks before FDA approved Avonex. The relationship between FDA's issuance of the guidance document and its approval of Avonex is not clear. FDA and Biogen both point out that the guidance document was not mentioned in the administrative record. FDA's explanation -- that "the agency applied the policy described in the comparability guidance" but "did not rely on the guidance in doing so" -- is murky. FDA's Opposition to Plaintiff's Motion for Summary Judgment, 7. For purposes of this analysis it will be assumed that (1) FDA attached considerable importance to the [**18] comparability guidance document and (2) the issuance of the guidance document and the approval of Avonex were in fact related events. Those assumptions make it necessary to address Biogen's claim that the guidance document was improperly issued.

HN10↑The APA requires notice-and-comment rulemaking when an agency issues new "legislative" or "substantive" rules that establish binding norms having the force of law. 5 U.S.C. § 553; American Mining Congress v. Mine Safety & Health Admin., 302 U.S. App. D.C. 38, 995 F.2d 1106, 1109 (D.C. Cir. 1993). "Interpretive" rules, however, are expressly excused from the notice-and-comment requirements. 5 U.S.C. § 553(b)(3)(A). An interpretive rule is one "issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers." Shalala v. Guernsey Memorial Hosp., 131 L. Ed. 2d 106, 115 S. Ct. 1232, 1239 (1995). In this circuit, a rule is legislative, rather than interpretive, if any one of the following four questions is answered in the affirmative:
(1) whether in the absence of the rule there would not be an adequate legislative basis for . . . agency action to confer benefits or ensure the [**19] performance of duties,
(2) whether the agency has published the rule in the Code of Federal Regulations,
(3) whether the agency has explicitly invoked its general legislative authority, or
(4) whether the rule effectively amends a prior legislative rule.

American Mining Congress, 995 F.2d at 1112.

In this case, all four questions are answered in the negative. First, as noted in the previous section of this memorandum, FDA had statutory authority to approve Avonex without requiring clinical trials. Second, the rule was not published in the Code of Federal Regulations. Third, the agency did not invoke its general legislative authority with respect to the guidance document. And fourth, the comparability guidance document did not effectively amend a legislative rule because it neither repudiates nor is inconsistent with any pre-existing FDA regulations. See Shalala v. Guernsey Memorial Hosp., 131 L. Ed. 2d 106, 115 S. Ct. 1232, 1239 (1995); National Family Planning and Reproduction Health Ass'n, Inc. v. Sullivan, 298 U.S. App. D.C. 288, 979 F.2d 227, 235 (D.C. Cir. 1992).

The existing FDA regulation requires the submission of "data derived from nonclinical laboratory [**20] and clinical studies." 21 C.F.R. § 601.2(a). In the guidance document, FDA interpreted that language to include data from clinical studies completed on "comparable" biological products. Comparability Guidance Document, 3. That interpretation extended the boundaries of previous FDA actions and policies, to be sure, but it did not "run[] 180 degrees counter to the plain meaning of the regulation," as did the agency directive at issue in National Family Planning and Reproduction Health Ass'n, Inc. v. Sullivan, 298 U.S. App. D.C. 288, 979 F.2d 227, 235 (D.C. Cir. 1992). In National Family Planning, the Department of Health and Human Services had announced to the public that its interpretation of a regulation (concerning the provision of abortion counseling by physicians) was [*27] clear and definitive, and that interpretation was indeed upheld by the Supreme Court. Under different political leadership, the agency then issued a "directive," without notice-and-comment rulemaking procedures, that effectively reversed its earlier position. The Court of Appeals set the agency action aside, ruling that the agency

had amended a legislative rule. 979 F.2d at 231-32. In this case, by contrast, [**21] FDA's decision to rely upon the clinical trial of a "comparable" drug was not a reversal of course. It was a policy development with identifiable antecedents.

Nor has Berlex succeeded in demonstrating that the guidance document conflicts with any other FDA regulation. Berlex's assertion of potential conflicts that might arise between the comparability guidance document and other FDA regulations at some future time falls short of a showing that clear inconsistencies now exist.

Because the comparability guidance document was interpretive and not legislative, its issuance did not require notice-and-comment rulemaking.

CONCLUSION

FDA did not act unlawfully when it: 1) determined that Avonex is "clinically superior" to Betaseron; 2) approved Avonex for use by patients with MS without requiring clinical trials of Avonex; and 3) issued its comparability guidance document without notice-and-comment rulemaking. FDA's determination that Avonex is safe, pure and potent is amply supported by the record. An appropriate order accompanies this memorandum.

James Robertson

United States District Judge

October 7, 1996

ORDER

For the reasons stated in the accompanying memorandum, [**22] it is this 7th day of October, 1996,

ORDERED that plaintiff's motion for summary judgment [# 48] is DENIED. It is

FURTHER ORDERED that defendants' motions to dismiss [# 36, # 39] are treated as motions for summary judgment and GRANTED and this case is DISMISSED.

James Robertson

United States District Judge

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 11 December 2003
EMEA/CPMP/BWP/3207/00/Rev 1*

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

GUIDELINE ON COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES

DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY	December 2003
TRANSMISSION TO CPMP	December 2003
ADOPTION BY CPMP	December 2003
DATE FOR COMING INTO OPERATION	December 2003

Note:

* The document of 20 September 2001 has been updated to make changes such as 'drug substance' to 'active substance', 'drug product' changed to 'finished product', 'note for guidance' to 'guideline', 'marketed' to 'authorised', etc. The paragraph mentioning the difference between essential similarity and comparability is removed in the light of the reference to similar biological medicinal products in the new annex to Directive 2001/83/EC. This guideline should also be read in conjunction with the guideline on non-clinical/clinical issues.

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COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE QUALITY ISSUES

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Purpose

It is well acknowledged that medicinal products of biotechnological origin i.e. medicinal products containing proteins derived from r-DNA and hybridoma techniques are often subject to change in their manufacturing process (active substance and/or finished product). Improvement of product quality, increase in production yield and global productivity or improving process economics are the main reasons for introduction of such changes. These changes can be introduced either during the development phase or after the Marketing Authorisation has been granted. Whatever the production step at which the change occurred, there is a necessity to compare the product derived from the modified process to the one derived from the currently used process, essentially to ascertain that introduction of the change did not alter the physico-chemical and biological characteristics of the product. These characteristics (mainly reflected by the current in-process controls and release specifications) are of utmost importance as they are the basis on which quality, safety and efficacy of the product are claimed. A change in these characteristics may lead to a different safety or efficacy profile of the product. As a consequence, a comparability exercise should be considered for a given product following change made in its manufacturing process.

This Guideline does not cover changes introduced at a very early stage of development (namely before pre-clinical studies and initial clinical trials to evaluate preliminary safety are conducted).

In addition, there is a need to consider the necessity for conducting comparability studies for situations where a manufacturer is seeking approval of a Marketing Authorization for a biotechnology-derived product claimed to be similar to one already authorised.

Whatever the situation, the reasoning (step by step approach) as regards the comparability exercise should be identical. In this approach, the following parameters should be considered as key points: i) characterisation studies, ii) validated manufacturing process, iii) release data, iv) stability data, and, in wider perspective v) pre-clinical and clinical studies.

This Guideline has been prepared with reference to the scientific principles already developed, for example in the following documents:

1.2 Regulatory framework

- CPMP Guideline on Production and Quality Control of Medicinal Products derived by Recombinant DNA Technology.
- CPMP Guideline on Production and Quality Control of Monoclonal Antibodies
- CPMP/ICH/365/96 Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B).
- CPMP/ICH/139/95 Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products (Q5B).
- CPMP/ICH/138/95/ Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C).
- CPMP/ICH/294/95 Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products (Q5D).
- CPMP/ICH/295/95 Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products derived from Cell Lines of Human or

Animal Origin (Q5A).

These Guidelines address the key elements on which specifications for quality control of biotechnology-derived proteins should be set. Further guidelines on general quality requirements should also be taken into account.

1.3 Scope

This Guideline addresses the issue of demonstration of comparability for medicinal products of biotechnological origin i.e. containing proteins derived from r-DNA and hybridoma techniques so-called biotechnology-derived proteins. As a consequence the principles adopted and explained in this document should apply to proteins and peptides, their derivatives and products of which they are components (e.g. conjugates). These proteins are produced from recombinant cell-culture expression system and can be highly purified and characterised using an appropriate set of analytical procedures. The principles and arguments outlined in this document may be used as a framework when envisaging similar situations for other biological products not covered by this Guideline.

1.4 Comparability exercise

Comparability is the exercise that will demonstrate that two products have similar profile in terms of Quality, Safety, Efficacy. The comparability exercise should be viewed as a sequential process. The claim of comparability in terms of Quality, Safety and Efficacy can be deduced from quality studies (partial or comprehensive) and may need to be supported by bridging preclinical/clinical studies.

The comparability exercise and the claim of comparability is applicable to the two situations and two different procedures:

- change introduced by one manufacturer (or related manufacturers) into its own process for a given product (variation) either before the granting of a marketing authorisation or after the granting of a marketing authorisation (variation procedure).
- for a product claimed to be similar to another one already authorised (new application).

2. COMPARABILITY EXERCISE FOR CHANGE INTRODUCED IN THE MANUFACTURING PROCESS OF A GIVEN PRODUCT

As mentioned in the introduction, it is frequent for a manufacturer, in the life cycle of a product, to introduce changes in the production process. These changes can be introduced either during the development phase (see also 2.2.1) or after the marketing authorisation has been granted. In all cases, whatever the stage of development where the change is introduced, it is the responsibility of the manufacturer to assess to what extent the change introduced i) modify the quality profile of the resulting product and ii) may potentially impact on safety and efficacy.

In this chapter, the various key elements to be considered in designing the comparability exercise and extensiveness of the required studies are presented.

2.1 Points to consider in performing comparability studies

The comparability exercise should be considered as a whole set of interrelated considerations encompassing the three evaluation criteria of quality, safety, and efficacy.

Indeed, any change or modification made to a production process may impact on the quality, safety and efficacy of the finished product. Many different types of changes can be introduced in the manufacturing process. Annex I lists the most common changes introduced in the manufacturing process. Regulations have classified pharmaceutical variations as minor and major. However this classification may not be appropriate as the basis for designing

comparability strategies since even changes considered as minor may result in relevant modifications of the quality profile of the product. Consequently, it is advisable not to classify *a priori* any changes as minor or major based on the type of change itself, but to consider the potential consequences (which will be major or minor) of the change introduced on product quality, safety and efficacy.

Depending on the consequences in terms of quality, safety and efficacy of the introduced change, various situations with different levels of complexity can be foreseen and thus the comparability exercise:

- will be limited to the strict process validation of the change introduced.
- will be extended to various quality criteria such as in-process controls, stability data, thorough analytical and biological characterisation of the product.
- cannot be fully carried out based solely on quality criteria and needs to be further documented as regards *in vivo* safety/efficacy profile.

Consequently, extensiveness of the comparative studies will depend on:

- the stage of development when the change is introduced
- the quality criteria consideration regarding the potential impact of the change introduced on the purity as well as physico-chemical and biological properties of the product
- the suitability and availability of analytical methods to detect potential modification(s) as regards product characteristics.
- the relationship between quality criteria set with safety and efficacy results, based on the overall pre-clinical and clinical experience (safety and efficacy criteria consideration).

2.1.1 Stage of development when the change is introduced

The comparability exercise should be carried out when change is introduced either during development, i.e. after critical studies (demonstration of product consistency, stability studies, pre-clinical studies, pivotal phase II/III clinical studies) have been initiated or after the marketing authorisation has been granted. Needless to say that where change is introduced at a very early stage of development (namely before pre-clinical studies and initial clinical trials to evaluate preliminary safety are conducted) the basic issue of comparability is not raised.

2.1.2 Quality criteria consideration

The complexity of the concerned molecular entity should be considered as a major criterion in discussing comparability. Indeed, depending on the physico-chemical properties of the molecule (e.g. from primary to quaternary structure, length of the sequence, post-translational modifications such as extent and nature of glycosylation, N/C terminal modifications), it can sometimes be difficult to define precisely the product and there is a need to use an extensive series of analytical techniques exploiting the various physicochemical properties (size, charge, hydrophobicity, etc.) and biological activity of the molecule.

In many cases, due to the inherent variability of the biological process, the end-product consists of a complex mixture of molecules (product-related substances). This heterogeneity, which is taken into account when assessing the in-vivo behaviour of the product, should be characterised to assure batch-to-batch consistency. Heterogeneity contributes to the difficulty of the comparability study due to the complexity of these products. The *Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* stipulates that specifications for active substances and finished products should be considered as the result of a total quality control strategy which includes cloning strategy, expression and genetic stability, thorough product characterisation, validation and consistency

of the manufacturing process (in-process controls, quality monitoring of raw materials and reagents), stability data, as well as quality of the batches used in pre-clinical and clinical studies. It is noteworthy that, in some cases, it may not be sufficient to demonstrate only compliance with the approved specifications and additional studies on protein structure, impurity profile and/or biological activity may be needed.

Consequently, as an initial approach when introducing a change in a given process, the following parameters, on which specifications have been based, should be considered as key points: i) characterisation studies, ii) validated manufacturing process, iii) release data, iv) stability data, and, in wider perspectives v) pre-clinical and clinical experiences. They should be evaluated in a step by step approach when discussing comparability.

2.1.3 Suitability of available analytical methods

Given the complexity of the molecule and its inherent heterogeneity, it is sometimes difficult to guarantee that the set of analytical techniques (even state-of-the-art and acknowledging the huge progress made in the field) selected by the manufacturer will be relevant or able to detect any slight or discrete modifications of the characteristics of the biotechnology-derived product. It is however the demonstration of absence of such discrete modifications which could authorise a manufacturer to declare its product indistinguishable in all aspects pertinent to the evaluation of quality.

Whenever a change is introduced in the production process, manufacturers should provide assurance that a comprehensive quality control program has been developed and an appropriate set of analytical methods have been selected in order to assess the comparability of the product before and after the change have been introduced. The degree of validation of the analytical methods used should be appropriate to the stage of development. Whatever the impact of the change(s), the analytical methods should allow suitable assessment of the manufacturing process as well as specifications regarding both the active substance and the finished product. The main task will be to establish to what extent the analytical methods used are able to detect any slight modification possibly introduced by the change

2.1.4 Safety and efficacy criteria consideration

It should be noted that specifications for active substance and finished product are based on data derived from batches, which have been used in pre-clinical and clinical studies. This means that specifications applied have been validated both by and for the *in vivo* use of the product.

When a change in the manufacturing process results in modifying the specifications (active substance/finished product) and/or in process controls, it should be considered whether the comparability exercise can be restricted to quality aspects or, if quality aspects are not sufficient, it should also include safety and/or efficacy criteria. In situation where differences either are identified or are suspected, appropriate pre-clinical and clinical studies could be considered as the only definite way to demonstrate comparability, at least for some specific features such as immunogenicity.

In this respect, the nature and the extent of the pre-clinical and/or clinical studies to be performed when assessing the potential consequences of the change introduced should be justified and designed taking into account the degree of knowledge of the molecule, its mode of action and the experience already gained as regards *in vivo* behaviour.

2.2. Strategies of comparison depending on the change introduced in the manufacturing process

The manufacturer, when introducing a change in a manufacturing process (active substance or finished product) is confronted with two different approaches as regards the strategy to be

applied:

a) the initial hypothesis considers that the change introduced will not have any impact on the quality criteria of the product. In this case, assurance has to be provided that the in-process control and/or the release data found (active substance or finished product specifications), as compared to those obtained using the previous process, have not been modified. The comparability exercise can be acceptable provided that the methods used are sensitive enough to detect slight differences in the structure of the molecular entity. When routine tests are considered as inappropriate to pick up subtle differences, additional studies, using more powerful analytical methods such as those previously performed in characterisation studies (during the initial development), should also be envisaged. In case the expected quality acceptance criteria are not met, a complete validation program should be carried out (see point 2 here below).

b) the initial hypothesis considers that the change introduced will impact on the quality of the product. In this case, consequences of the change(s) on the characteristics of the product should be investigated using a full set of validation data with particular emphasis on characterisation, batch-to-batch consistency and stability. In addition, the potential impact of the change as regards safety and efficacy has to be taken into consideration.

Depending on the process level where the change is introduced, several controls (monitoring, follow-up) would have to be performed sequentially all along the process leading to the final intended finished product.

2.2.1 Change with no impact on quality criteria (in-process controls as well as active substance and/or finished product specifications)

In this case, the comparability exercise can be restricted to the change introduced. Manufacturer should focus on the modification introduced and illustrate that the change has no impact on the whole set of quality acceptance criteria by the results obtained for a suitable number of consecutive batches (in-process controls and release specifications). However, depending on the change introduced, the need for stability data cannot be systematically excluded. Such change does not call into doubt the quality of the active substance/finished product and thus does not put into question what has already been established dealing with safety/efficacy.

This case could be encountered in situations such as: change in reagent supplier, change in excipient supplier, etc. In such cases, if the quality results for one batch are found different, assurance that these results are directly linked to the specific change introduced (and not linked to any other adverse events) should be provided and the others situations, as described hereafter, should apply.

2.2.2 Change with impact on in-process controls without impact on active substance and/or finished product specifications

Consequent to the change (introduced, although there are no modification with respect to release specifications (active substance and/or finished product), some in-process controls needs to be refined in a way to guarantee reproducibility of the modified process. Data (revised in-process controls but unmodified release specifications) on a suitable number of consecutive batches have to be provided to i) illustrate the consistency of the manufacturing process and ii) ascertain that release specifications remain unchanged. In addition, stability studies should be initiated and data provided on several batches (active substance and/or finished product). In this situation, as for the one mentioned in section (3.1), change introduced does not put into question what has already been established dealing with safety/efficacy.

The comparability exercise can be acceptable provided that the methods used are sensitive

enough to detect slight differences in the structure of the molecular entity. When routine tests are considered as inappropriate to pick up slight differences, additional studies, using more powerful analytical methods such as those previously performed in characterisation studies (during the initial development), should also be foreseen.

2.2.3 Change with impact on quality criteria (in-process as well as active substance and/or finished product specifications) and no anticipated consequences on safety/efficacy

Demonstration of comparability should be based on the following:

- Quality: validation of the process based on results from a suitable number of consecutive batches, and stability data. As a consequence, based on thorough characterisation studies (including analytical state-of-the-art methods/tools used in initial development but not retained as part of the routinely performed tests), the specifications have to be re-discussed and changed.
- Safety/Efficacy: in the light of the identified modifications in terms of molecular identity (including heterogeneity and impurity profile), the argument that there are no consequences regarding safety and efficacy should be discussed and justified by the manufacturer.

2.2.4 Change with impact on quality criteria (in-process as well as active substance and/or finished product specifications) and anticipated consequences on safety/efficacy

If the modification identified as regards quality criteria raise scientifically-based questions in terms of safety/efficacy, additional pre-clinical and/or clinical studies may be necessary to provide assurance about the safety and efficacy of this product.

Considering the degree of knowledge available at the end of pivotal clinical studies or post-marketing as regards the relationship between clinical efficacy and quality characteristics of the product, the manufacturer should provide data, based on a suitable clinical study protocol, on possible consequences in terms of safety and efficacy. These considerations are product specific and consequently, depending on the specific situation the manufacturer is confronted with, the protocol will consist either i) in a suitable and well justified bridging study or ii) in more extensive studies (see Guideline on non-clinical and clinical issues).

3. COMPARABILITY EXERCISE FOR A PRODUCT CLAIMED TO BE SIMILAR TO ANOTHER ONE ALREADY AUTHORISED

In this case the manufacturer, although possessing all the necessary information on his own manufacturing process, would normally not have access to all necessary information that could allow comparison in terms of quality with any other products already on the market. Indeed, the expression/vector system, production and purification process, facility/equipment, analytical techniques, etc. may be different from other manufacturers; the extent of the difference cannot be evaluated by the second applicant.

It should be recognised that, in most cases, comparison can be made against the published data, such as in a pharmacopeial monograph with respect to gross physico-chemical or biochemical characteristics of the molecule such as molecular weight, pI, biological activity, etc. However, as explained in this guideline, comparison based on testing and characterisation of active substance and finished product is not sufficient to establish all aspects pertinent to the evaluation of quality, safety and efficacy for a biotechnology-derived protein.

Consequently, with the above considerations in mind, this situation represents the most complicated case. As such, an extensive comparability exercise will be required. The extent

of the pre-clinical and/or clinical bridging studies will depend on the nature of the active substance and formulation, and the complexity of its molecular structure as well as the possible differences as compared to the reference product (including impurities and stability, and in some cases the finished product formulation).

4. CONCLUSION

The following factors should be taken into consideration in any comparability study:

i) the complexity of the molecular structure,

ii) the type of change(s) introduced in the manufacturing process, and

iii) their impact on quality, safety and efficacy.

For each individual situation, a step by step approach should be used to identify any potential impact consequential to process change(s) on the molecular integrity and consistency. A flexible approach should be adopted taking into account progress in science and technology. For products claimed to be similar to another already authorised, the comparability strategy may require bridging studies to address the underlying issues relating to pre-clinical pharmacology/toxicology, and clinical safety/efficacy. It should be recognised that in cases, where satisfactory comparability may not be demonstrable, a full preclinical and clinical data package will be required.

ANNEX I

Type of changes to a manufacturing process

Many different types of changes can be introduced in a manufacturing process. A non-exhaustive list of changes following the sequence proposed in the Biotech Headings Notice to the Applicants is detailed below.

- Formulation and filling
  - Excipient
  - Equipment
  - Change in the manufacturing protocol
  - Scale
  - Change or additional manufacturing site/facility
  - Shipping conditions
- Finished product
  - Batch definition
  - Shelf-life
  - Container/closure system
  - Shipping conditions
  - Storage conditions
- Expression system
  - Master cell bank:
    - new bank derived from existing cell line or initial clone
    - Raw material change
    - Storage conditions
  - Working cell bank:
    - Manufacturing change: raw material (cf. fermentation), new method of production.
    - Storage conditions
- Fermentation/culture process
  - Raw materials: new supplier, specifications, addition/substitution/elimination of raw materials, media composition
  - Cell culture conditions: pH, oxygen, temperature, time, mode
  - Scale of fermentation/cell culture
  - Equipment
  - Change or additional fermentation site/facility.
- Purification process
  - Column/resin change : size of the column, supplier, cleaning and storage conditions
  - Reagents: new supplier, specifications, replacement of raw materials
  - Purification protocol: addition, substitution, elimination of a specific step
  - Scale of the downstream process
  - Change or additional purification site/facility
  - Equipment

- Active substance
  - Batch definition, pooling strategy
  - Shelf-life
  - Container/closure system
  - Shipping conditions
  - Storage conditions

[U.S. Food and Drug Administration]

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

Center for Biologics Evaluation and Research (CBER)

Center for Drug Evaluation and Research (CDER)

APRIL 1996

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April 1996

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

I. Introduction

FDA is issuing this guidance document as part of its on-going initiatives to provide manufacturers with increased flexibility to bring important and improved human biological products to market more efficiently and expeditiously. This document addresses the concept of product comparability and describes current FDA practice concerning product comparability of human biological products regulated by the Center for Biologics Evaluation and Research (CBER), including therapeutic biotechnology-derived products, regulated by CBER, and therapeutic biotechnology-derived products regulated by the Center for Drug Evaluation and Research (CDER). It describes those steps that manufacturers may perform and which FDA may evaluate to allow manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy.

As with other guidance documents FDA does not intend this document to be all inclusive. It is intended to provide information and does not set forth requirements. Manufacturers may follow the procedures outlined in this document or may choose to use alternative procedures that are not provided in this document. Prior to using alternative procedures a manufacturer may wish to discuss the matter with FDA to prevent expenditure of resources generating data that FDA may later determine to be unacceptable.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency's current thinking on demonstration of product comparability. Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

II. Background

Historically, biological products have been complex mixtures of molecular species that were difficult to characterize as individual entities. In some cases, the specific active moiety could not be identified, or the active moiety existed in a milieu of other components that had the potential to affect many of its characteristics. In other cases, the source materials had the potential for transmitting infectious agents. Because of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), a biological product was often defined by its manufacturing process. The manufacturing process for a biological product encompassed manufacturing methods, equipment, and facilities, and was a reason for the current establishment license application (ELA) requirement for biologics. FDA recognized that changes in the manufacturing process, equipment or facilities could result in

changes in the biological product itself and sometimes required additional clinical studies to demonstrate the product's safety, identity, purity and potency.

Improvements in production methods, process and control test methods, and test methods for product characterization have led to the evolution of the regulation of biological products. For example, when a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study, it may not be necessary for the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent. A sponsor may be able to demonstrate product comparability between a biological product made after a manufacturing change and a product made before implementation of the change through different types of analytical and functional testing, with or without preclinical animal testing, described in this document. FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency.

FDA recognizes that a manufacturer may seek to make changes in the manufacturing process used to make a particular product for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. FDA has examined proposed manufacturing changes on a case-by-case basis to determine the type of data, including clinical data, that were necessary to determine product comparability. FDA's evaluations were based, in part, upon the type of manufacturing change and the type of biological product involved. In 1990, in the "Cytokine and Growth Factor Pre-Pivotal Trial Information Package," FDA stated that "significant changes in the manufacturing process...between the time of pivotal clinical studies and submission of the PLA may result in the need to conduct additional validation, animal and *in vitro* studies, and/or clinical studies". In the 1994 " Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use," FDA included a section entitled "Issues Related to Manufacturing Changes (Demonstration of Product Equivalence)." In discussing manufacturing changes during clinical development in this document, FDA acknowledged that such changes were frequent. FDA stated that "depending on the type of *in vitro* assays and animal studies and quality of the data, extensive clinical data demonstrating equivalence may not be necessary." Manufacturers were expected to document all manufacturing changes made during development so that the procedures and manufacturing changes used in the pivotal clinical trials could be validated and the relationship to the marketed product used in earlier trials could be determined.

In the past, FDA has approved manufacturing changes made during or after completion of clinical studies in situations where comparability data have provided assurance that the product would continue to be safe, pure, and potent (effective). Such manufacturing process changes, implemented before or after product approval, have included changes implemented during the expansion from pilot scale to full scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the

manufacturing process such as fermentation, purification, and formulation. In each case, FDA reviewers have used their collective scientific and regulatory experience to provide the best evaluation consistent with the applicable regulatory scheme and current knowledge.

For manufacturing changes prior to product approval, FDA interprets the phrase, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency," in 21 CFR 601.2(a) to include clinical data generated from a precursor product, made prior to a manufacturing change, so that the manufacturer can demonstrate that the precursor product is comparable to the manufactured product. Therefore, a manufacturer may demonstrate comparability between a product made before a manufacturing change and a product made after a manufacturing change. If a manufacturer is able, in FDA's judgement, to demonstrate comparability, FDA may permit the manufacturer to implement the changes without conducting an additional clinical trial(s) to demonstrate efficacy.

FDA recognizes that improvements in production methods, process and control test methods, and test methods for product characterization have allowed manufacturers of biological products to readily identify and assess the impact of changes made to production processes and production facilities. For example, techniques for isolation of macromolecules, product and process related, have improved greatly in recent years. The manufacturer's ability to establish sensitive and validated assays for characterizing the product and biological activity and to evaluate the significance of differences noted in such assays can provide the basis for FDA to assess product comparability without the necessity of repeating clinical efficacy studies.

FDA has reviewed its existing guidance documents in order to clarify inconsistency or ambiguity that could potentially arise from this document and existing guidance. FDA has not found past guidance that it considers inconsistent with the guidance set forth here. However, to the extent that there is any prior guidance from FDA that is interpreted by manufacturers or others as inconsistent with this document, such guidance is superseded. To the extent that a manufacturer may have found or interpreted previous guidance to be ambiguous concerning the issue of manufacturing changes, FDA now clarifies that the comparability guidance described in this document and currently employed by FDA is FDA's operative policy for these products. See, e.g., 1983 Interferon Test Procedures: Points to Consider in the Production and Testing of Interferon Intended for Investigational Use in Humans; 1990 Cytokine Pre-Pivotal Trial Information Package (including reference that a product used in a pivotal clinical trial should be manufactured in a manner which is essentially identical to the manufacturing process that the manufacturer intends to use after approval); and 1995 FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products (including reference that certain aspects of pilot production should be identical to those applied to a full commercial scale).

III. Product Comparability Testing

This document addresses comparability testing for manufacturing changes made prior to product approval and after product approval. For manufacturing changes prior to product approval, under currently applicable laws and regulations, the manufacturer must fully describe the change in any license application or investigational new drug application (IND). FDA urges manufacturers to consult with FDA prior to implementing changes that may result in comparability testing, in order to avoid delay in the review of applications.

Manufacturing changes may result in no observed alteration in a product. Alternatively, a minor alteration in one or more product characteristics, with no previously documented effect, can have either no effect or a substantial effect on the pharmacology of the product. Likewise, a major alteration in one or more product characteristics with no documented effects on the pharmacology of the product, can have either no effect or a substantial effect on the pharmacology of the product. The most important factor to FDA as it assesses product comparability is whether it is anticipated that any of any of these manufacturing changes will translate into significant changes in clinical safety or efficacy.

Manufacturers should carefully assess manufacturing changes and evaluate the product resulting from these changes for comparability to the pre-existing product. Determinations of product comparability may be based on chemical, physical, and biological assays and, in some cases, other non-clinical data. If a sponsor can demonstrate comparability, additional clinical safety and/or efficacy trials with the new product will generally not be needed. FDA will determine if comparability data are sufficient to demonstrate that an additional clinical study(ies) is unnecessary.

Knowledge of the process involved in the manufacture of the product is an integral component in determining the design of an appropriate comparability assessment program. In determining the types of tests needed, FDA may consider the extent of the manufacturing change(s) and the stage of manufacturing at which the change(s) occurs. Comparability testing programs may include a combination of analytical testing, biological assays (*in vitro* or *in vivo*), assessment of pharmacokinetics and/or pharmacodynamics and toxicity in animals, and clinical testing (clinical pharmacology, safety, efficacy), with the usual progression of complexity from analytical to animal studies to human pharmacokinetics and/or pharmacodynamics to clinical safety and efficacy studies. However, comparability testing is not simply a hierarchical system in which a particular test result necessitates the next level of testing. In fact sometimes many of the tests performed are complementary. For example, analysis of the pharmacokinetics profile often suggests biological events not reflected in other types of analyses, e.g., *in vitro* assays.

Manufacturers should provide to FDA extensive chemical, physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. When available, fully characterized reference standards for drug substance and final container material should also be used. Tests should include those routinely used for release of the bulk drug substance and final drug product in addition to tests specifically directed at fully evaluating the impact of the change on the product. Additional testing usually includes in-process assays at the manufacturing step(s) which are most likely affected by the manufacturing change(s).

Manufacturers may use the following categories of tests:

A. Analytical Testing

Analytical testing includes both chemical and physical assays. Tests should be selected which are sensitive to the full range of differences which might result from the process change. The sensitivity and breadth of analytical testing is an important determinant of the nature and extent of additional testing which should be done. These tests should include tests routinely done on all production lots, those initially used to fully characterize product structure and identity and establish product consistency from one production lot to another, and new tests if applicable.

B. Bioassays

Bioassays are functional tests which sponsors should use to assess the activity/potency of the product. These tests may also serve as measurements of the biological integrity (e.g., correct conformation) of the product and thus complement other analytical measurements. Sponsors should validate these assays and have a specific range of acceptable values for defining product activity. They may include appropriate *in vitro* tests (e.g. cell growth, enzymatic activity, anti- viral assays, infectivity assays) or *in vivo* tests in relevant animal models. If the *in vivo* mechanism of action of the product is known, the bioassay (when possible) should reflect this activity. Consideration should be given to *in vivo* and/or *in vitro* models as predictors of the biological effects in humans. For example, with vaccines, sponsors should evaluate the degree of correlation of the test(s) performed (e.g., assessment of immunogenicity) with clinical protection and submit such information to FDA so that it may be determined if a clinical study should be conducted following manufacturing changes. In cases where a product has multiple activities which are not completely correlated or the mechanism of action for clinical usage is unknown, manufacturers may need to consider performing more than one functional assay. When a drug substance has more than one form and a manufacturing change shifts the distribution of forms, determination of the bioactivity of the various forms may be of value in assessing the impact of the change.

The combined precision of the analytical and functional tests and their ability to assess significant aspects of the product are important. Both sponsors and FDA should evaluate data from both types of testing modalities to determine the extent of additional tests needed.

C. Preclinical Animal Studies

In addition to the various *in vitro* studies, *in vivo* studies in animals may be used in comparability evaluations to determine pharmacokinetics parameters, pharmacodynamic activity, or toxicity endpoints. Animal pharmacokinetics data may be needed to assess comparability even in the absence of demonstrated differences in the analytical testing or the functional assays for the product. This is because analytical testing may be insensitive to changes affecting pharmacokinetics, and *in vitro* functional tests may not reflect the time-dependent aspects of distribution. Differences in *in vivo* exposure originating from differences in pharmacokinetics may lead to differences in therapeutic activity. Therefore, assessment of pharmacokinetics is often considered complementary to the functional assay. For hormones however, *in vivo* potency assays often take into account potential pharmacodynamics and pharmacokinetics profiles in animals. For these hormone products, when bioavailability is in question, clinical pharmacology studies may be needed to demonstrate comparability.

Adequate pharmacokinetics measurements may include determination of Cmax, Tmax, AUC and t ½ in either parallel or cross-over study designs. In cases where complications may arise from immune responses to heterologous proteins, cross-over design may be inappropriate. In other cases, sponsors should consider complicating factors related to binding proteins and levels of endogenous protein. In cases where animal studies may not be relevant, clinical pharmacology studies may be needed to show comparability.

Prior to product approval, manufacturers generally should not need to repeat all toxicology studies that were performed with the product manufactured by the previous manufacturing process in order to demonstrate product comparability. In some cases, additional animal studies may only be needed if immunogenicity is the major safety concern. The necessity and extent of additional toxicity studies may depend upon the safety profile of the pre-existing product and on the magnitude of the manufacturing process change and/or effect on the product. Situations in which additional studies may be needed include those where the product has a narrow therapeutic range or where specific safety concerns are present, e.g., when the manufacturing process change raises concerns about possible toxic impurities or adventitious agents which cannot be assessed by analytical testing.

D. Clinical Studies

Clinical studies include human pharmacology studies, immunogenicity, safety, and/or efficacy trials. Although comparability testing can include some form of clinical efficacy studies, usually one of the purposes of comparability testing, not including efficacy studies, is so FDA may determine on the basis of such comparability data that additional clinical efficacy studies, of a sufficiency to support initial licensure or approval, are unnecessary. Human pharmacology studies, generally, may be needed to evaluate changes which may affect product pharmacokinetics or pharmacodynamics, e.g., change in product formulation.

In cases where a manufacturing change(s) results in a product with structural and/or bioactivity differences, and/or differences in pharmacokinetics patterns, and those differences are meaningful with respect to potential impact on the product's safety, purity, or potency (efficacy), an additional clinical study(ies) usually may be needed to evaluate the product's safety and/or efficacy. Additionally, when the analytical and other preclinical testing is not sufficiently sensitive or broad enough to detect such meaningful differences, additional clinical study(ies) may be needed.

E. Additional considerations

In terms of comparability testing, manufacturers should generally perform extensive analytical testing complemented by functional testing if manufacturing changes occur in the process of producing the bulk drug substance. Examples of such changes include the following: a change in manufacturing site; modifications to cell or seed strains, including changes to the master cell bank; fermentation; and isolation or purification. In some cases, complementary pharmacology data or biologic response data (e.g., antibody titers for vaccines) may be needed.

Changes made to the final drug product, such as changes in storage containers, dosage forms (e.g. from a solution to lyophilized powder for reconstitution), or filling sites, may only need comparative data on final release specifications and product stability data. However, changes in the final product formulation may need comparative pharmacokinetics studies or other types of studies.

Since each manufacturing change and each product may present unique safety, identity, purity, and potency concerns, manufacturers should consider the type of manufacturing change, stage of product development, and clinical characteristics (i.e., patient population, clinical endpoints, dosing route, steepness of the dose response curve, regimen, and duration) in any comparability testing program. In-process and final product testing should focus on the manufacturing steps affected by the process change. Manufacturers should validate the modified manufacturing process and provide data on qualification lots. The appropriate process validation criteria will vary depending on the nature of the change. The ability of the manufacturer to use validated and sensitive assays to demonstrate a product's identity and structure, biological activity and clinical pharmacology provide a basis for determining whether product comparability can be established without repeating clinical efficacy studies.

IV. Documentation of Product Comparability

This document on comparability describes testing that may be used by applicants with pending applications, licensed or approved applicants, IND sponsors, and FDA to determine the types of data that may be necessary to document product safety, purity, potency/effectiveness. FDA will determine the extent to which different types of comparability testing are necessary. For

example, in some cases FDA may determine that no clinical study(ies) is necessary. In other instances FDA may determine, on

the basis of comparability data, that a clinical efficacy study(ies) is necessary.

In the interest of efficient review and approval of product applications, FDA encourages sponsors of unapproved applications or products under IND to consult with FDA regarding proposed manufacturing changes before implementing such changes prior to product approval. A sponsor may provide FDA with information regarding a manufacturing change by including a description of the change, a description of corresponding comparability tests conducted, and the comparability test data and validation information in license/ new drug applications, INDs, or amendments to pending license/ new drug applications and INDs in effect. For biological products that FDA has approved, an applicant should submit information about manufacturing changes pursuant to 21 CFR § 601.12 or 21 CFR § 314.70(g), and any FDA guidance on changes to be reported.

21 CFR § 601.12 prescribes which changes must be reported to FDA and which changes require prior approval. FDA has proposed amendments to this regulation. Manufacturers should consult the current regulation and any applicable guidance to determine the need and mechanism of reporting.

In each instance, adequate information should be available in order that FDA reviewers and investigators may understand the type of change made, the stage of production at which the change was made, and the product(s) affected. Such information should include appropriate validation of non-clinical studies and clinical studies which may vary for different products and for the manufacturing stage at which the change is implemented.

V. Conclusion

FDA may determine that manufacturers of biological products, including therapeutic biotechnology-derived products regulated as biologics or drugs, may make manufacturing changes without conducting additional clinical efficacy studies if comparability test data demonstrate to FDA that the product after the manufacturing change is safe, pure, potent/ effective.

VI. References

1. Points to Consider in the Production and Testing of Interferon Intended for Investigational Used in Humans (1983).
2. Cytokine and Growth Factor Pre-Pivotal Information Package (1990).
3. Changes to Be Reported for Product and Establishment License Applications; Guidance (April 6, 1995; 60 FR 17535).
4. FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products (July 11, 1995; 60 FR 35750)
5. Changes to an Approved Application; Proposed Rule (January, 1996; 61 FR 2739).

July 1, 1996 http://www.fda.gov/cder/compare.htm

BIOGRAPHY FOR PATRICK VINK

Patrick Vink, M.D., is Mylan's Senior Vice President, Global Head of Biologics, a position he has held since March 2008. He is responsible for developing and implementing the company's biologics strategy.

Vink has 20 years of experience in the pharmaceutical industry. Most recently, he was an independent consultant for life sciences companies, venture capital firms, private equity investors and non-governmental organizations. He also served as global head of business unit biopharmaceuticals at Sandoz, leading the successful development and registration of the first biosimilar pharmaceutical in the United States and Europe, a landmark event for the industry. Prior to Sandoz, Vink held leadership positions at Biogen and Sanofi-Synthelabo.

Vink earned his doctorate of medicine from the University of Leiden in the Netherlands and an MBA from the University of Rochester in New York.

Chairman WU. Thank you very much.

Dr. Kozlowski.

STATEMENT OF DR. STEVEN KOZLOWSKI, DIRECTOR, OFFICE OF BIOTECHNOLOGY PRODUCTS, OFFICE OF PHARMACEUTICAL SCIENCE, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION (FDA), DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. KOZLOWSKI. Good morning, Chairman Wu, Ranking Member Smith and Members of the Subcommittee. I am Dr. Steven Kozlowski, Director of the Office of Biotechnology in the Center for Drug Evaluation and Research at the FDA. Thank you for this opportunity to discuss how the development of measurement science standards and related technologies might make it easier to understand the composition of FDA-regulated biological products and the benefits that could be gained from these advances.

The term ''biological product'' or ''biologic'' includes products that have been manufactured using a biological process such as a cell line with altered DNA to produce a monoclonal antibody. There are different types of biologics presently on the market but I will focus on one type today, therapeutic proteins. As part of the FDA's responsibility of ensuring the safety and effectiveness of drugs and biologics sold in the United States, it is important that we be able to understand, or to characterize, the composition of these products. We want to know what materials they are made up of and how the materials are arranged at a molecular level; that is, what is the molecular structure. I will begin with a general description of biologics with a focus on therapeutic proteins and explain why they are so difficult to characterize. I will then discuss potential benefits that could follow from improved analytical methods and measurement standards.

Please take a look at the slide on the displays.[1] This is a graphic representation to scale of a single molecule of the drug aspirin and a single molecule of the protein product human growth hormone. You can see the relative size and complexity. But in comparison to other biologics, human growth hormone is actually simple and well characterized. I was initially going to show a graphic comparing aspirin to a monoclonal antibody, which is five times the molecular size of human growth hormone, but then the aspirin would have been rather difficult to even see.

[1] See last page of testimony.

I would like to point out three specific limitations of our current analytical methods. First, there are additional components not shown on this graphic that we call post-translational modifications. For monoclonal antibodies and many other proteins, these modifications include sugar chains of various sizes, and our current analytical methods are not sufficient to fully assess these additions. Second, we are unable to fully characterize the three-dimensional structure of a biologic, and third, we currently lack methods to measure and quantify the aggregation or the clumping together of protein molecules.

I will now turn to three specific benefits we might see from improved analytical methods and measurement standards. Improved analytical methods would enable quicker and more confident assessments of the potential effects of manufacturing changes in process, equipment or raw materials. This could reduce the requirements for animal or human studies for evaluating these manufacturing changes. In addition, for products that have abbreviated pathways for approval, improved analytical methods could facilitate comparison of products and detection of differences between different manufacturers. Number two, the development of analytical methods would evaluate the quality of a biologic throughout the manufacturing process and that could provide a superior system for ensuring product quality in the manufacture of all biologics. Improved analytical methods would increase general knowledge in the field of biopharmaceuticals. The FDA can use this knowledge from improved analytical methods to inform our regulatory decisions and industry can use this knowledge to design even better products. With the development of new analytical methods comes the need for new standards to evaluate them. The term "standard" can apply to measurements or processes, and although process standards are valuable in ensuring effective manufacturing process operation and validation, today I will focus on measurement standards.

A measurement standard can be a standardized test or standardized materials used to evaluate the performance of a measurement method. Standardized test materials can be used to evaluate the precision and accuracy of many different types of analytical technologies and thus, are more likely to foster competition and development of new and improved analytical methods by industry and academia. The development of such measurement standards would also be extremely valuable for ensuring both current and future methods are working properly and provide consistent results from assay to assay and from laboratory to laboratory.

In conclusion, the field of biopharmaceuticals is advancing rapidly, in many ways more rapidly than analytical technologies. We have identified three specific properties of biologics that we cannot sufficiently measure but that are very important to medicinal activity: post-translational modifications, three-dimensional structure, and protein aggregation. Furthermore, reliable and discriminating material standards would enhance use of current technologies and encourage new technologies to fill current gaps.

Thank you for the opportunity to testify today. I am happy to address any questions you may have.

[The prepared statement of Dr. Kozlowski follows:]

PREPARED STATEMENT OF STEVEN KOZLOWSKI

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Steven Kozlowski, Director of Biotechnology Products in the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA or the Agency). I very much appreciate this opportunity to discuss how the development of measurement science, standards, and related technologies might make it easier to characterize FDA-regulated biological products.

I will begin with a general description of one type of biological product—therapeutic proteins—and explain some of the difficulties we face in characterizing these products. I will then discuss potential benefits that could follow from improved analytical methods and measurement standards. Finally, I would like to describe three specific properties of biological products that we cannot sufficiently measure, but that are very important for understanding the behavior of biological protein products. Better analytical methods to measure these three properties would be extremely helpful in determining the similarity of similar biological protein products.

Congress has charged FDA with ensuring the safety and effectiveness of drug and biological products sold in the United States. As part of fulfilling this responsibility, it is important that FDA be able to understand, or *characterize,* the composition of these products. We want to know:

- what materials they are made up of, and
- how the materials are arranged (i.e., the structure) at a molecular level.

For some medical products, characterization is relatively straightforward. Non-biological, often called *small-molecule,* drugs are typically of low molecular size and are manufactured in chemical reactors rather than biological systems. The structure of small-molecule drugs can be verified through established analytical testing. However, we are now in the era of molecular biology where many new therapies are manufactured by inserting novel genes into living cells so as to produce therapeutic proteins by biologic processes. For example, many therapeutic monoclonal antibodies are produced using cell lines with manipulated DNA.

Size and Complexity of Biologics: Protein Therapeutics

Compared to assessing the structure of small-molecule drugs, which generally have fewer than 100 atoms, assessing the structure of biologics is a formidable task. Therapeutic proteins are much larger than typical small-molecule drugs. Using molecular weight as a measure of size, human growth hormone is more than 150 times larger than aspirin and a monoclonal antibody is more than five times larger still than human growth hormone. Therapeutic proteins are also much more complex than typical small-molecule drugs. Attached is a graphic depiction of human growth hormone and aspirin, which illustrates the differences in size and complexity.

The manufacture of biologics is also quite complex. Most biologics are composed of many thousands of atoms linked together in a precise arrangement (called the *primary structure*). This organization of atoms is further organized into a three-dimensional *higher order structure* by the folding of the linked atoms into a specific pattern that is held together by relatively unstable connections. A protein molecule consists of a long chain of building blocks called amino acids, of which there are 20 types—a single protein chain can be made up of hundreds of amino acids. The sequential order of these building blocks in the chain can be critical for medicinal activity. Protein chains with the same sequence of amino acids can fold in different ways—much like a single piece of rope can be tied into a variety of different knots. The specific folding of these chains is also very important in carrying out their therapeutic functions.

In addition, many of the linked amino acids can have modifications attached. These attachments can be small (only a few atoms) or very large (similar in size to the rest of the protein). One commonly observed attachment is the addition of complex groups of sugar molecules, called *oligosaccharides.* Attachments occur at very specific locations on the protein and, like folding, can have great impact on the therapeutic function of the protein. A protein can thus be represented as a long chain with 20 different types of links with different possible attachments on the links.

To further complicate matters, biologics are not composed of structurally identical units. Instead, they are a mixture of products with slightly different features. This is referred to as *micro heterogeneity* and can be represented as a mixture of very similar chains that differ in a few links or in a few of the attachments. The protein chains themselves can then be linked together or aggregated (i.e., clumped). It is

a challenge to analyze and characterize the composition of such a mixture. Even with currently available analytical technologies, some uncertainty regarding the actual structure of a biologic usually remains. Simple measurements of biological activity, such as enzyme activity, may provide additional information about a product. But there is currently no way to, *a priori*, understand how the product will perform in patients (e.g., distribution in the body, immune responses against the product). As a result, nonclinical or clinical studies are necessary to assess the safety and effectiveness of the product.

Potential Benefits of Improved Analytical Methods

Advances in analytical tests during the last two decades have driven progress in biopharmaceutical manufacturing, but there is still room for significant improvement. New or enhanced analytical technologies and measurement systems and standards that can more accurately and precisely assess the higher order structure and attachments of biologics would provide additional assurance of the quality of biologics in at least three specific ways:

1. Improved analytical methods would enable quicker and more confident assessments of the potential effects of changes in the manufacturing process, equipment, or raw materials.

At present, manufacturers and FDA are hampered by the inability to fully measure structural differences that could be caused by changes in the manufacturing process. Since these unknown structural differences could change the properties of the product, FDA might only approve a manufacturing change after seeing the results of studies of the product in animals or humans. This can significantly slow the implementation of innovative process improvements and impede the manufacturer's ability to react to changes in raw material supplies, which could reduce the availability of the drug to patients who need it. Improved analytical methods could reduce the requirements for animal and/or human studies for evaluation of manufacturing changes. In addition, for products that have abbreviated pathways for approval, improved analytical methods could facilitate comparison of products and detection of differences between manufacturers.

2. The development of analytical methods that can evaluate the quality of the biologic throughout the manufacturing process would provide a superior system for ensuring product quality.

This would enable increased productivity and improved quality control during the manufacturing process.

3. Improved analytical methods would increase general knowledge in the field of biopharmaceuticals.

FDA can use knowledge from improved analytical methods to inform our regulatory decisions, and industry can use this knowledge to design better products. Experience to date with certain monoclonal antibodies, a type of therapeutic protein, illustrates how this increased knowledge can inform both regulatory decision-making and product design. Some monoclonal antibodies better direct a patient's immune system to kill tumor cells, and some do not. One reason for this difference was only discovered after the development of an analytical technique that enabled scientists to characterize the structure of the sugar chains attached to the antibodies. It was discovered that antibodies with certain sugar chains were more consistently able to direct an immune system to kill tumor cells than antibodies with different sugar chains. FDA initially used this knowledge to require monitoring and control of these sugar chains to ensure consistent clinical benefit to patients. But this knowledge has also enabled industry to design new monoclonal antibody products with enhanced tumor-killing activity.

Potential Benefits of New Measurement Standards

With the development of new analytical methods comes the need for new standards to evaluate them. The term *standard* can apply to measurements or to processes, and although process standards are valuable in ensuring effective manufacturing process operation and validation, today, I will focus on measurement standards. A *measurement standard* can be standardized test materials used to evaluate the performance of a measurement method, or it can be a specific analytical procedure used to take a measurement. Standardized test materials can be used to evaluate the precision and accuracy of many different analytical technologies and are, thus, more likely to foster competition and development of new and improved analytical methods by industry and academia. Standard test materials could be used

to test the ability of an analytical method to detect differences between product batches from a single manufacturer or products from different manufacturers. For example, if a method is being developed to assess the sugars attached to a protein, the analytical method could be used to test a set of related standard test materials in order to determine the precision and accuracy of the method. In this way, a given technology can be optimized or a variety of different technologies can be compared for their ability to accurately and quantitatively assess the quality of a product. The development of such measurement standards would also be extremely valuable for ensuring that current and future analytical methods are working properly and are providing consistent results from assay to assay and from lab to lab.

Three Specific Properties Needing Improved Measurement

FDA has identified three properties of therapeutic proteins that cannot be sufficiently measured at this time but that are very important for understanding the behavior of protein drugs. Improved analytical methods to measure these three properties would be particularly useful in determining the extent of similarity of biological protein products intended to be similar.

1. Post-translation Modifications

As indicated previously, proteins contain added structural features, such as attached sugar chains, that may be critical for their clinical activity. These attached modifications can be complex and heterogeneous, and we currently lack standardized analytical methods to qualitatively and quantitatively assess the structure as it relates to the intact protein and understand the relationship of the modifications to potency and clinical performance. We are particularly interested in better methods for analyzing the sugars (glycosylation) and other modifications known to affect the medicinal activity of these products.

2. Three-dimensional Structure

As described previously, proteins must be folded into a three-dimensional structure to become functional (sometimes a three-dimensional structure can be misfolded). The proteins within a biologic will have one major three-dimensional structure along with a distribution of other variants differing in three-dimensional structure. Our current ability to predict the potency of biologics would be enhanced if we had improved ability to measure and quantify the correct (major) three-dimensional structure, aberrant three-dimensional structures (misfolding), and the distribution of different three-dimensional structures.

3. Protein Aggregation

Some biological products can stick to one another. When many protein molecules stick together, they are referred to as *aggregates* and have the potential to cause adverse immune responses in patients. There are many forms and sizes of aggregates and many current methodologies have gaps in their ability to detect different types of aggregates. Our ability to minimize adverse immune reactions would be enhanced if we had improved ability to measure and quantify different types of aggregates.

CONCLUSION

The field of biopharmaceuticals is advancing rapidly—in many ways more rapidly than analytical technologies. New measurement tools and standards would be of value in all the areas I have discussed. In particular, reliable and discriminating material standards would enhance use of current methodologies and encourage new technologies to fill current gaps. Moreover, as the field of biopharmaceuticals continues to advance, there is the potential for greater research and development in the evolving area of follow-on biologics, which could provide significant savings for consumers and the Federal Government over time.

Thank you again for the opportunity to testify today. I am happy to address any questions you may have.

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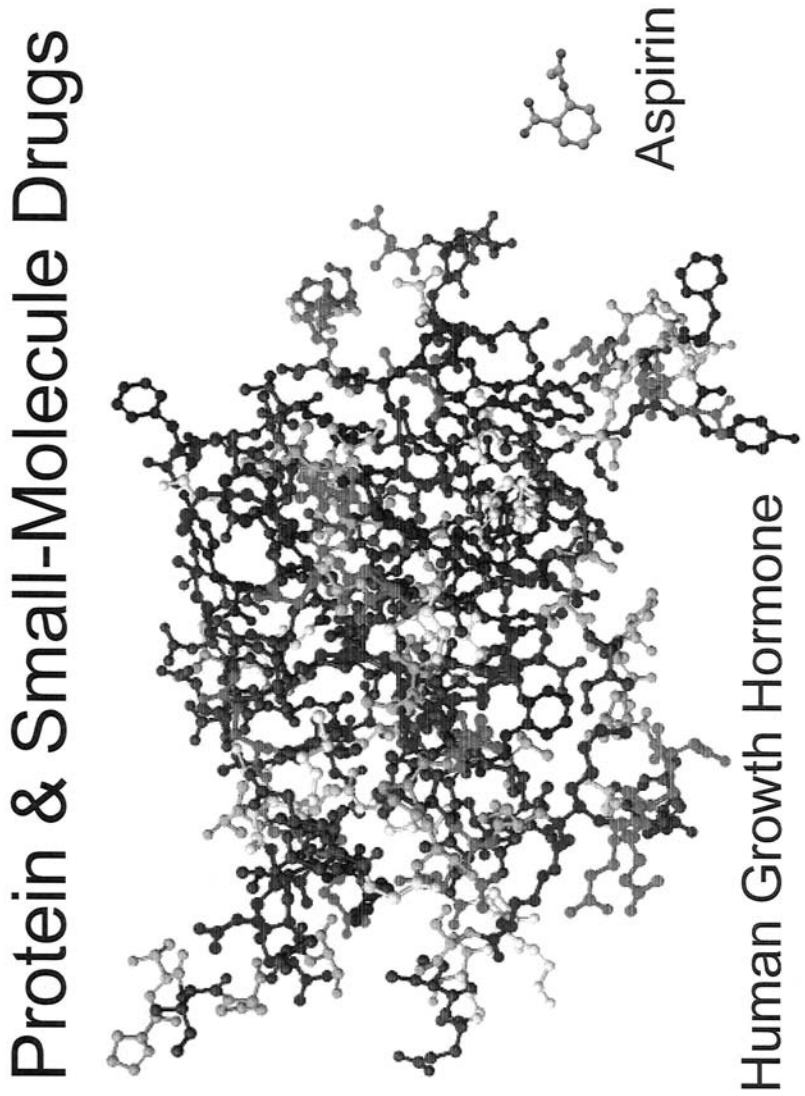
Protein & Small-Molecule Drugs
Aspirin
Human Growth Hormone

BIOGRAPHY FOR STEVEN KOZLOWSKI

Steven Kozlowski is the Director of the Office of Biotechnology Products (OBP), Office of Pharmaceutical Science, at the Center for Drugs Evaluation and Research (CDER), Food and Drug Administration (FDA). OBP is responsible for the quality review of monoclonal antibodies and most therapeutic proteins at CDER. OBP also provides expertise on immunologic responses to therapeutic proteins and performs mission-related research. Dr. Kozlowski received his medical degree from Northwestern University and trained in Pediatrics at the University of Illinois. Prior to joining FDA, Dr. Kozlowski worked as a staff fellow in the Molecular Biology Section of the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases at the National Institutes of Health. He studied the immune responses to proteins and peptides during his fellowship. Dr. Kozlowski joined the Division of Monoclonal Antibodies in 1993 and was tenured as a Senior Investigator in 2000. He has been involved in all phases of the regulatory process as a reviewer, from pre-IND product development through inspections, licensing and post-approval supplements. Dr. Kozlowski served as the Acting Director of the Division of Monoclonal Antibodies from 2004–2005. He has also served as an instructor and as an adjunct clinical reviewer at FDA. Dr. Kozlowski's research interests include the effects of drugs on the immune system. He has been very involved in promoting Quality-by-Design approaches for the manufacture of biopharmaceutical products.

Chairman WU. Thank you, Dr. Kozlowski.

Dr. May, please proceed.

STATEMENT OF DR. WILLIE E. MAY, DIRECTOR, CHEMICAL SCIENCE AND TECHNOLOGY LABORATORY, NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (NIST)

Dr. MAY. Good morning, Chairman Wu, Ranking Member Smith and Members of the Subcommittee. Thank you for the invitation to testify today. I am Willie May, Director of the Chemical Science and Technology Laboratory at the National Institute of Standards and Technology. Additionally, for the past several years, I have led a strategic planning effort for NIST program growth in the biosciences.

The previous speakers have discussed the need for additional measurement science and measurement standards to improve the quality and efficiency and the development, manufacture and regulatory approval of biologic drugs. Therefore, I will focus my comments on our past experiences in successfully responding to other health-related measurement problems and our capabilities for addressing the measurement and standards needs associated with biologic drugs.

We have used our expertise in measurement science and standards to address important problems in health care since the 1920s. Over the years our capabilities and our programs have expanded and evolved in accordance with both societal and industry needs. The primary focus of our current program in health care is on the provision of reference methods and human serum-based standards for clinical diagnostics and on standards for medical imaging. In both these areas, NIST-traceable measurement standards and calibrations are reducing misdiagnoses, wasteful repeat testing and treatment decisions based on inaccurate measurement results.

NIST can also make critical contributions to underpin the development and the regulatory approval process for biologic drugs. NIST brings to the table our unique combination of expertise in the physical, chemical and biological measurement sciences. These along with our expertise in statistics and information science provide us with the tools required to support: more accurate assess-

ment of the sameness of biologic drugs made by different manufacturers and/or by differing manufacturing processes, improved safety and efficacy, and improved efficiency and reliability in the manufacturing processes.

Based on extensive discussions with our colleagues at FDA and the pharmaceutical industry, we have identified five critical areas where improved measurement methods and standards would benefit both FDA and companies that produce innovator as well as generic biologic drugs.

First, the assessment of structural sameness. In this area, NIST expertise in the determination of protein structure and function and protein measurement science could be used to develop quality assurance standards for the measurement methods used to compare post-translational modifications and three-dimensional structure.

In predicting adverse immune response in patients, in addition to developing reference methods and standards for protein aggregation, our expertise in protein measurement science and cell system science can be expanded and applied to support a better understanding of the protein aggregation process and its induction of adverse human responses to biologic drugs.

Developing a comprehensive understanding of the inner complex workings of production cells, NIST's expertise can enable a better understanding of the genetics and complex biochemical networks of cells used in bioreactors. This would support industry efforts to optimize the production of drugs with desired features, namely low immunogenicity and the appropriate post-translational modifications and three-dimensional structure to facilitate efficacy.

Predicting drug function and toxicity—NIST's expertise in cellular and protein measurement science, genetic testing and bioinformatics could be used to support more accurate characterizations of the human cell types most often used in toxicity assays. This would in turn support development of more accurate measurement systems and modeling tools for predicting therapeutic function and adverse human reactions to candidate drugs.

And finally, contamination from the manufacturing process and packaging. In this area NIST expertise in analytical chemistry and protein chemistry can provide the reference methods and quality assurance standards for measurements used to detect and quantify potential contaminants such as unwanted proteins from production cells, viruses, metals and various organic compounds.

NIST has already begun to act on some of these needs. We have started a pilot effort focused on improved measurement methods and standards for glycosylation and aggregation. However, NIST, and I am sure my colleagues from FDA and industry, would agree that there is much more to be done.

We at NIST will continue our outreach to stakeholders and determine and refine the best path forward for addressing the critical measurement and standard challenges associated with biologic drugs.

So in summary, measurement science and measurement standards for biologic drugs would facilitate scientifically sound and fact-based decision-making in research and development, manufacturing and the regulatory approval process for biologics.

Mr. Chairman, thank you for this opportunity to testify today. This completes my statement and I too will be happy to answer questions.

[The prepared statement of Dr. May follows:]

PREPARED STATEMENT OF WILLIE E. MAY

Chairman Wu, Ranking Member Smith, and Members of the Subcommittee, thank you for the invitation to testify today. I am Willie E. May, Director of the National Institute of Standards and Technology's (NIST) Chemical Science and Technology Laboratory (CSTL). Additionally, for the past four years, I have been responsible for assessing, developing and coordinating NIST programs in the Biosciences. I am pleased to be offered the opportunity to participate in this morning's discussion regarding the *"Potential Need for Measurement Standards to Facilitate Research and Development of Biologic Drugs."* My testimony will explain NIST's role in this area and some of the critical measurement challenges that we have identified.

The Need for Additional Measurement Science and Measurement Standards to Improve the Quality and Efficiency of Health Care

The rising cost of health care and increased prevalence of chronic diseases, such as heart disease and diabetes, are having a significant impact on the economy and quality of life for many in the United States. The Obama Administration is committed to improving quality and enhancing the efficiency and delivery of health care. The provision of the necessary measurement science and standards potentially can drive innovation and make the drug and biologics development process more efficient. NIST's unique mission, core competencies in measurement science and standards, and history of relevantly addressing such needs in other areas, provide strong evidence that NIST can help accelerate this innovation.

NIST's Historical and Current Role

NIST's mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life. Over the years, NIST traditionally has focused its research and measurement service activities on the physical science and engineering disciplines—and become internationally renowned in that regard as demonstrated by our world-premier measurement and standards program and many internationally-recognized awards in measurement science, including three Nobel Prizes in Physics since 1997.

In keeping with the spirit of our mission to address the measurement barriers to innovation that are the highest risk to U.S. economic security and quality of life, the biosciences have been identified as a new area for significant emphasis at NIST, with health care being our initial area of focus. To help define our efforts, NIST has engaged in extensive outreach to the Food and Drug Administration (FDA), National Institutes of Health (NIH), US Pharmacopeia, and the medical diagnostic and pharmaceutical industries over the last five years. The consistent feedback from those efforts have indicated that major improvements are needed in the measurement science and measurement technologies that support efforts to predict, diagnose and manage disease, as well as for those used to discover and develop safe and effective medical therapies. The lack of adequate standards to ensure accurate and comparable measurements is an issue that must be addressed to fully realize the potential impacts of new innovations in health care and its delivery, whether it be for *in vitro* diagnostic and medical imaging biomarkers, predictive toxicology for drug safety, medical device materials biocompatibility, genetic testing, or biopharmaceutical manufacturing. Whether quantifying the amount of protein in a cancer cell or determining which drug will be most efficacious with minimal side-effects on an individual basis, measurements are the foundation for improving our understanding of biological systems. This is critical to guide and support the efficient knowledge-based, development of new tools for meeting next generation of health care needs. NIST's FY 2010 budget request includes $14 million to support new initiatives in health care, including standards and measurement work to address the information technology and medical diagnostic issues mentioned here.

NIST is not a new player in the health care arena. Improvement in measurement science, our foundational role and area of expertise, is and has always been critical to technological innovation in the health sciences. For example, we have:

- a collaborative program with the American Dental Association begun in the late 1920's which has led to, among other things, the development of polymer composite dental fillings and the air-driven turbine drill now found in virtually all dentist offices;
- a program in Radiation Physics begun in the 1920's that is responsible for the standards used in the calibration of X-rays, mammography, and other radiotherapies like those used in the treatment of prostate cancer; and
- a program in Clinical Diagnostics begun in the 1970's that initially focused on high purity primary references for electrolytes (e.g., sodium, potassium, calcium), and metabolites (e.g., cholesterol, creatinine, glucose, uric acid, urea).

NIST's current efforts are focused on improving quality and reducing the cost of health care by targeting the measurement and standards needs associated with clinical diagnostics and medical imaging. The typical patient is often unaware of the inaccuracies associated with most medical testing that contribute to the high cost and sub-optimal quality of health care. For example, standards exist for only about 10 percent of the 700 most commonly ordered clinical tests, and there are no traceable, quantitative standards for MRIs, CT scans, ultrasounds, and other medical imaging technologies, even though such images account for $50 billion in annual health care spending. Lack of traceable measurement references and the resulting lack of demonstrable accuracy and comparability of results in clinical testing and medical imaging contributes to misdiagnosis and/or wasteful repeat testing, and treatment decisions based on inaccurate information.

NIST works closely with industry, academia, and other government agencies to identify the measurement and standards tools required to improve the quality of laboratory medical tests and medical imaging. Our efforts have resulted in significant breakthroughs such as the development of calibrations for radiotherapies and mammography that led to reduced exposure to radiation and made treatments safer; and identification of potential new biomarkers associated with the onset of Type 2 diabetes, metabolic syndrome and cancer. We have also expanded our program in clinical diagnostics to include blood serum-based standards to reduce measurement errors and associated costs of clinical testing to support early cancer diagnosis and treatment.

NIST could potentially impact yet another area associated with the increasing cost of health care: the growing use of biologics to treat disease. These therapies can substantially improve patients' health and quality of life, but also can be very expensive. To help bring down costs for both patients and the Federal Government, the President has proposed to establish a pathway for FDA approval of "generic" biologics that would provide seven years of data exclusivity for innovator products. We can contribute to the President's proposal by leveraging our expertise in measurement science and measurement standards to:

- improve efficiency and reliability of the manufacturing processes involved in the production of biologics ; and
- put in place the measurement tools to facilitate the approval of such drugs, such as measurement methods or reference materials that would allow the FDA to accurately assess the "sameness" of a biologic made by different manufacturers.

A discussion of the measurement challenges that we have identified in this area will be the focus of the remainder of my testimony.

Measurement and standards barriers for the efficient manufacturing and characterization of safe and effective biopharmaceuticals

Based on input from the FDA and biopharmaceutical manufacturers, NIST has identified a number of measurement and standards challenges that, if addressed, will enable:

- a more complete understanding of the biopharmaceutical manufacturing process;
- better control over the chemical, physical, and biological processes involved in manufacturing complex protein pharmaceuticals; and
- improved methods for physical, chemical and biological characterization of the finished product.

A key measurement need, whether for manufacturing process scale-up, process changes or for the regulatory approval of generic biologics (or "biosimilars"), is the ability to measure the "sameness" between different batches of manufactured pro-

teins and to gain a better understanding of the variations that are critical to the efficacy and safety of the drug.

Working with stakeholders, NIST has identified the following critical phenomena and measurement barriers as areas where the development of improved measurement technologies and methods would have great potential to positively impact the biopharmaceutical manufacturing industry and improve the ability of FDA to regulate "generic biologics" as proposed by the President.

Immunogenicity—There is currently no measurement infrastructure in place to ensure the accuracy and comparability of the various methods used to measure key attributes of protein biologics that cause immunogenicity. Immunogenicity is the ability of a protein therapeutic to provoke an immune response in a patient. An immune response may range from neutralization of the drug rendering it ineffective to a life-threatening allergic reaction. A key attribute of protein biologics linked to immunogenicity is aggregation. Aggregation is the process by which one or more proteins may "clump" together to form visible or invisible particles. For regulatory approval, all protein therapeutics must be carefully examined for the presence of aggregates; however, detecting and measuring the wide size range of possible protein aggregates remains difficult. Manufacturers often use different measurement tools and protocols that can lead to contradictory results.

Improving the measurement science for protein aggregates would benefit manufacturers and patients in several ways. For example, development of protein particulate standards would support harmonization of results across different measurement platforms used by manufacturers and provide a better scientific framework for regulatory requirements and decisions. These standards would also facilitate the development and acceptance of improved tools for measuring protein aggregates during manufacturing and in final products. Improved measurement of aggregation would ultimately lead to better understanding and prediction of protein aggregation and immunogenicity. The ability to predict immunogenicity of new biopharmaceuticals would, in turn, increase the probability for their successful development.

Three-dimensional (3–D) protein structure—Biopharmaceutical proteins are synthesized in cells as linear chains of amino acids that must be "folded" into a three-dimensional shape that allows them to function as intended. The improper folding of a biopharmaceutical affects several aspects of how it functions as a drug once injected into the patient. Potency, efficacy and safety can all be severely compromised by misfolding events. At present there are no consistently reliable physical or chemical characterization methods for determining the 3–D structure of biologic drugs.

Standards and improved methods for the characterization of 3–D structure would help biopharmaceutical manufacturers and instrument vendors verify the accuracy and comparability of the structures of manufactured biopharmaceuticals. These efforts would help to ensure that the manufacturer is producing the same product from one batch to the next and would also allow for direct structural comparison of the new product to the original product form. Standards would also help determine the relationship between the structure of a biopharmaceutical and its function, which is critical to our understanding of how the biopharmaceutical will act in the body. Standards for protein 3–D structure would make the biopharmaceutical marketplace more efficient in these key areas: authentification of identity, and determining the inter-comparability of the drug from batch to batch.

Post-translational modification (PTM) of manufactured proteins—The majority of approved protein therapeutics contain post-translational modifications. PTMs are chemical modifications to the protein that occur after it is synthesized such as the addition of sugar molecules, lipids, or biochemical functional groups. Among these, the addition of sugar molecules, or glycosylation, is the most important because over half of all protein therapeutics are glycosylated. PTMs are known to be critical to the safety and efficacy of many biopharmaceuticals and consistent PTM profiles must be maintained for manufactured biologics. There are multiple and varied methods for determining PTMs; however, assessing the accuracy and comparability of results from different methods remains difficult. In order to evaluate the sameness of protein products, these modifications must be fully understood and characterized. Due to the complex and varied nature of the modifications, methods are currently lacking which quantitatively assess the structure and how it impacts protein stability and functionality.

Improved measurement methods and standards would enable instrument vendors and biopharmaceutical manufacturers to develop measurement systems for determining PTM of products. Characterizing the PTM signature of products would enable more streamlined comparative analysis, could also be used as a basis for the

authentication of manufactured products and help safeguard against counterfeit drugs, and would reduce the cost of comparing the PTM of batches of biopharmaceuticals produced by different methods or companies.

Contaminants in the manufacturing process—There is currently no measurement infrastructure in place to help ensure the accuracy and comparability of the methods needed by manufacturers, regulators, and investigators to identify and protect the public from the intentional and unintentional introduction of substances in pharmaceuticals and biologic drugs. Chemical contaminants, such as heavy metals or organic chemical compounds, can leach from the manufacturing vessels, containment vials used in producing biologic drugs or packaging materials. These contaminants can alter protein therapeutics in ways that harm patients. For example, a major adverse clinical event occurred when batches of erythropoietin (EPO, a glycoprotein hormone that controls red cell production) were contaminated with leachable chemicals from primary manufacturing containers. The unidentified contamination caused aggregation of EPO, triggering an immune reaction that destroyed the patients' abilities to regenerate red blood cells.[1] Contamination by proteins originating from the host cells used to produce a protein therapeutic is also a concern. Additionally, cellular contamination problems have occurred where the unknown presence of a host cell enzyme destroyed the biopharmaceutical protein once it was packaged, rendering the product useless.

Standards (reference measurement procedures, reference data and certified reference materials) would enable regulators and biopharmaceutical manufacturers to develop and critically evaluate measurement systems for adulterant detection, which would improve the safety of biopharmaceuticals and vaccines. For example, it might be useful to develop certified reference materials for organic leachates found in biopharmaceutical products and/or a reference data base of process and packaging materials and their corresponding leachates. Additionally methods for identifying host cell protein contaminants would facilitate their removal, reducing the possibility of toxic or immunogenic adverse drug events.

Production cell unpredictability—Biomanufacturing processes are highly variable and unpredictable due to a lack of tools to measure the internal workings of the cells that synthesize, modify and secrete the desired biopharmaceutical product. Most protein therapeutics are produced in Chinese Hamster Ovary (CHO) cells, but numerous problems are routinely encountered where CHO cells, for unknown reasons, do not perform appropriately. When this occurs, weeks or months of production time are wasted. Industry has indicated to NIST a strong desire to have available measurement tools to enable a more complete understanding of the CHO cell system to a point where it can better be manipulated and controlled. This would require the ability to identify, quantify and measure the thousands of biomolecules and signaling pathways that govern the inner working of these tiny biopharmaceutical factories.

Industry and academia would be better equipped to understand changes in the cell function and the associated production capacity by using a systems biology-based approach to monitor production cell behavior. However, this would require greatly improved measurement capabilities and a robust measurement infrastructure to support analysis of cell behavior at this level, particularly in a manufacturing environment. With such robust capabilities available, a more fundamental understanding of bioprocessing would be possible, enabling the agile, low cost manufacturing of safe and effective protein- and cell-based products.

Quality-by-Design (QbD) Implementation—According to the FDA,[2] under a quality by design paradigm, biopharmaceutical manufacturing will depend on a risk-based approach linking attributes and processes to product performance, safety, and efficacy. QbD relies heavily on the use of process measurement technology and process understanding. Currently, there is no measurement science support in place to help manufacturers develop and validate new process measurement tools and improve biological manufacturing processes. Often when new measurement tools are introduced, each manufacturer must expend considerable effort and expense to validate their performance. As a result, there is much duplication of effort, and manufacturers are often hesitant to accept new tools. In addition, manufacturers are reluctant to adopt process changes that might increase manufacturing efficiency for fear of unpredictable changes to the product.

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[1] McKoy, J.M., et. al., Epoetin-associated pure red cell aplasia: past, present, and future considerations, *Transfusion,* Vol. 48 (August 2008), pp. 1754–1762.

[2] FDA, Submission of Quality Information for Biotechnology Products in the Office of Biotechnology Products; Notice of Pilot, *Federal Register,* Vol. 73, No. 128 (July 2, 2008).

Viral clearance—Removal of potential viral contaminants by filtration is a key operation in the manufacture of biologic drugs. Both filter vendors and biopharmaceutical manufacturers agree that standardized test methods for classifying and identifying virus filters are needed to better assess performance and comparability of different filters. Establishing and understanding uncertainties in the measurements of virus size using different methods, which often give conflicting results, is the key to developing robust filter challenge protocols. In addition, there is well known variability in virus preparations obtained from different contract testing labs used to challenge filters.

Improved viral size measurements and preparation methodologies would enable manufacturers of biopharmaceuticals to better evaluate filter performance and compare different filters. The development of standard materials and methods to support the detection of viral particles present at low levels in biologic drugs would support product safety and quality assurance.

A longer range and broader challenge for the industry is the **unpredictable nature of biopharmaceutical function—**Presently we do not fully understand the interplay between all of the ongoing interactions that take place in our bodies that ultimately define our health. This incomplete understanding makes it difficult to completely predict the effect of new drugs, as we do not know how the drug will impact other parts of the biological system beyond the part it was designed to address. This lack of understanding poses a challenge to the development of new drugs and biologics because we are not able to confidently measure or predict how effective the products under development will be, or how toxic they might be. Multiple biologics have been subject to market recalls and withdrawals due to unpredicted side effects.

Addressing this challenge will take a significant multi-disciplinary approach and a significant amount of fundamental research. Critical to this effort is the development of improved measurement capabilities that are essential to the creation and validation of reliable new functional assays and predictive toxicology tools that would help the biopharmaceutical and drug development industry streamline drug development and approval processes.

NIST's Role in Biopharmaceutical Manufacturing

NIST has the unique Federal role of providing measurement science and developing the measurement standards needed to help the American economy innovate and compete. The biopharmaceutical industry (Companies that innovate the original products and those that produce generic products) faces many challenges to further grow and succeed in a globally competitive marketplace. Biotechnology drugs, protein and cell-based therapeutics, represent the fastest growing category of therapeutic drugs in the United States. Improved characterization and manufacturing of biologic drugs will support the growth of a new industrial sector that could produce generic biologics eligible for FDA approval, as proposed by the President, which would reduce the cost of health care for patients and the Federal Government. We have developed a comprehensive program plan that would broadly address critical measurement and standards issues associated with the manufacturing of both innovator and generic biopharmaceuticals such as:

- The **structural sameness** of the manufactured biopharmaceutical
- The propensity of the biopharmaceutical to induce an **immune response** in patients
- The presence of **contaminants** coming from manufacturing and packaging
- The ability to better **predict safety and efficacy** of candidate biopharmaceuticals
- The comprehensive understanding of **complex inner workings of production cells**

NIST already has begun a pilot intramural effort focused on physico/chemical measurements of protein structure, glycosylation & aggregation.

Summary

NIST has been, and continues to be, a critical resource for addressing the measurement and standards challenges associated with innovation in health care. The cost of developing new drugs (including biologics) is certainly a contributor to health care costs. We look forward to a successful partnership with key stakeholders in industry, government and academia to address the measurement science and measurement standards challenges associated with the cost-effective production of both innovator and generic biologic drugs.

New measurement science and standards for biologic drugs will facilitate fact-based decision-making regarding:

- research and development, manufacturing and the regulatory approval process;
- reduced manufacturing costs and increased safety; and
- the determination of "sameness" in the production of both "innovator" and generic biologic drugs.

Mr. Chairman, thank you for the opportunity to testify today. This completes my statement and I will be happy to entertain questions.

BIOGRAPHY FOR WILLIE E. MAY

Dr. Willie E. May is Director of the Chemical Science and Technology Laboratory (CSTL), one of the ten technical operational units within the National Institute of Standards and Technology (NIST) and has ~325 technical staff of and an annual Budget of approximately $90M. The NIST Mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve quality of life. CSTL supports NIST's Mission by addressing customer needs for measurements, standards, and data in the areas broadly encompassed by chemistry, chemical engineering and the biosciences. Areas of growth and/or increased emphasis include bioscience and health, nanometrology, climate change science, and renewable energy technologies. CSTL is organized into six Divisions along disciplinary lines:

- *Analytical Chemistry:* Chemical measurements research and services in: inorganic, organic and electroanalytical chemistry; atomic, molecular and mass spectrometry; and microanalytical technologies
- *Biochemical Science:* DNA chemistry, sequencing; Protein structure, properties, and modeling; Biomaterials; Biocatalysis and bioprocessing measurements
- *Chemical and Biochemical Reference Data:* Experimental, theoretical, and computational research on the identity and reactivity of chemical species, emphasizing data, information, and protocols for the identification of chemical and biochemical species
- *Process Measurements:* Research, calibration services, and provision of primary standards for temperature, pressure, vacuum, humidity, fluid flow, air speed, liquid density and volume, and gaseous leak-rate measurements; Sensor research
- *Surface and Microanalysis Science:* Nanoscale chemical characterization; Particle characterization and standards; Electronic and advanced materials characterization; Surface and interface chemistry; Advanced isotope metrology
- *Thermophysical Properties:* Experimental, theoretical, and simulation research on the properties of gases, liquids, and solids, emphasizing thermophysical properties.

Prior to his current position, Dr. May led NIST's research and measurement service programs in analytical chemistry for more than 20 years. His personal research activities were focused in the area of trace organic analytical chemistry, with special emphasis on the development of liquid chromatographic methods for the determination of individual organic species in complex mixtures and the development of liquid chromatographic methods for the determination of physico-chemical properties such as aqueous solubilities, octanol/water partition coefficients, and vapor pressures of organic compounds. This work is described in more than 100 peer-reviewed publications. During his 35+-year professional career, he has presented more than 300 invited lectures at U.S. industrial sites, colleges/universities and technical meetings throughout the world.

Dr. May has several leadership responsibilities in addition to those at NIST. He is a member of the 18-person International Committee on Weights and Measures (CIPM), whose principal task is to promote world-wide uniformity in units of measurement and oversee the activities of the International Bureau of Weights and Measures in Paris, France (BIPM); Chairs the CIPM Consultative Committee on Metrology in Chemistry's Organic Analysis Working Group; Chairs the Interamerican System for Metrology's Chemical Metrology Working Group, Co-Chair's the Joint Committee on Traceability in Laboratory Medicine's Working Group on Reference Materials and Reference Procedures; and Chairs the Executive Board for the Hollings Marine Laboratory in Charleston, SC.

Honors and Awards: Department of Commerce Bronze Medal Award, 1981; National Bureau of Standards (NBS) Equal Employment Opportunity (EEO) Award, 1982; Department of Commerce Silver Medal Award, 1985; Arthur Flemming Award for Outstanding Federal Service, 1986; NOBCChE Percy Julian Award for Outstanding Research in Organic Analytical Chemistry and Presidential Rank Award of Meritorious Federal Executive, 1992; Department of Commerce Gold Medal, 1992; American Chemical Society Distinguished Service in the Advancement of Analytical Chemistry Award, 2001; Keynote Speaker for the 2002 Winter Commencement Ceremonies, University of Maryland, College of Life Sciences; Council for Chemical Research Diversity Award, the NOBCChE Henry Hill Award for exemplary work and leadership in the field of chemistry, Science Spectrum Magazine Emerald Award, in 2005, and the 2007 Distinguished Alumnus of the Year Award from the College of Chemical and Life Sciences, University of Maryland.

DISCUSSION

Chairman WU. I thank the panel, each and every witness. We are now going to start questions from the panel and each Member will have five minutes to ask questions, and I will begin with myself.

It has been a while since I have been exposed to biochemistry so please bear with me. When you all talk about biologics and biosimilars and measurement, what you can measure and what the need areas are, if you will, Dr. Kozlowski, you seem to list a couple areas where we need work and I think that that was implicit or explicit in each of your testimonies. Are you saying that we can—well, what we have is the translation process but that post-translation, whether it is glycosylation or aggregation or the folding, the 3D structures that, you know, beyond the translation stage, there is, shall we say, a whole lot of wiggle in what the same translational product ultimately becomes?

Dr. KOZLOWSKI. There have been a lot of advances to date in being able to characterize molecules and we do know a lot about post-translational modifications with cutting-edge technologies but we don't know everything. There are areas where we are lacking the capabilities. Some of these capabilities are more in academic labs and not necessarily translatable as well to industry routine use, so I think we are much better at knowing the very primary structure, the list of amino acids in sequence in a protein, but our ability to account for all the different ways they are modified is lacking. That is not to say we can't do it at all, and I think that, you know, in terms of the molecules that I showed in my slide, human growth hormone was approved through an abbreviated pathway, both in the United States and Europe, through the 505 pathway, and so we felt we knew enough from the characterization of that molecule to make some judgment about an abbreviated pathway. So I think we have a lot of capabilities now. The question is how to make them better because there is still a lot of uncertainty and gaps in those areas.

Chairman WU. So we are a lot better at the translational end and improvements will be helpful in the other arenas?

Dr. KOZLOWSKI. Yes.

Chairman WU. Thank you for that, purely a curiosity question, I guess, although hopefully it will be helpful to my understanding going forward.

I would like to ask you about each of your companies' interactions with NIST, your perception of NIST's attempts to engage

the biotech industry, what has been done well, what can be improved.

Mr. MIRE-SLUIS. So I can speak from my personal experience and Amgen's experience of working with NIST on this program. Through the work that I have done at NIBSC [National Institute for Biologic Standards and Control] and the World Health Organization, I am very well versed in the mechanisms for producing standard methods and reference standards. I have collaborated very closely with NIST on this effort, providing advice from an industry perspective as to our priorities. Obviously there are multiple different areas that we could explore from a scientific perspective. I mean, it is naive to think that we can do them all in one go. There has to be some form of prioritization. From our perspective, I think the protection of patient safety obviously rises to the top of the list, so the issues, for instance, of immunogenicity and linking structure to those possible potential side effects I think is of increased relevance.

I would also say that from a perspective of having worked specifically for institutes whose role is to improve methods and standards directly related to personal health, that I think transparency is a big requirement for any institute working in that manner. These methods and standards cannot be provided in a vacuum. There has to be the highest scientific rigor associated with these methods as described in our testimony. Making a bad standard does not do anybody any good, and therefore sharing industry and research expertise I think is vital. So I feel that outreach from NIST should be increased throughout the industry as well as the scientific community.

Chairman WU. Thank you very much, Dr. Mire-Sluis.

Dr. Vink.

Dr. VINK. Yes. Mylan, as a generic manufacturer, has interacted on several occasions with NIST, mainly via the work for the U.S. Pharmaceutical [USP] and other areas. Being now also entering into biologics as a generic manufacturer, we see a big role for NIST as was laid out in my testimony. We see big opportunity of laying down standards and making objective comparability tools available so that everybody is helped through the same standards. NIST can play a very big role in creating that transparency, creating standards that are applicable for everyone and we completely agree with what was said at the table here. Every progress we make is another step in better understanding biologics. We have come a long way in the past 15 years. Every step, especially for our area of biosimilars, will further help better characterizing these drugs, reducing the burden of clinical trials, which are currently still necessary.

Chairman WU. Thank you very much. My time is expired. Dr. May, since I have invited the other witnesses to comment about how NIST—what things NIST can do, when it comes back to my turn I plan to ask you about your views of how Congress can enable you to do your job better.

With that, Mr. Smith, five minutes.

Mr. SMITH. Thank you.

Dr. Kozlowski, could you tell us approximately how much funding currently is spent at FDA on biologics research and what the research really focuses on?

Dr. KOZLOWSKI. I am not really prepared to provide the exact funding for what happens with biologics at the FDA. I can tell you that there are laboratories within the Office of Biotechnology Products which look at the manufacturing of biologics, including characterization, and we are in discussion in fact with NIST on moving forward on some of those projects together. We also look at biological assays that measure the activity of molecules, which is another way of characterizing them, and there are other labs within the Center for Drug Evaluation and Research which characterize proteins using current methods and may actually look at some samples that are provided for them. So we have capabilities. Again, could we do more with more capabilities? That is always true.

Mr. SMITH. Could you speak to or share with us if you are comfortable that there is not a lot of overlap between NIST and FDA but yet still working together? I mean, that is sometimes a very delicate balance, both Dr. Kozlowski and Dr. May.

Dr. KOZLOWSKI. I think overlap is always a tricky question. It is a value to have some core capabilities in an organization simply so that they can communicate and work together, and so some level of overlap in technology is good. I think, you know, you need to be communicating and that is the way to leverage the least overlap in big ways and to get the most benefit. And for instance, the FDA and NIST just had a meeting a number of years ago on the issue of characterizing proteins that they co-sponsored and invited industry, and I think that was a great opportunity for dialogue and further meetings like this that involve both FDA, NIST and industry together may be good ways of figuring out what our overlaps are, how to work best together and how to do things in a way that as a combined group makes the most progress.

Mr. MAY. As you know, NIST has absolutely no regulatory authority. We are not lead agency on anything except measurements and we focus on measurement science, technology and standards that have impact across other areas where other agencies in the Federal Government do have lead agencies that have responsibility. So the only way for us to be successful is to collaborate with both the industry and other federal agencies in the areas where they have interest and lead agency responsibility and we do the things that we do well, that is, the underpinning measurement science, the technology and the provision of standards.

Mr. SMITH. Thank you.

And Dr. Vink, in your testimony you propose a repository within NIST, Federal Government basically that would then sell some of the information to other companies for testing and research, and given the nature of biologic drugs, do you think that such an arrangement might undermine the intellectual property [IP], you know, the facets of intellectual property and certainly the incentives to move forward in the future?

Dr. VINK. No, not per se. We believe that a repository is actually part of what we all need to know as a service to public health. This is the standard that we hold every product to which is approved to so we believe this is more a tool to guarantee for public health

that there is a standard for every product and that everybody who wants to compare itself to that standard can be measured in an objective, transparent way, and the IP is guaranteed by the IP legislation which is in place. This will only allow regulatory authorities to hold the current product comparable to the standard. Once the patent is expired, it will open up everyone who wants to make a similar product available and be measured to that standard. We don't believe that there is an IP issue around it per se.

Mr. SMITH. Thank you.

Thank you, Mr. Chairman.

Chairman WU. Mr. Luján—oops. Mr. Luján has slipped away to vote perhaps.

Ms. Biggert.

Ms. BIGGERT. Thank you, Mr. Chairman, and thank all of you for being here. I would like to just follow up on what Mr. Smith was talking about and find out what the other members of the panel think about that, and before that, I just wanted to ask one question. I think in your materials, Dr. Vink, you had a case, Berlex Laboratory versus the FDA. Is that part of your testimony or—I was concerned about the standards and the conclusion of the case where the FDA allowed a new drug to go on the market, which was never really tested but it was a test of another similar drug that allowed that. So I would like to know, you know, as far as intellectual property from the other members but also is that the way our regulations work that a drug really doesn't have to go through—what it says is, FDA did not act unlawfully when it determined that Avonex is clinically superior to Betaseron and to approve Avonex for use by patients with M.S. without requiring clinical trials of Avonex and issued its guidance document without notice and comment rule-making. Dr. Sluis, could you comment on that?

Mr. MIRE-SLUIS. Comment on the Avonex experience or——

Ms. BIGGERT. Well, on that and also the intellectual property question I think that Dr. Vink raises for allowing other companies to test somebody else's drug even before it is on the market.

Mr. MIRE-SLUIS. So I think as far as the intellectual property issue goes, it is all down to the timing. This is actually not a unique experience for the biotechnology industry. The pharmacopoeias have been supplying reference standards and monographs for products for many years and Amgen itself is collaborating with both the European pharmacopoeia and the U.S. pharmacopoeia to provide just that, reference material and the description of a test we use for our products. So I think this is nothing unusual. As I say, it is just a matter of timing. What we don't want to do is to lose the intellectual property that allows for innovation. I mean, the innovative industry is the industry that is producing new and novel drugs to benefit our patients.

Ms. BIGGERT. Do you think that we are losing the innovation and creativity? Again, Dr. Vink's testimony talked about the fact that we are behind the European countries and so many other companies in our development of drugs.

Mr. MIRE-SLUIS. I am not sure that that perspective is entirely correct in the sense that in Europe the regulations for the pathway for biosimilars is somewhat more advanced than it is in the United States. I think the standards that have been created in Europe are

those necessary to maintain the safety and efficacy for patients and to include the requirement for clinical studies for biosimilar products. So I think it is a matter of the United States now has to develop similar regulations that focus on patient safety, product efficacy whilst retaining those incentives that are not going to damage the innovative work that the innovation industry does or we will lose the chance to create new and novel medicine for our patients.

Ms. BIGGERT. Dr. Kozlowski, could you comment on that?

Dr. KOZLOWSKI. So I think there is no technological advantage that Europe has in considering these products. So again, I think that there are technological issues for everybody in terms of better methods to facilitate, you know, how much clinical information is necessary, but I don't think there is actually a scientific advantage. I think it is a question of what pathways are available for what types of products.

Ms. BIGGERT. Dr. Vink, maybe you can comment since you are the one that raised the issue.

Dr. VINK. Commenting on the last part where I did not yet comment on what is the difference between the different areas of the world, which was actually the last part, I think as Dr. Kozlowski and also Dr. Mire-Sluis said, the difference is that there is a pathway. We believe that the pathway that is actually present in Europe is working well. It leaves scientific discretion with the regulatory authority. Not every molecule is the same every time, and that is also why we support so much NIST. The more—the better we characterize the drug, the more we can shift the balance from actual characterization of the drug to that part of establishing the sameness and reducing the burden of unnecessary clinical conformity trials. The better you know what you are talking about, the less that is needed. But one thing is clear: safety of patients is at the foremost important thing for everybody in the industry.

Ms. BIGGERT. Thank you. I will yield back.

Chairman WU. Thank you.

We have two votes called and they are approximately six minutes. That is NBA time, six minutes, before the clock runs out. It is my intention to try to get to everyone's questions and then adjourn the hearing if possible, and if not, I will ask the witnesses to kindly stay until we can return.

Dr. May, I promised to give you a shot at how Congress can do a better job, so other than sending NIST more money, what are some legislative improvements that would help NIST do its job better?

Mr. MAY. Certainly providing legislation that authorized more research in general or supported research in general on the five critical areas that I mentioned, and those funds need not necessarily come to NIST but certainly there needs to be a lot of work on measurement science to understand the underlying mechanisms and phenomena that are associated with things like aggregation and many of the phenomena that we have all said are critical to the regulatory approval of biologic drugs. Obviously we would certainly be happy to see you support any budget initiatives that come from the executive branch in this area.

Chairman WU. Thank you, Dr. May.

Dr. Vink, Mylan, you try to do or you do biosimilars. Since a pathway exists in Europe and currently either does not exist or is a very narrow pathway here in the United States, is your biosimilars activity primarily in Europe and then you are looking at the pipeline in the United States? I am just trying to understand Mylan's business.

Dr. VINK. Mylan has recently entered the area of biosimilars. After the integration of two companies, we became a global company, and our activity is a global one. Our effort is a global one. We believe that the biosimilar scientific standards are the same or very much aligned between the different continents so we aim at global product files and a global strategy and we do believe that the United States will also offer a tremendous opportunity for patients, health care and companies to enter the area of biosimilars. So of course, currently the market for us is open in Europe and has recently opened in Japan. We have a strong belief that this will be also soon in the United States, so we do not make any difference for regions with respect to our strategy.

Chairman WU. But your activity is a little bit higher in those other areas right now and part of it is a biosimilars pathway but further research and reference materials and metrology would assist in those efforts?

Dr. VINK. Absolutely.

Chairman WU. Well, we have a number of other questions. This is the nature of this institution that you adjust upon contact with reality. I thank the witnesses. We would like to submit further questions in writing and perhaps you and the organizations that you represent would be kind enough to respond.

With that, again, I want to thank each and every one of you for coming here, for testifying, and we will adjourn this hearing. Thank you very much.

[Whereupon, at 11:01 a.m., the Subcommittee was adjourned.]

Appendix 1:

ANSWERS TO POST-HEARING QUESTIONS

ANSWERS TO POST-HEARING QUESTIONS

Responses by Anthony Mire-Sluis, Executive Director, Global Product Quality, Amgen Inc.

Questions submitted by Chairman David Wu

Q1. To the best of your knowledge, do the seven areas of scientific research identified by NIST in its testimony complement or overlap research being conducted by the FDA, other federal agencies or the private sector?

A1. The seven areas of scientific research identified by NIST (immunogenicity, three-dimensional protein structure, post-translational modification of manufactured proteins, contaminants in the manufacturing process, production cell unpredictability, quality-by-design implementation, and viral clearance) are currently being conducted to varying degrees by FDA and other federal agencies and by industry, although not specifically in the area of standardization.

Standard method development and reference standard[1] preparation is a very specific area of research that is usually conducted under the auspices of specialized institutions such as the World Health Organization, the National Institute for Biological Standards and Control ("NIBSC," a center within the U.K. Health Protection Agency), the pharmacopeias (e.g., the United States Pharmacopeia and the European Pharmacopoeia), and the U.S. NIST. These seven areas complement the basic research and general method development that are being undertaken by other organizations. The reference materials will help to compare between methods and to assure that methods are working properly.

Q2. What are the potential benefits to innovation and encouraging the growth of the biotech industry or other industries, such as biologics manufacturing, if analytical tools in the seven areas of scientific research identified by NIST in its testimony are developed?

A2. There are distinct benefits to developing standards in the seven areas identified by NIST, so long as such development is carried out properly.

For example, providing reference standards will allow each company to evaluate its performance against expectations of how well their methods are working. Better methods, in turn, will allow for a better understanding of the way medicinal products in development work—what makes them safe and efficacious—and therefore could increase the success rate of getting safe and effective biotechnology products to patients.

Improved methods and analytical tools will also allow for a better understanding of how the manufacturing process works and may ultimately result in lower manufacturing costs through increased yields and reduced waste. Improved standards in the area of immunogenicity, for example, would allow clinicians and regulators to better compare the safety aspects of medicines in development and to ensure that the methods used in conducting such comparisons are detecting the correct safety signals with appropriate sensitivity.

Q3. As you stated in your testimony, key public/private partnerships between federal agencies such as NIST, government regulatory bodies such as the FDA, and industry scientists will greatly improve the chances of successfully developing standard methods, validation procedures and reference materials. What are your recommendations on how these partnerships should be structured? What has been your experience with these types of partnerships and what lessons have you learned?

A3. In my experience, there should be one central coordinator responsible for gathering the technical experts in each area of standardization being considered, in order to develop the most appropriate, state-of-the-art standard methods and/or reference materials. At present, there are very few institutions capable of creating, storing, and distributing reference materials—particularly biological materials—so this must be taken into consideration in assessing who should lead this effort.

The coordinating body should approach recognized experts in the area and develop a plan on how a standard method or reference material is going to be generated. It is best to have representation from several organizations as this process begins—usually the coordinating institution, regulators, industry, and research concerns, de-

[1] "Reference standards" are samples of material, the properties of which are already known and carefully measured, that can be used to compare results in order to ensure uniformity in measurement.

pending on the topic. The parties typically would execute an agreement that would govern, for example, how the materials will be used, the use of confidential information, and publication obligations.

It is important that the coordinating institution is capable of running the methods itself to assure that it has the technical knowledge needed to balance any differing viewpoints expressed by various stakeholders.

For a standard method and/or validation protocol, a draft would be written by the selected group and published in a widely-available journal for public comment. Transparency in the final approval of the standard method and/or validation protocol is essential. Any comments received would be incorporated—as appropriate—in a second draft. Depending on the volume and nature of the comments received, the method protocol could be sent out for a second round of comments, or could be published as final and made freely available.

The development of a reference standard is more complex than developing a method, and as such, requires careful consideration so as not to cause chaos or disruption in the research and industrial communities. In standards development, it would be desirable to obtain several "candidate" preparations of the same material—from different sources if at all possible—to ensure that the most appropriate material can be selected. The preparations then would be filled into containers in an amount that will be appropriate for its use in checking and standardizing assays. The reference material must be extremely stable, and because it should be made available around the world, it must be in a form that can withstand transport. A standard that loses its activity over time, or breaks down, could provide false results in assays—which would be worse than having no standard at all, since it would give users a false sense of security.

There are very few institutions capable of preparing reference materials in this way, so the coordinating institution must be carefully selected. Once materials are collected, a "trial fill" would be undertaken, usually with one or more different formulations, to determine which formulation will make the most stable standard. The coordinating institute would then provide the trial material to a limited number of expert laboratories, recognized in the field, for testing. If a formulation is proven to be stable, then a "collaborative study" would be organized.

A "collaborative study" is organized by a coordinating body that has advertised (in widely-read scientific journals) for participants. It is essential to have a good range of laboratories to test the candidate reference materials, including laboratories associated with regulatory agencies, industry, research entities, and the coordinating body itself. The more laboratories testing the candidate materials, the more likely it is that a successful candidate preparation will work in every laboratory that requests it, once the reference materials are established.

It is vital that the participants in the collaborative study are provided guidance on how to store, open, and use the materials provided. In addition, it is essential to involve statisticians during the development of the study protocol, in order to ensure that the data provided by the study participants is in a format that can be readily analyzed when it is received.

Coded materials would then be sent out to the participating laboratories, along with a protocol and results sheet. Each collaborative study participant would then send its data back to the coordinating body for analysis. A report would be written and circulated to the participants for comment, including a recommendation for the most appropriate reference material. A final report would then be published, and the reference material would be made publicly available.

Questions submitted by Representative Adrian Smith

Q1. Please provide your company's comment on and reaction to the broad plan of work for biologics measurement and standards outlined by Dr. May in his testimony. Do you support the identified research activities or have any concerns or suggested modifications?

A1. Amgen commends NIST for the comprehensive program plan it has developed for future work in biologics-related measurement science, as described in the testimony that Dr. May presented to this subcommittee. NIST's program plan is very extensive in scope, however—ranging from developing better standards for characterizing proteins' three-dimensional structure, to a deeper understanding of host cell systems and behaviors, to analyzing the performance of filtration systems in viral clearance, to Quality-by-Design initiatives. Given the broad range—and necessarily deep scope—of the activities envisioned in Dr. May's testimony, we believe that it will be essential for NIST's biologics-related initiatives to be prioritized.

For more than 25 years, Amgen has been a leading human therapeutics company in the biotechnology industry, and our mission, first and foremost, is to serve patients. As such, Amgen believes that patient safety and ensuring product quality must remain the primary concern for both industry and government and a priority for the work that NIST proposes to execute.

Immunogenicity-Related Measurement Standards. From a patient safety perspective, the main area that would directly benefit from the application of measurement science, standards and technology is in the detection and measurement of immunogenicity towards a biologic. Biologics raise immunogenicity concerns not implicated by small molecule drugs. Due to the small size of drug products and the extensive understanding of the mechanisms by which these products work, drug products rarely elicit an immune response. In contrast, biologics can trigger an unpredictable—and potentially catastrophic—immune response in the human body.

There are a number of assays currently used to detect and measure immunogenicity, but they are not well standardized—and reference materials are not now available to assist in the understanding of the sensitivity or accuracy of the measurement methods. Therefore, it requires extremely diligent development and validation of such methods by industry in order to produce meaningful results that can identify the nature and extent of any immune response a patient may raise against a biologic.

The future availability of standard methods, validation and reference standards would reduce the risk that immunogenicity assays would be unable to accurately detect antibodies that could expose patients to avoidable risks to their health. Because of this, government support of scientific research in developing improved technologies for measuring the causes of immunogenicity reactions—including standards for detecting and measuring protein particulate aggregation—should be given high priority.

Methods and Standards for Characterizing Proteins. Biotechnology medicines are complex molecules that require a thorough understanding of their structure and function to ensure their safety and efficacy. In comparison to standard chemical drugs, biotechnology medicines (proteins) are hundreds of times bigger and more complicated. They are a chain of building blocks (amino acids) that are often folded in many ways and (as described by Dr. Kozlowski in his written testimony before this subcommittee) they can have complex groups of sugar molecules or additional moieties attached to them which, like folding, can greatly impact the protein's therapeutic function. Because biotechnology medicines are usually made using living cells, each protein molecule can be slightly different, making a product a mix of many different forms, or variants, of a single protein. Due to this potential variability, it is extremely important that companies are able to use the most rigorous and reliable methods in order to understand their medicines and know what parts of the protein are important, to ensure that patients receive the safest and most effective medicines.

Although a protein's primary structure (that is, its amino acid sequence) can be characterized utilizing currently available analytical techniques, the exact spatial location of every atom in a protein cannot yet be determined—nor can all of the modifications that can occur with respect to the amino acids. A greater understanding of the structural characteristics of a biologic could be gained as a consequence of improved method capability and standardization. This in turn could result in the ability to focus clinical studies on quality attribute differences that might have specific impact on safety or efficacy. Patient safety would thus be served if the scientific community works to develop better, and more standardized, methodologies for characterizing proteins' complex three-dimensional structures. Therefore, governmental initiatives in this area, such as those described in Dr. May's testimony, should also be prioritized.

Amgen strives to serve patients by transforming the promise of science and biotechnology into therapies that have the power to restore health and save lives. As a pioneer in developing medicines to treat serious illnesses, Amgen supports prioritization of future NIST work in developing improved measurement technologies in the areas of immunogenicity assessment and protein characterization. Amgen and other innovator biotechnology companies have worked, and continue to work, in collaboration with the World Health Organization, NIST and other organizations in their efforts to develop robust biologics-related reference standards, in order to ensure that safe and effective biotechnology medicines will be available to patients around the world.

Q2. With respect to measurement science and standards, where should the Federal Government role end, particularly with respect to NIST? How do we ensure that the Federal Government's biologics research activities are broad-based and

foundational, rather than pertaining to the interests of individual companies or products?

A2. The Federal Government can play a critical role in ensuring the development of robust measurement standards, methods and tools in the area of biologics science. NIST has played a unique role in this regard as the preeminent U.S. agency for measurement science in support of American innovation and industrial competitiveness.

As Dr. May recounted in his testimony before this subcommittee, NIST's work over the last 90 years in establishing health care-related reference standards has supported important innovation in clinical diagnostics, the therapeutic and diagnostic use of radiation, and dental care. We encourage continued support of NIST as it carries out its current and planned programs in support of biologics-related measurement science.

Amgen believes that NIST should continue to work closely with other federal science agencies—especially FDA and the National Institutes of Health—in developing biologics-related standards, methods, and tools. In addition, other appropriate health-related institutions—including the United States Pharmacopoeia—and the academic community should continue to play a key role in these efforts. We also believe that NIST and these other organizations and agencies should conduct this critical work in close conjunction with biologics manufacturers, especially the biotechnology pioneers such as Amgen, who have unique experience in bringing safe and effective biotech medicines from the lab, to the manufacturing plant, and ultimately to patients.

As a global biotechnology innovator, Amgen also believes that cooperation with international standards-setting, scientific, health, and regulatory bodies will be essential. These organizations include, for example, the World Health Organization, the International Committee on Harmonization, the U.K.'s National Institute for Biological Standards and Control, and the European and other national and regional pharmacopoeias.

Governmental involvement, along with other appropriate public health related organizations, will be critical to ensure that biologics-related measurement science is developed and established in a broad-based, foundational manner, rather than pertaining to the interests of any particular manufacturers, products, or product classes. In this regard, an open, transparent process should be followed, including all relevant stakeholders throughout the international scientific and regulatory community.

Q3. Please characterize the impact of the current shortcomings in measurement science and standards related to biologics. Is drug development or regulatory approval being delayed or completely sidetracked due to gaps in scientific understanding?

A3. The ability to characterize proteins to a very high level of certainty and sensitivity is very important to how well we can ensure that a biologics manufacturing process produces high quality medicine—as pure, consistent and stable as possible—that is efficacious and safe. In this way, rigorous characterization increases the chance that the medicine will be successful in the clinic, thus making new and novel medicines available to improve the health of the American people and those around the world. Rigorous characterization of proteins will thus also help prevent the enormous investment in product development from going to waste. Robust manufacturing processes in themselves lead to reduced failures, less wasted material and rework, and thus reduce the associated costs.

The earlier on in development a biologics manufacturer can develop and implement good methods, the earlier it can alter the product or the process as necessary to ensure its success—before expensive clinical studies are started and before patients are given a medicine that may not work as expected. Having a standard method and reference materials available as soon as product development begins would give manufacturers a head start in creating a successful product.

The availability of standard methods and reference standards would also ease the burden on regulatory reviewers to ensure that the methods used by the manufacturer were appropriately developed, validated and routinely run. This would reduce the need for continuous in-depth evaluation of methods from product to product, and from company to company.

As described above, the main area of testing from a patient perspective that would directly benefit from standardization is detecting and measuring whether, and how, a patient's immune system is reacting towards a biologic medicine—that is, immunogenicity testing. This testing has to be carried out in clinical studies because this is the only way to really understand what is going on inside a patient. There

are a number of different assays used by companies to detect and measure immunogenicity, and each one is developed in conjunction with a particular medicinal product and is unique to that product—and each such assay uses internally produced, custom made materials to make it work. Because the methods are unique to each company and product, they are not well standardized, and reference materials are not easily available. This makes it very difficult to understand exactly how sensitive or accurate these methods are.

It takes a large amount of work by any particular company to produce good immunogenicity assays that will ensure that the sponsor is able to pick up signs of an immune response as early in patients as possible. The future availability of methods, validation and reference standards would reduce the chance that immunogenicity assays are not able to detect the antibodies that could expose patients to health risks. The more sensitive the method, the more likely an immune response can be picked up and stopped before it has a chance to harm a patient.

At the moment, we are not exactly sure what makes the body recognize a protein product as foreign and thus attempt to clear it from the body, and no non-human animal model mimics the human immune system adequately to replace human trials. Consequently, clinical studies have to be used to determine what happens when you inject the medicine into patients. Scientists have been working hard to develop ways to predict what might happen in patients before we give a medicine to them, in the hope we can prevent adverse events in clinical studies. Developing better ways to predict immunogenicity will help to ensure the continued discovery and availability of safe and effective protein-based biotechnology medicines that do not cause unwanted side effects for patients.

ANSWERS TO POST-HEARING QUESTIONS

Responses by Patrick Vink, Senior Vice President and Global Head of Biologics, Mylan Inc.

Questions submitted by Chairman David Wu

Q1. To the best of your knowledge, do the seven areas of scientific research identified by NIST in its testimony complement or overlap research being conducted by the FDA, other federal agencies or the private sector?

A1. We believe that NIST can play an important role in all seven areas that were mentioned in the testimony of Dr. May. In all of these areas extensive research is being conducted in the private as well as in the public area but significant advances can still be made. NIST's independence and ability to create standards, publicly available to everyone can certainly enhance pharmaceutical science and the quality of biologics research and developmente—specially further improvements of the characterization of biologics that can advance patient safety and reduce the burden of unnecessary clinical trials. The future research agenda of NIST should be coordinated with FDA but we see an important unmet research need that can be filled by the plans of NIST.

Q2. What are the potential benefits to innovation and encouraging the growth of the biotech industry or other industries, such as biologics manufacturing, if analytical tools in the seven areas of scientific research identified by NIST in its testimony are developed?

A2. As mentioned in the answer to Question 1, we see significant opportunities in improving patient safety when biologics (new entities and biosimilars) can be held to the same standards. Furthermore, the advancement of developing improved quality parameters to guarantee manufacturing compliance will be very helpful.

Questions submitted by Representative Adrian Smith

Q1. Please provide your company's comment on and reaction to the broad plan of work for biologics measurement and standards outlined by Dr. May in his testimony. Do you support the identified research activities or have any concerns or suggested modifications?

A1. We believe that the areas identified by NIST are very appropriate areas and that science can be further advanced. For example, immunogenicity is an area of concern for every biologic. Improving our understanding of measurement standards of key attributes of a protein could reduce clinical testing and safety risks to humans. The seven areas identified by Dr. May offer a very comprehensive and meaningful approach.

Q2. With respect to measurement science and standards, where should the Federal Government role end, particularly with respect to NIST? How do we ensure that the Federal Government's biologics research activities are broad-based and foundational, rather than pertaining to the interests of individual companies?

A2. As was outlined in my testimony, we see an important role for NIST in developing measurement standards for biologics (and advancing the science in the area). Biologics reference standards would improve transparency, as all products would need to comply to these standards; patient safety; and, most important, access to medicine would be improved by avoiding unnecessary duplication of research and development efforts.

Q3. Please characterize the impact of the current shortcoming in measurement science and standards related to biologics. Is drug development or regulatory approval being delayed or completely sidetracked due to gaps in scientific understanding?

A3. We believe that the scientific understanding of biologics has improved very significantly over the past decade. The evolution of the biopharmaceutical industry has improved health care to a great extent, providing patients and doctors with new therapeutic options. At this moment we are able to characterize biopharmaceuticals far better than we could 10 years ago. NIST's proposed program can help us all further advance our knowledge and understanding of biologics. By doing so, it will contribute in a very meaningful way to the improvement of health care.

One of the key problems is that access to medicines and patient choices has been limited by the absence of a pathway for the FDA to approve biosimilar versions of

existing products, based on an abbreviated regulatory application. We strongly believe the science is available and legislation would provide the FDA with the opportunity to determine, based on prevailing science, the standards to be met for any given submission of a biosimilar pharmaceutical.

ANSWERS TO POST-HEARING QUESTIONS

Responses by Steven Kozlowski, Director, Office of Biotechnology Products, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Department of Health and Human Services

Questions submitted by Chairman David Wu

Q1. To the best of your knowledge, do the seven areas of scientific research identified by NIST in its testimony complement or overlap research being conducted by the FDA, other federal agencies or the private sector?

A1. The National Institute for Standards and Technology's (NIST) testimony identified seven areas of scientific research that could promote innovation and improve efficiency in the drug and biologic development process: immunogenicity, 3–D structure, post-translational modifications, contaminants, production cell behavior, viral clearance, and biopharmaceutical function. Advances in these areas could also help enhance FDA regulatory decision-making when evaluating the safety and efficacy of drugs and biologics.

FDA performs research in these areas and actively participates in standards development activities, including development and maintenance of select material standards. However, we typically do not create and maintain material standards in the seven areas identified. NIST has expertise in creation and maintenance of such standards to ensure that the analytical methodologies used across industry are performing similarly.

In addition, the seven named categories are extremely broad, encompassing multiple specific research activities. For example, industry, NIH, FDA, and academia are all currently studying various aspects of immunogenicity. In general, industry focuses on the technology it needs to develop specific products and meet regulatory requirements.

FDA generally focuses on areas and tools that will benefit a wide range of products and/or enable informed decision-making and guidance. Academia and NIH ordinarily focus on the biology necessary to enable more meaningful research in these areas. Thus, there are multiple questions within the topic of immunogenicity that different groups could study without overlapping research efforts. For example:

a) Protein aggregation (clumping) can present one risk for immunogenicity. Different groups could study how to better detect aggregates without overlap; one group might look at tools for large aggregate detection and another at tools sensitive to small aggregates. Still other groups might research how to improve manufacturing processes to decrease aggregation or study the biological impact of different types of aggregates on immune cells and *in vivo* models.

b) There are causes for immunogenicity other than aggregates. Different groups can conduct studies to better understand how the impurities that lead to immunogenicity can affect product safety,

c) It is also important to understand the potential consequences of immunogenicity. Groups who use animal models might study the potential consequences of immune responses to a particular therapeutic product through the use of animals genetically engineered to better reflect human immune responses.

d) Once immunogenicity does develop in patients, it would be useful to have better ways to measure it. Industry often develops assays for immunogenicity but it is difficult to compare results from company to company. Groups can work to develop improved detection methods and standards so we can better compare immune responses.

e) It would be very useful to discover interventions to prevent or alleviate problematic immune responses. Different groups can work to develop and study potential interventions that might accomplish this goal.

Interactions and communication between different groups can lead to synergy and ensure that related efforts are complementary. Thus, if a group develops a better way of separating out aggregates and collaborates with a group that has an improved animal model, real progress is possible. Research also needs some level of overlap to reproduce, verify and generalize conclusions—if one research group has an important result, it may be due to something specific to the exact protocols and systems they are using. However, if other research groups reach the same conclusion with slightly different approaches, the result is likely to be generalizable across

many laboratories. Although many groups perform research on basic biological questions, there are far fewer research groups that focus on issues directly related to product quality and manufacturing.

Q2. Can you describe the interactions between NIST and the FDA that have led to the development of the seven areas of scientific research for improved measurement technologies and methods in the biologics identified by NIST in this testimony? How do you see NIST working with the FDA to facilitate development of these technologies and methods?

A2. NIST and FDA have met on a number of occasions to discuss ways in which the research program at NIST could enhance FDA's ongoing regulation of biopharmaceutical regulation. Representatives from FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) met with NIST's Chemical Science and Technology Laboratory (CSTL) on January 30, 2008, to discuss what information, technologies, and standards are most needed for advancing the development and regulation of biological products. FDA also sent a representative to CSTL's strategic planning go-away at the end of July 2009 to provide input on general issues facing the pharmaceutical industry and FDA. Further meetings and collaborative projects could facilitate development of these technologies and standards.

Q3. You mentioned that advances in analytical tools during the past 20 years have driven progress in biopharmaceutical manufacturing. Could you please provide some examples? Also, were these analytical tools developed primarily by federal agencies, private industry or some combination?

A3. One example where an advance in analytical tools has driven progress in biopharmaceutical manufacturing is the development of improved analytical tools used to measure sugars attached to proteins. These sugars are a type of post-translational modification to a protein. The importance of these sugars to the biological function of proteins was not widely appreciated 20 years ago and the tools to evaluate them were very limited. Early analyses focused only on the amount of each sugar present in total but did not examine how the sugars were attached to each other or to the protein. Academia, government and industry all worked to learn more about the biological impact of these sugars and their specific structures. As knowledge improved and FDA began to require drug sponsors to submit information regarding the structure of the sugars in their products, industry continued to improve methodologies to detect sugars and their structures. This information has proved useful in many settings.

In 2002, the Nobel Prize in Chemistry was awarded to scientists in both academia and industry for the application of two techniques, Nuclear Magnetic Resonance and Mass Spectrometry, to the study of large molecule structures. FDA's own research on the use of Nuclear Magnetic Resonance to evaluate complex sugars enhanced the development of polysaccharide vaccines in addition to enhancing FDA regulation of polysaccharide vaccine quality.

In 2002, a published industry study[1] showed the importance of one particular sugar called fucose. The absence of fucose was shown to significantly enhance the ability of monoclonal antibodies to kill tumor cells. Many other groups in both industry and academia verified and extended this finding. Based on this knowledge, FDA now expects applications for such anti-tumor antibodies to provide information about fucose content. This knowledge has also enhanced industry's development of improved products.

Many companies now engineer their antibodies to lack this sugar and have more potent anti-tumor potential. The ability to measure fucose thus led to an understanding of its biological effect, which, in turn, allowed for progress in biopharmaceutical manufacturing.

This example also shows the need for robust standards and the importance of NIST's involvement in this area. When FDA began requiring companies to submit information relating to fucose, each company would submit data using their own methods and standards for detecting this sugar. Without standardization, it was difficult to compare these results. However, FDA did not want to slow the development of new methods by requiring that all companies use one particular method. NIST has the necessary expertise to develop material standards that allow for comparison of different methods being used. When NIST develops material standards, FDA can

[1] Shields, R.L., J. Lai, R. Keck, L.Y. O'Connell, K. Hong, Y.G. Meng, S.H. Weikert, and L.G. Presta, Lack of fucose on human IgGlN-linked oligosaccharide improves binding to human Fegamma RIII and antibody-dependent cellular toxicity. *J Biol Chem,* 2002. 277(30): pp. 26733–40.

improve our ability to ensure consistent quality while allowing industry the freedom to develop innovative new analytical methods.

With better standards, our current knowledge can be extended more quickly and the remaining gaps can be more rapidly addressed. Just as the impact of fucose was not known more than five years ago, there may be other important post-translational modifications that we do not understand today. Improved standards will accelerate this understanding.

Questions submitted by Representative Adrian Smith

Q1. How much does FDA currently spend on biologics research? What is this research focused on and under what programs is it carried out?

A1. For Fiscal Year (FY) 09, FDA Centers that regulate biological products expended approximately $31 million on biologics research (including salaries and benefits).

FDA's biologics research activities are focused on scientific endeavors aimed at ensuring the safety, efficacy, and availability of biological products that advance the public's health. FDA achieves these goals through highly skilled scientific staff, modern laboratories and up-to-date equipment, and ongoing scientific collaborations with the Department of Health and Human Services (HHS) operating divisions and other stakeholders. These research activities support all biologics regulated by FDA, including vaccines, therapeutic proteins, monoclonal antibodies, plasma derivatives, blood, cell, tissues, and gene therapies. Research is conducted in such diverse areas as adventitious agent detection, product characterization (including understanding the mechanism of action and development of biological assays), immunogenicity, and evaluating product toxicities.

In addition, FDA research is involved in facilitating the development and application of analytical technologies by biologic manufacturers and regulators in the development and manufacturing control of biologics.

FDA research capabilities also facilitate Agency testing and characterization of products. The research activities at FDA create new knowledge that provides scientific expertise, new laboratory and testing tools, and generate data that support science-based regulatory decision-making and policy development and that facilitate regulation of existing products and development of novel biologics. In addition, by maintaining an active multi-disciplinary research program, FDA is poised to respond to emerging issues relevant to the agency's regulatory responsibilities.

Q2. Have the respective biologics research roles of FDA and NIST been defined in any way? Where would NIST's role begin and end, and is there an agreed upon "division of labor" to pursue the identified research needs?

A2. Although there is no formal definition of the research roles of FDA and NIST, each focuses on different types of research.

FDA's research staff performs research related to ensuring the safety, efficacy, and availability of biological products that advance the public's health. FDA research staff stays current with product problems and new areas of product development. They are responsible for testing products taken from the field and performing research on development of analytics, bioassays and quality-by-design manufacturing approaches, along with research on immunogenicity and adventitious agents. However, FDA is not in a position to develop novel analytic technologies. For example, FDA can use Nuclear Magnetic Resonance to study and develop approaches to better regulate products, but we cannot create a next generation Nuclear Magnetic Resonance instrument. Unless there is an emergent need, FDA does not usually create and maintain material standards that will ensure a particular analytical methodology is performing appropriately. Such standards are of value to FDA and across industry and academia.

If NIST performs related research in the same areas as FDA and the agencies communicate with each other effectively, synergies will be likely. As indicated above, there is no shortage of important topics in the seven research areas indicated by NIST. If collaborating in these areas facilitates NIST development of material or performance standards that FDA, academia, and industry can use, that would be a tremendous boon to the development of biopharmaceutical science. Additionally, NIST possesses expertise in engineering, physics, and material sciences, which FDA, industry, and academia could leverage to streamline product development and review. When multiple groups with different perspectives and expertise collaborate, they cannot only focus on improving an existing method, but may develop truly novel methods that no one group would have developed on its own.

For example, collaboration between FDA and NIST could be of value in the development of analytic "signatures." The 3–D structure of a protein can be evaluated by actually measuring spatial coordinates (a picture of the protein). For very large complex molecules and for the routine quality control of all proteins, measuring 3–D structures by using such methods may be onerous and challenging. An alternative strategy is to measure only a defined number of important features of 3–D structures and extrapolate the rest. Extrapolating information from a signature subset of the data is a powerful tool for analysis of very complex proteins. But this only works if the signature is sufficient to uniquely identify the structure. NIST expertise may be helpful in developing standards for signature methodologies that ensure that the signature used is sufficiently unique to identify the structure.

Q3. More generally, how are NIST and FDA working together on biologics? Have coordination or research activities been formalized in any way? Relatedly, please provide FDA's comment on and reaction to the broad plan of work for biologics measurement and standards outlined by Dr. May in his testimony. To what extent would this research support and advance FDA's regulatory decision-making needs? To the extent it would, should a joint FDA–NIST funding arrangement for such activities be considered?

A3. FDA and NIST have met a number of times to discuss biologics. FDA and NIST co-sponsored a valuable meeting with the New York Academy of Sciences on protein characterization in 2005. At present, the coordination of research activities has not been formalized.

All of the research areas in Dr. May's testimony are important, and additional research in these areas would be of great benefit to FDA in regulating drugs and biologics. Specifically, the collaborative development of robust material standards and novel methodologies in these areas would assist FDA and industry in biopharmaceutical development, review, and regulation. FDA could contribute its scientific knowledge and research on biological products and NIST could contribute its extensive experience in setting standards and its multi-disciplinary expertise in engineering, physics, and material sciences. The example of the development of analytics to study sugars described in Question 3 shows how research and standards development can benefit FDA in our regulatory decision-making.

Any collaborative efforts could be funded through NIST and FDA budgets. If additional joint funding is provided, clear accountability and authority over such additional joint resources would need to be established and detailed definition of the specific objectives of any targeted joint funding would be advisable.

Q4. Please characterize the impact of the current shortcomings in measurement science and standards related to biologics. Is drug development or regulatory approval being delayed or completely sidetracked due to gaps in scientific understanding?

A4. FDA is very capable of approving biologics and many manufacturing changes with current technologies. However, as indicated above, although analytical methods have advanced over time, there are areas that are in need of further development. In particular, better approaches to measurement of 3–D structure, post-translational modifications, and aggregates would be very beneficial. With improved methodologies and standards, manufacturing changes could be more rapidly implemented, abbreviated pathway approvals facilitated (where authorized by statute), and manufacturing efficiency improved.

ANSWERS TO POST-HEARING QUESTIONS

Responses by Willie E. May, Director, Chemical Science and Technology Laboratory, National Institute of Standards and Technology (NIST)

Questions submitted by Chairman David Wu

Q1. The NIST advisory committee, the Visiting Committee on Advanced Technology (VCAT) provided recommendations to NIST for a program to support the evolving field of biologics and the biotechnology industry in general. How will NIST propose to incorporate those recommendations into current plans for research in support of reference standards and analytical methods for biologics?

A1. NIST values the advice of the VCAT and is systematically reviewing and responding to their input. We have undertaken an internal strategic planning process for bioprogram growth that has involved extensive outreach, including the hosting of an international conference in October of 2008 entitled *"Accelerating Innovation in 21st Century Biosciences: Identifying the Measurement, Standards, and Technological Challenges,"* to help identify and prioritize measurement standards and technology barriers to new discoveries in agriculture, energy, the environment, manufacturing, and medicine. The measurement and standards needs identified through this and previous outreach efforts dating back to 2005 have resulted in three documents:

1. **The Report From the October 2008 Conference—***which describes critical measurement and standards needs that are being used to guide research at both at NIST and throughout the measurement standards community worldwide.*
2. **Measurement Challenges to Innovation in the Biosciences: Critical Roles for NIST—***a high level document outlining our strategic approach for addressing the bioscience measurement barriers of the highest risk to economic security and quality of life.*
3. **Measurement Science and Measurement Standards to Support Innovation in Health Care—***an internal planning document currently being vetted with the health care community that catalogues measurement and standards needs articulated to us by the medical professional community, industry, FDA and NIH.*

Standards for health care is our initial area of focus within the biosciences. Programs for "standards for biologic drugs," along with clinical diagnostics, medical imaging and health-IT are included in internal program planning documents that will feed into the annual update to the NIST Three-Year Programmatic Plan and inform the budget process.

Q2. What role has VCAT played in the development of the seven areas of scientific research for improved measurement technologies and methods in biologics identified by NIST in its testimony? Have they provided comments or feedback?

A2. The critical needs for additional measurement science research and standards identified in the written testimony were based on extensive discussions with our colleagues at FDA and in the biopharmaceutical industry.

The seven areas were taken from document #3 identified in the response to the previous question. Document #3 has been shared with the VCAT Subcommittee on Bioscience.

Q3. What additional consultation has NIST had with VCAT since the March 6, 2007 meeting in which a strategic planning process for health care, biotechnology and life science was presented? What efforts have been made to incorporate VCAT's comments from that meeting?

A3. Discussions of NIST plans for bioprogram growth and implementation have been discussed with VCAT on an ongoing basis since the March 2007 meeting. Presentations concerning our programs in bioscience and progress on our strategic planning process have been made to VCAT in August 2007, December 2007, June 2008 and October 2008. Dr. James Serum, VCAT Chair, was a member of the Steering Committee and attended the October 2008 Bioscience Conference.

While no formal presentations have occurred at the two VCAT meetings in 2009, VCAT has been kept abreast with our activities through e-mails and conversations during those meetings.

Q4. With whom did NIST consult to develop the seven areas of scientific research identified in your testimony? What government agencies and biotechnology and

pharmaceutical companies have been involved in the identification of these seven areas of research?

A4. See response to Question 2. More specifically, measurement and standards needs for biopharmaceutical manufacturing have been discussed with:

- FDA
- Amgen
- Mylan Pharmaceuticals
- Biogen Idec
- Eli Lilly
- Genentech
- BIO (Biotechnology Industry Organization)
- The Generic Pharmaceutical Association

Questions submitted by Representative Adrian Smith

Q1. Have the respective biologics research roles of FDA and NIST been defined in any way? Where would NIST's role begin and end, and is there an agreed upon "division of labor" to pursue the identified research needs? More generally, how are NIST and FDA working together on biologics? Have coordination or research activities been formalized in any way?

A1. The FDA is responsible for protecting the public health by ensuring the safety, effectiveness, and security of human and veterinary drugs, biological products, and medical devices, and the safety and security of our nation's food supply, cosmetics, and products that emit radiation and by reducing mortality and morbidity associated with tobacco use.

NIST's mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life.

The need for measurement standards was clearly articulated in the FDA testimony. Through our lead agency role in measurement science, standards and technology, NIST is regularly called upon to provide measurement and standards solutions to support other government agencies in carrying out their missions.

The FDA has requested that NIST provide reference methods, standards, and validated protocols to enable increased confidence in measurement results used to evaluate biologic drugs.

NIST and FDA are beginning scientific collaborations concerning critical measurement and standards needs for biologic drugs. Activities are currently underway to address measurement and standards needs associated with immunogenicity and viral clearance.

Q2. With respect to measurement science and standards, where does the Federal Government role in supporting biologics end, particularly with respect to NIST? How do we ensure that these research activities are broad-based and foundational, rather than pertaining to the advancement of individual companies or products?

A2. NIST research will address the broad based measurement science and standards needs identified in the testimony that will be of benefit to the producers of both innovator and generic biologic drugs, namely:

- more accurate assessment of the "sameness" of a biologic drug made by different manufacturers and/or different manufacturing processes;
- improved safety and efficacy; and
- improved efficiency and reliability in manufacturing processes.

Appendix 2:

ADDITIONAL MATERIAL FOR THE RECORD

VerDate 11-MAY-2000 16:32 Dec 21, 2009 Jkt 052285 PO 00000 Frm 00107 Fmt 6601 Sfmt 6601 C:\DWORK\T&I09\092409\52285 SCIENCE1 PsN: SCIENCE1

Bruce A. Leicher
Sr. VP and General Counsel
(617)395-2786

September 23, 2009

By Email and Mail

The Honorable Bart Gordon
Chairman
Committee on Science and Technology
Subcommittee on Technology and Innovation
2321Rayburn House Office Building
Washington, DC 20515

Attention: Victoria Johnston

Re: The Need for Measurement Standards To Facilitate Research and Development of Biologic Drugs

Dear Mr. Chairman:

On behalf of Momenta Pharmaceuticals, Inc., thank you for the opportunity to submit comments to the questions under consideration at the September 24, 2009 Subcommittee regarding "The Need for Measurement Standards To Facilitate Research and Development of Biologic Drugs". Momenta Pharmaceuticals is a biotechnology company specializing in the engineering and characterization of complex drugs and biologics (a general description of our business is attached). Our technology platform was licensed from our founders' laboratory at the Massachusetts Institute of Technology, and is now focused as well on how one would measure "sameness" of biologics. Our research activity involves the characterization of complex drugs such as heparin, a biologic-like complex product, as well as the characterization of biologics in order to fully understand their structure and develop biogenerics. In addition, we also conduct research and development into the relationship of these structures to biologic function so that we can engineer new drugs and biologics that offer the potential for improved therapeutic qualities and greater safety. Thus, the core of our business model is the development of cutting edge technologies for the research and development of novel as well as generic biologics.

We appreciated the opportunity to discuss these matters with you and your staff in July, and have subsequently spoken with the staff at the National Institute of Standards and Technology. We have reviewed the Hearing Charter and offer the following comments on the Charter and the questions posed.

675 WEST KENDALL STREET CAMBRIDGE, MA 02142 T: 617.491.9700 F: 617.621.0431 WWW.MOMENTAPHARMA.COM

Question 1: Is there a need for measurements, reference materials, reference standards, standard processes and validation of procedures to improve the research, development or regulatory approval of biologics?

We believe that the answer is no because it would be premature to attempt to develop these standards apart from the development of individual products. For biologics, the technology is not yet mature enough for standardization – instead, it requires fundamental scientific research and development before it can be standardized.

Today there is an incentive for companies like Momenta Pharmaceuticals to invest in characterization technology and tools, to develop and better understand characterization technology, and to raise capital to fund this research based on the opportunity to develop specific products whether they are biogenerics or novel improved biologics. If the National Institute of Standards and Technology (NIST) attempted to set standards at this stage, it would significantly impede and likely stifle the significant investment and private capital funding research into biologic characterization technology. The competitive advantage offered by advancing the science would be undermined, and the result, we believe, would put at risk the global competitive edge currently held by companies in the United States.

Because the European development of follow-on biologics has been largely focused on biosimilar development rather than biogeneric development, the technological demand overseas for characterization technology development is significantly less than in the United States, if it exists at all. Because the pending follow-on biologics legislation has contemplated FDA scientific discretion for product-by-product approval of biogenerics as well as biosimilars, and because the FDA also has discretion to determine the need for clinical trials in addition to characterization data, investment in characterization technologies in necessary. Consequently, our biotechnology industry has a global competitive edge.

If NIST assumes the role of determining uniform standards for characterizing biologics, or for measuring "sameness," and supplants the current competition of scientific ideas, we believe that we will significantly remove the incentive for investment and innovation by individual companies. This matters because the science in this field at this time is highly dependent on the kind of product to which it is applied. In addition, determining national standards at this time could result in the freezing of the advancement of this science because if the standards are not connected with actual product development activities, the standards would likely not keep up with evolving science that is highly dependent on the interplay between the manufacturing process and the tools used to measure the product. We are very concerned; therefore, that centralizing standardization and related research in a single agency, rather than allowing companies developing biologics to compete scientifically would be the wrong approach at this time.

Question 2: If developed, how would these measurements, reference materials, reference standards, standard processes, and validation procedures: (a) reduce manufacturing costs or improve safety monitoring during the manufacturing process for biologics; and/or (b) reduce the need for or improve the accuracy of preclinical trials for biologics and biosimilars?

We do not believe the development of these measurements as reference standards would achieve (a) or (b). We do believe that these kinds of measurements with respect to a specific product would achieve (a) or (b). It is important to distinguish the value of having product-specific characterization information from having reference standards. Given the rapidly expanding state of the science of characterization, there is a need for the development of standards on a product-by-product basis in conjunction with the development of manufacturing processes and quality and safety assurance for each product. For example, quality issues related to scale up of biotechnology manufacturing processes may be one of the key challenges relating to the application of characterization information, and it is not clear that NIST would have real time access to commercial scale manufacturing. At this time, we believe individual biotechnology companies are in the best position to develop the technology by applying it to their products. We are concerned that the establishment of standards could deter these activities, curtail investment and inhibit advancement of the science. In our own experience, the knowledge gained in our research function is best validated as it is applied and tested through the entire process of commercial product development and scale-up.

For example, Momenta Pharmaceuticals focused its characterization technology on heparins when it was founded, and was able to develop a set of proprietary tools and standards for heparin that enabled it to fully characterize its structure and glycosolation to support an ANDA filing. In addition, as a consequence of having characterized a complex heparin mixture, Momenta Pharmaceuticals was able to assist MIT in its collaboration with the FDA last year in identifying the contaminant that triggered last year's heparin contamination crisis. Our heparin characterization technology is a key proprietary asset that allowed for the financing of our company, and the development of a complex generic product candidate. This is analogous to the EPREX matter cited in the Hearing Charter. As biogeneric and brand companies embark to characterize EPO, they will similarly be able to adopt more precise quality and manufacturing release standards. With new product-specific information, changes to the molecule caused by a manufacturing process change or by a stopper change will be more easily monitored and controlled.

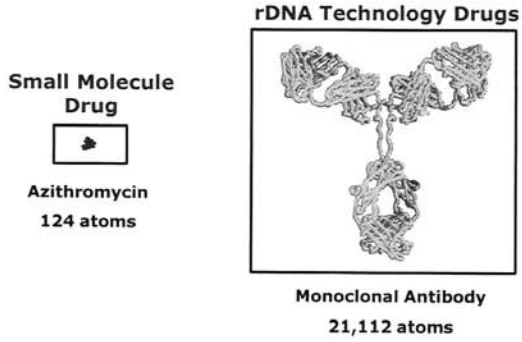
We are now developing similar characterization tools for biologics. If the opportunity to compete in developing the new technology is supplanted by NIST standards, the incentives for companies like Momenta Pharmaceuticals will diminish if not evaporate entirely. Moreover, our scientists believe that there is unlikely to be a single set of standards, or at least it is too early to tell if there will be a single set of standards for all biologics, and that to create a standardization policy will slow down the progress we and others have achieved to date. In short, we believe that these kinds of scientific advances are best left to scientific competition to encourage innovative investment in product characterization and quality improvement.

Question 3: What are the current scientific challenges to assessing the "sameness" of two biological molecules produced by different processes, or to comparing different batches of biologics produced by the same process? What measurements, reference materials, reference standards, standard processes and validation procedures can be developed to address these challenges and how would they benefit the biotechnology industry and patients?

Fundamentally, we believe that it is scientifically possible to thoroughly characterize a biologic and that our initial work in characterizing heparins created a foundation for that work. We are now engaged in characterizing biologics and believe others are doing the same. This work will facilitate the development of technologies for assessment of sameness and lead to biogenerics that are the same as a brand product using innovative biotechnology. It will allow a biotechnology company to develop different and improved analytic and manufacturing methods that can be controlled and engineered to make the same biologic. These tools will also make it easier for brand companies to make manufacturing changes and to open new, more efficient and competitive plants as they control their improved process to match the original biologic product. Perhaps more importantly, it will lead, we believe, to the ability to engineer safer and better brand biologics as well as link structure to function of products that were previously not well understood. If standardization ensues too soon, then the power of scientific competition will not drive these activities at Momenta Pharmaceuticals and other biotechnology companies.

While the scientific challenge of characterizing biologics is real, the current debate is infected with a little too much fear and too few facts. As represented by the following graphic, characterizing a biologic is certainly more challenging than characterizing a drug. We are concerned though that those seeking to preserve market share are using fear of science as a weapon rather than as a tool to unlock future advances and discoveries.

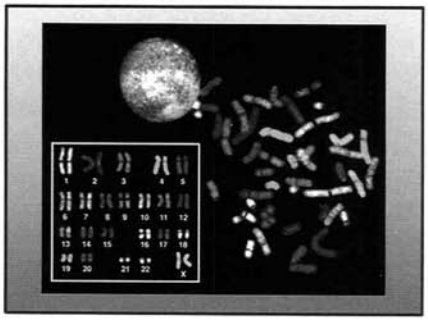
Hiding behind "Science" as a Scare Tactic ..



A protein is clearly more complex than a small molecule drug. At the same time, we have increasingly powerful analytical tools at our disposal that allow us and others to understand proteins. From our perspective, the challenge of characterizing a protein is no more complicated than the challenge to sequence the human genome.[1]

... Or using Science to Meet the Challenge.

Complex Issues Solved



Human Genome

3 billion base pairs

In short, we believe the best policy at this time is to encourage the biotechnology industry to develop these tools on product-by-product basis through the filing of applications at the FDA. It is too early to consider standardization. The FDA needs to carefully screen products as they proceed through the approval process or the review of manufacturing process changes. The FDA should insist on high standards but needs discretion to consider alternative approaches to promote innovation and investment. Biotechnology companies need the opportunity to advance the science to attract scarce investment capital. When the science matures, which could take a number of products and a number of years, then one might consider the advantages and disadvantages of standardization of commonly applied techniques. To do so now, however, would put in jeopardy U.S. global leadership in this field.

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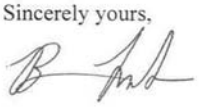
[1] By analogy, protein characterization in the 1980s and 1990s may have been much like space exploration in the 1700 and 1800s. We were able to identify stars and determine their movement, but little was known about their composition. As the fields of chemistry and physics emerged and the technology for measuring chemical composition and physical composition evolved, scientists are now, as the Committee understands perhaps more deeply than us, able to determine the composition and character of stars in the distant universe. By combining analytical methods and developing new techniques for applying them and analyzing their data, it is now possible to understand and thoroughly characterize biologics.

We appreciate the opportunity to submit these comments and we would be pleased to meet or speak with you or your staff at your convenience.

Sincerely yours,



Bruce A. Leicher
Senior Vice President and General Counsel

Cc: Victoria Johnston (by email)
Holly Prutz (by email)
Enc.

MOMENTA

Momenta Pharmaceuticals
Company Overview

Momenta is a biotechnology company, founded in 2001 based on a technology platform initially developed and licensed from Massachusetts Institute of Technology. We currently employ approximately 170 employees at our offices in Cambridge, Massachusetts. We are developing both novel and complex generic drugs by applying our innovative technology for the detailed structural analysis of 'complex mixture drugs'. Complex mixture drugs are compounds which have highly complex molecular structures that can be challenging to bioengineer and manufacture. We leverage this platform to study the *structure* (i.e., thorough characterization of chemical components), *structure-process* (i.e., design and control of manufacturing process), and *structure-activity* (i.e., relating structure to biological and clinical activity) of complex mixture drugs. The development product candidates and research programs from our generic and novel portfolios are outlined below.

Momenta Pharmaceuticals—Product and R&D Pipeline

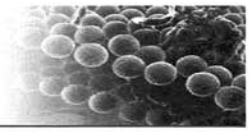
Drug Candidate	Program Objectives	Status
Complex Mixture Generics		
M-Enoxaparin*	Generic version of Lovenox®	ANDA under FDA review
M356*	Generic version of Copaxone®	ANDA under FDA review
Glycoprotein*	Follow-on version of marketed protein drug	In development
Novel Drugs		
M118	Next-generation anticoagulant engineered for Acute Coronary Syndromes	Phase 2a completed
Oncology	Novel sugar-based anti-cancer compound	Preclinical Development

*In collaboration with Sandoz, the generic pharmaceuticals division of Novartis.

Sandoz Collaborations

Under the terms of a 2003 Sandoz Collaboration, we and Sandoz agreed to exclusively work with each other to develop and commercialize injectable enoxaparin for any and all medical indications within the United States. In addition, we granted Sandoz an exclusive license under our intellectual property rights to develop and commercialize injectable enoxaparin for all medical indications within the United States. In 2006 we expanded the geographic markets covered by the 2003 Sandoz Collaboration related to M-Enoxaparin to include the European Union and further agreed to exclusively collaborate on the development and commercialization of three other follow-on and complex generic products for sale in specified regions of the world.

MOMENTA



Complex Mixture Generics Portfolio

Our complex generics effort is focused on building a thorough understanding of the *structure* and *structure-process* of complex mixture drugs to develop generic versions of marketed products. We utilize a similar development approach across all of our product candidates. Our first objective is to apply our core analytical technology to thoroughly characterize the marketed product by defining its chemical composition. Using this information, we then build an extensive understanding of the structure-process relationship to design and control our manufacturing process to reproducibly manufacture the product. Our goal is to obtain FDA approval for and commercialize generic or follow-on versions of complex mixture products, thereby providing high quality, effective, safe, and affordable medicines to patients in need.

Our most advanced product candidate, **M-Enoxaparin**, is designed to be a technology-enabled generic version of Lovenox® (enoxaparin sodium injection), a low molecular weight heparin, or LMWH, used to prevent and treat deep vein thrombosis, or DVT, and to support the treatment of acute coronary syndromes, or ACS. This drug is a complex mixture of polysaccharide chains derived from naturally sourced heparin. Our second major generic product candidate is **M356**, a technology-enabled generic version of Copaxone® (glatiramer acetate injection), a drug that is indicated for the reduction of the frequency of relapses in patients with Relapse-Remitting Multiple Sclerosis, or RRMS. Copaxone® consists of a complex mixture of polypeptide chains. With M356, we have extended our core characterization capabilities from the characterization of complex polysaccharide mixtures to include the characterization of complex polypeptide mixtures.

Follow-On Biologics – Biologics represent a sizable segment of the U.S. drug industry, with sales expected to exceed $60 billion by 2010. Most of these products are glycoprotein drugs, which contain branched sugars attached to a protein backbone that vary from molecule to molecule. These sugars can impart specific biological properties to the glycoprotein drug and often comprise a significant portion of the mass of the molecule. Given the inadequacies of standard technology, many of these glycoproteins have not been thoroughly characterized. Our follow-on biologics program is focused on extending our technology for the analysis of complex sugars and peptides to glycoproteins. The goal of the program is to facilitate the development of biosimilar, and potentially biogeneric, versions of major marketed glycoprotein biologics.

Our product candidate with Sandoz, and our ongoing **FOBs (Follow-On Biologics) Research Program** are focused on developing generic or follow-on versions of marketed therapeutic proteins. All therapeutic proteins are derived from natural or cell based manufacturing sources that create complex mixtures. With this effort, we are further extending our core characterization and manufacturing capabilities to additionally include the characterization of complex glycoprotein products.

Novel Drugs Portfolio

Our novel drug research and development efforts leverage our analytical technology platform and structure-process knowledge to study the *structure-activity* of complex mixtures and develop novel drugs. With our capabilities to thoroughly characterize complex mixtures, we are targeting our efforts to understand the relationship between structure and the biological and therapeutic activity of various complex mixture drugs. Our goal is to capitalize on the structural diversity and multi-targeting potential of these complex mixtures to engineer novel drugs that we believe will meet key unmet medical needs in various diseases. While we believe that our capabilities to engineer improved and novel complex mixture drugs can be applied across several product categories with significant therapeutic potential (i.e., polysaccharides, polypeptides and glycoproteins), our initial focus has been in the area of complex polysaccharide mixtures.

Our lead novel drug candidate, **M118**, is a LMWH that has been engineered to possess what we believe will be an improved therapeutic profile (compared with other currently marketed products) to support the treatment of ACS. Within our research program, we are seeking to discover and develop novel therapeutics by applying our technology to better understand the function of these polysaccharide mixtures in biological processes, with an initial focus in **Oncology**.

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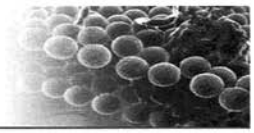

Momenta Technology

Our integrated technology platform for the study of complex mixtures utilizes three different types of analytical tools. First, we have accumulated a comprehensive library of enzymes that we use to break down the components of a complex mixture into smaller, measurable units. Second, we apply proprietary improvements to established analytical techniques (such as Matrix Assisted Laser Desorption Ionization-Mass Spectrometry, or MALDI-MS, nuclear magnetic resonance, or NMR, and capillary electrophoresis, or CE, among others), to gather and analyze information regarding the components, structure and arrangement of the chemical building blocks of the complex mixture. Third, we apply proprietary mathematical methods that integrate the disparate information obtained from these analytical techniques to arrive at a specific, numerically-derived solution that describes the complete composition of a specific complex mixture. It is the combination of these tools that enables us to characterize complex polysaccharide, polypeptide and glycoprotein mixtures.

While a similar integrated analytical approach is applied across different product categories, we develop a unique characterization toolkit for each specific complex mixture. Once the chemical components of the complex mixture are known (*structure*), we (1) further employ these methods and data sets in the design and control of our manufacturing process (*structure-process*) to produce generic versions of marketed drugs, and (2) relate structure to biological and clinical activity (*structure-activity*) to engineer novel drugs which meet key unmet medical needs in various diseases.

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