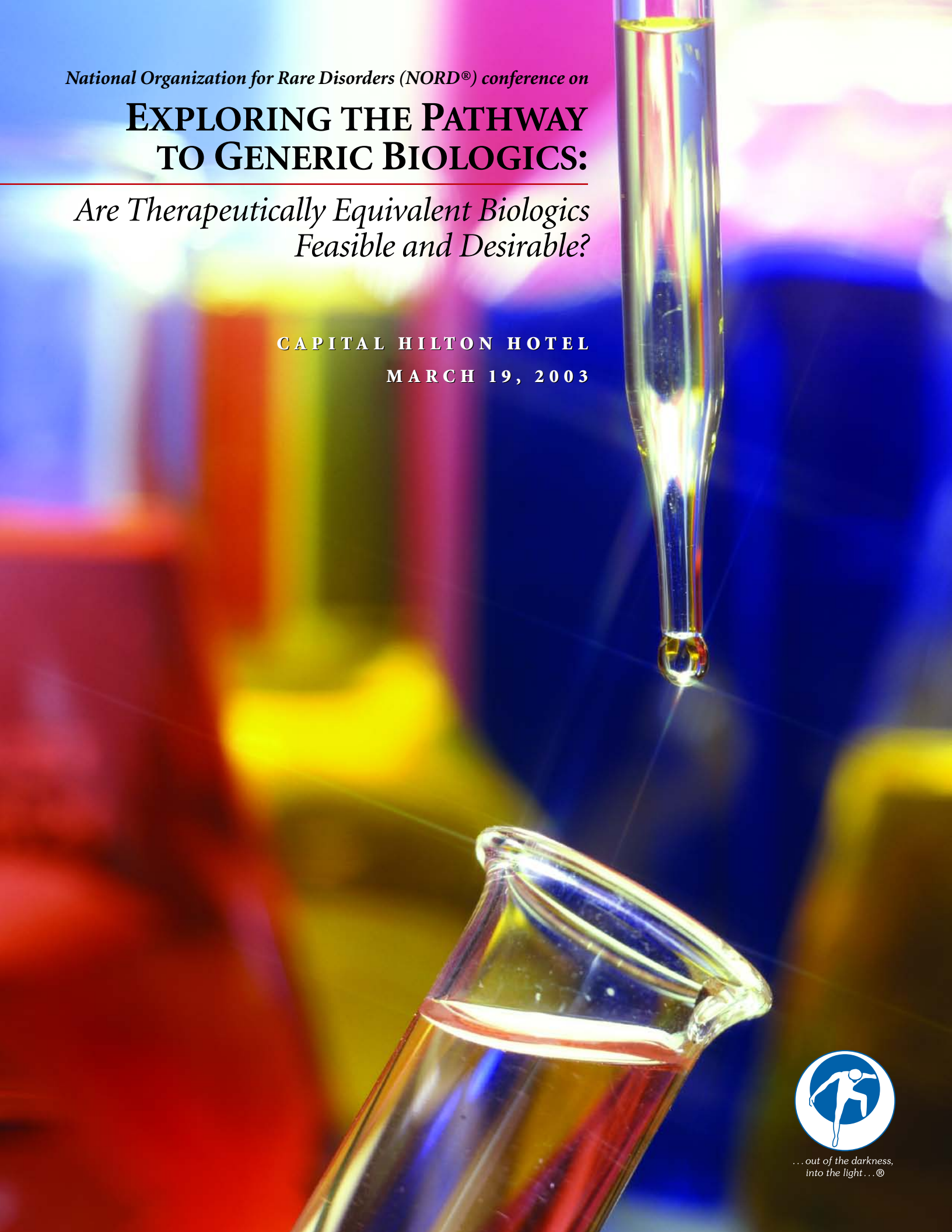

National Organization for Rare Disorders (NORD®) conference on

EXPLORING THE PATHWAY TO GENERIC BIOLOGICS:

Are Therapeutically Equivalent Biologics Feasible and Desirable?

CAPITAL HILTON HOTEL

MARCH 19, 2003

. . . out of the darkness, into the light . . .®

ACKNOWLEDGMENTS

The National Organization for Rare Disorders (NORD®) wishes to thank Agnes Varis for making it possible to convene the conference and produce this white paper.

In addition, NORD would like to acknowledge and thank the speakers at the conference, who contributed their time, insight, and expertise to this effort to define the issues surrounding generic biologics. NORD is also grateful to Carolyn Asbury, Ph.D., and Janet Lowenbach for co-authoring the white paper and to NORD's President, Abbey Meyers, for her helpful editing.

NORD hopes that this initial exploration will catalyze national efforts to address the scientific, legal, and economic issues attending generic biologics.

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National Organization for Rare Disorders (NORD®) conference on

EXPLORING THE PATHWAY TO GENERIC BIOLOGICS:

Are Therapeutically Equivalent Biologics Feasible and Desirable?

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Executive Summary

The emerging issue of therapeutically equivalent ("generic") biologics is an important one for the National Organization for Rare Disorders, Inc. (NORD®), and the rare disease community that NORD® represents. For more than 20 years, NORD® has campaigned on behalf of the more than 25 million Americans with rare "orphan" diseases and on behalf of their families, helping them secure the care they need. Orphan diseases are those affecting fewer than 200,000 people in the U.S. A flagship accomplishment was the *Orphan Drug Act of 1983*, which conferred seven years of exclusive marketing rights for drugs that treat rare disorders. After expiration of the exclusivity or patent period (if the drug is patented), others can market generic versions of the drugs.

Within five years, $10 billion worth of biopharmaceutical products will lose their exclusivity or come off patent.…Biologics constitute a large and growing percentage of products being developed and marketed for orphan and common diseases.

As of May 2003, as many as 240 orphan products were on the market, including many biologics. These products of genomic and proteomic sciences are usually recombinant therapies capable of treating a range of diseases from hemophilia to rare cancers, at costs to patients and insurers that generally greatly exceed those of standard small molecule drugs. Within five years, $10 billion worth of biopharmaceutical products will lose their exclusivity or come off patent. This is a new opportunity that raises the question of whether Americans, including the millions with orphan diseases, should have the chance to purchase safe and less expensive generic versions of biologics. Affecting that question are issues of science, medicine, regulatory law, economics, ethics, and politics. The answers can be reached only through debate by all parties concerned about public health. The debate must not go on behind closed doors, but in the light of day, with all stakeholders having a voice.

NORD® sponsored such a debate in Washington DC on March 19, 2003, at the Capital Hilton Hotel. We invited experts to address the questions and to suggest additional areas of inquiry. We bring you this paper so that you can join us in solving a critical question: are generic biologics scientifically feasible and publicly desirable?

NORD®'s interest in this topic is driven by an overriding concern that patients with rare diseases and those with more common conditions have access to biologic treatments. FDA has reported that 50 percent of all approved biologics on the American market today are intended for use in orphan conditions, and 20 percent of all marketed orphan products are biologics. We know that biologics are the products of choice for many orphan diseases. Today's genomic and proteomic advances are unleashing incredible opportunities for the future. We at NORD® want to make certain that this potential remains available for patients with rare and common diseases, that the incentives that attract companies to biologic development will remain intact, and that after a patent or exclusivity expires, scientifically feasible competition will be allowed and will reduce costs to patients.

Is the development of safe and effective therapeutically equivalent biologics scientifically feasible? Would these products appreciably reduce costs to patients? What is the best regulatory pathway? The answers to these questions are not yet clear. NORD® conferees initiated this critical debate, starting from the premise that safety must remain the first and foremost issue.

Highlights of the Conference's Main Points

Biologic and Drug Differences Affect Testing Needs

- Since biologics are made from living organisms, their interactions with the patient's body can affect safety and efficacy characteristics. This suggests that generic biologics will require more clinical testing than that required for generic drugs. Clinical testing is the most expensive part of product development and would therefore add to development costs, and presumably prices, of generic biologics.

Why Are Generic Biologics an Issue?

- Biologics constitute a large and growing percentage of products being developed and marketed for orphan and common diseases. Additionally, the science of genetics and proteomics (the proteins the genes produce to carry out their work) is expected to lead to development of highly specific biologic (and drug) therapies that target small

"orphan" subsets of patients with common diseases. Scientific advances also are likely to identify patients who will not respond, or who will respond adversely, to specific biologic (and drug) therapies. Therefore, access to highly effective, specific biologic treatments will be critical for patients with orphan and common diseases.

Affecting that question are issues of science, medicine, regulatory law, economics, ethics, and politics. The answers can be reached only through debate by all parties concerned about public health.

- Several factors threaten access to existing biologics. Production problems have limited supply and created the need to ration treatment in several instances. Biologics' costs to consumers and their insurers tend to be significantly higher, on average, than drug costs. Over the past five years, for instance, drug costs to a major health plan have nearly doubled, while biologic costs have nearly tripled and are expected to double again in the next two years. As one panelist commented, a biologic that is not affordable is neither safe nor effective.

Scientific Issues Are Key But Lack Systematic Assessment

- Slight changes in manufacturing processes or product composition can give rise to major changes in safety and efficacy. One of the major complications that biologics can produce is serious or life-threatening immunogenicity (untoward immune system responses to biologics). Scientists need to determine the testing required to demonstrate whether a generic biologic is therapeutically equivalent and comparable to the originator product for each type of biologic. Scientists need to categorize biologics according to several characteristics, such as complexity and size and determine the testing required for each category. Science, rather than "science obstructionism," as one panelist remarked, should rule.
- The U.S. Pharmacopeia, which sets standards and performs necessary testing for each item listed in its official list of medicinal drugs, passed a resolution in 2002 to explore the "feasibility and advisability of developing guidance on principles and approaches to assure equivalence of complex active ingredients [of]…agents of biologic/biotechnological origin, including their regulatory control." USP scheduled a scientific conference this fall on methods that could be used to determine and assure equivalence of therapeutic and other types of biologics (such as vaccines and blood products). NORD® applauds this important action.

Europe's Experience Suggests Generic Biologic Feasibility

- Some European countries have approved several therapeutically equivalent biologics, including EPO, alpha interferon, and human growth hormone. Their prices are well below those of the originator's prices.*
- European manufacturer PLIVA markets generic biologics in seven central and eastern European markets. PLIVA reports that the extent of pre-clinical and clinical "bridging" studies is dependent on the nature of the substance and formulation, complexity of the molecule, and possible distinction from the reference product. PLIVA's therapeutically equivalent recombinant human Erythropoietin (EPO) product has demonstrated profiles of quality, safety, and efficacy equivalent to the innovator products and interchangeable with those products, PLIVA representatives report.

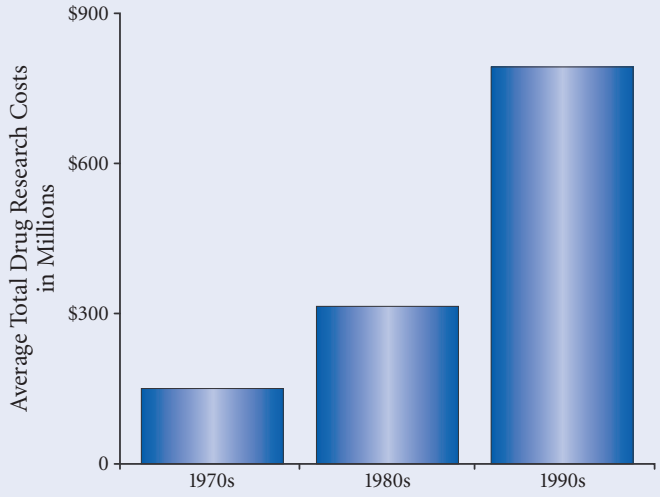
No Explicit Regulatory Path for Generic Biologics in U.S.

- The FDA regulates drugs under the *Food, Drug & Cosmetic Act* (FD&C). The 1984 *Drug Price Competition Act* provides a mechanism under the FD&C Act to regulate generic drugs. Biologics are regulated under the *Public Health Service Act* (PHS), which does not currently have an explicit regulatory pathway for approval of therapeutically equivalent biologics (generic biologics).
- Authority for therapeutic biologics recently shifted from FDA's Center for Biologics Evaluation and Research (CBER) to its Center for Drug Evaluation and Research (CDER). FDA has not yet issued guidelines concerning potential development of therapeutic equivalents for the early biologics that were approved and regulated as "drugs" prior to CBER's creation.
- Current FDA definitions of "sameness" are contradictory. Under the *FD&C Act*, FDA contends that all biologics are "different," requiring a Biologics License Application (BLA) filing for each. FDA's interpretation under the *Orphan Drug Act*, however, is that all "similar" biologics are the "same" as the initially approved orphan biologic unless competitors can prove that their products are "dif-

ferent." How can these two interpretations be reconciled? What are the implications for generic biologics?

- FDA has no explicit policies concerning regulation of generic therapeutics. But FDA's actions on a few prior biologics suggest that there may be administrative processes for securing approval of generic biologics. A 1996 "Comparability Guidance" essentially established that the end product, rather than the process, defined the biologic. A company might use this to demonstrate to FDA's satisfaction that the product is comparable to an earlier version of the product. This would require access to the innovator's data, possibly through 505(b) 2 (for generic drug approval). Some contend this would be tantamount to intellectual property theft.
- "Quasi-legal" approaches to approval, according to one panelist, would create uncertainty, limiting the number of generic manufacturers willing to take the risk.

RISING COSTS



Total Costs of Research in 1990s, in millions

	Out-of-Pocket Expenses	Including Cost of Capital
Preclinical	$121	$336
Clinical	$282	$466
Total	$403	$802

SOURCE: TUFTS UNIVERSITY

Would Generics Substantially Reduce Biologic Prices?

- In the classic economic model for generic drugs, clinical testing requirements, and therefore development costs, are minimal. The brand's price remains the same (or even rises) when the first generic is put on the market. The initial generic price is about one-half that of the originator's. When additional generic versions enter the market, their competition lowers the generics' prices to about one-third that of the brand drug's. The brand's market share eventually falls to about ten percent.
- This model may not predict the market behavior for generic biologics. Development and regulatory requirements profoundly affect total costs and prices, and these have not yet been determined for generic biologics. Likely clinical testing requirements, however, are anticipated to add to costs of generic biologics compared to those of generic drugs. Nonetheless, other factors also may affect—increase or decrease—the costs and prices of generic biologics. Factors are presented on both sides of the equation.
- There may be additional *pre-market* development costs.
  - — Product quality and comparability programs could bring the total investment by generic biologic manufacturers to between $50–$400 million, according to one panelist, based on previous examples of unexpected changes in safety and imunogenicity factors.
  - — Biologics manufacturers tend to "bundle" the substance and its delivery system into the "product." Generic manufacturers would need to demonstrate that both the delivery system and substance are equivalent to the originator's product.
- There may be additional *post-market* costs.
  - — Because biologics are primarily injected or given intravenously, they are generally administered in hospitals or clinics. This adds to costs (for both brands and generic biologics).
  - — Physicians would have to perceive that the generic forms are as safe and effective as the originator biologic.
  - — Intensive post-marketing surveillance will be needed to determine the biologics' effects over time. (Applicable to both brand and generic versions.)
  - — Costly litigation would likely be prevalent, since extensive entry cost barriers would extend the effective product life cycle of most brand biologics.
- Other factors support the expectation that costs and prices of biologics (both brand and generic) will decrease in the future:
  - — Computer modeling and genetic data may reduce the time and cost required to produce products for highly targeted markets.

— This may be the case particularly for drugs and biologics intended to prevent disease in people at risk for a specific genetic disease. Nonetheless, the bar for demonstrating safety will be higher, because the intended population is not currently ill.

— Genomics and proteomics may help to identify patients who are at risk for side effects from specific drugs or biologics. This could enable developers to peremptorily exclude these patients from clinical trials, shortening the time needed to determine safety and efficacy.

— Some biologics are blockbusters, a fact that will attract a number of generic competitors, and this would likely bring down costs.

Other Economic Considerations

- Since the technology is so complex, only a few generic manufacturers are expected to develop generic biologics, according to one panelist. Introduction of only a few generic versions of a biologic may not result in substantial price reductions.
- Competition from generic biologics is likely to lead to increased innovation, through market competition, much as it has for generic drugs, according to one panelist.
- Generic biologics may help to avert implicit federal regulation of prices of costly brand biologics. For instance, with Epogen®, according to one panelist, Medicare has placed limits on doses and per dose payment. The payment system, which reimburses biologics at significantly higher prices than traditional oral medications, contributes to the interest in defining a pathway for generic biologics, according to this panelist.

Costs of biologics are increasing much faster than drug costs overall. Coverage is eroding, and employers are resisting increases in pharmaceutical premiums.

- Generic biologics will help the market set realistic prices for biologics, according to a Health Plan panelist. Since data to date have not supported the expectation that drugs would reduce hospitalizations and their costs, it is an open question whether the same will be the case for biologics. Costs of biologics are increasing much faster than drug costs overall. Coverage is eroding, and employers are resisting increases in pharmaceutical premiums.

Summary of Main Points

Scientists need to address the scientific feasibility of developing safe and effective generic biologics systematically. Access issues, such as manufacturing problems that limit production and product cost contribute to the importance of undertaking this effort. Regulatory policies need to be developed that are consistent with the science. Economists need to study the likely cost implications of generic biologics to consumers, insurers, and public payers. The resultant findings need to inform policy. Informed policy decisions are needed sooner rather than later. Consumers need to promote this process.

I. *Introduction*

Therapeutically Equivalent Biologics: NORD® Frames the Debate

ABBEY S. MEYERS
President, National Organization for Rare Disorders

Access to reasonably priced biologic products is an important issue for NORD®, a non-profit voluntary health agency dedicated to identifying, treating, preventing, and curing the 6,000 rare diseases that jointly affect some 25 million Americans and their families.

NORD® is concerned about all of the issues—scientific, economic, and regulatory—that affect access to therapeutically equivalent biologic treatments, not only for people with rare diseases, but also for all consumers with serious medical conditions. This conference was designed to stimulate public interest and debate about all of the factors that affect the ability of patients to gain access to biologics that they desperately need.

When speaking of the potential for less expensive copies of patented biologics, the accepted term is *therapeutically equivalent*. We, however, use the expressions *generic* and *therapeutically equivalent* interchangeably, because the public is familiar with the term *generic drugs*. Still, it is important to note that *generic* has a different meaning when applied to biologics than it does when applied to drugs. Therapeutic biologics include human proteins, enzymes, and blood or

plasma products; they are large molecule products that are complicated to produce and verifiably reproduce. Most drugs, on the other hand, are small molecule chemical entities that are relatively simple to copy and verify for efficacy and equivalency. In using the term *generic biologics,* we are speaking of a therapeutically equivalent biologic, which must be judged by FDA to be equally safe and therapeutic to the innovator product if the FDA is to grant marketing approval.

Moreover, these new scientific fields are likely to create small subsets of patients with common diseases that respond to highly targeted therapies. Thus, subgroups of patients who have common illnesses will ultimately fall into "rare" disease classifications of those common conditions.

NORD®'s interest in therapeutic equivalents *(generic biologics)* is multidimensional. Molecular biology and molecular genetics hold the promise of developing completely new classes and types of therapies to prevent, treat, or cure diseases. This is the case not only for rare diseases, but also for common disorders. Moreover, these new scientific fields are likely to create small subsets of patients with common diseases that respond to highly targeted therapies. Thus, subgroups of patients who have common illnesses will ultimately fall into "rare" disease classifications of those common conditions. Today, according to FDA's Office of Orphan Products Development, approximately 65 percent of "FDA-designated" orphan products (including those under development as well as those that are already marketed) are biologics, and 20 percent of all currently marketed orphan products are biologics.

These figures demonstrate the growing importance of biologics for treating orphan diseases and increase the urgency for determining how best to improve access to these critically needed therapies. NORD® has several concerns and questions about access to needed biologics, and we anticipate that other stakeholders have additional items to add to the list.

Access is the primary concern.

Most orphan biologics are made by only one manufacturer, even after the originator manufacturer's seven-year orphan product exclusivity or patent expires. This is the case primarily because of the present lack of any explicit pathway for FDA approval of generic biologics.

The result: we have experienced critical shortages of several lifesaving biologic treatments because the sole manufacturer could not make enough product or has had problems with production. For instance, there have been repeated shortages of recombinant Factor VIII for hemophilia and Prolastin for Alpha-1-Antitrypsin deficiency, triggering rationing of these treatments. Other shortages will undoubtedly affect treatment of other diseases in the future. This is unacceptable, particularly because the biotech industry appears so vulnerable to manufacturing limitations.

Affordability of biologics is also a critical factor for access.

Access to *affordable* treatments is an issue repeatedly raised by public payers (Medicare and Medicaid), private health insurers, and patients. Generic drugs are significantly less costly to patients and their insurers than are brand name drugs. We ask if this might be the case for generic biologics, and we ask others to evaluate the likely economic effects if generic biologics were available. As biotechnology treatments proliferate, the health care system could implode from these extraordinary costs. In the heated debate about health care costs, there has been little discussion about the likely effects of developing and marketing generic biologics. If these products could be produced in less expensive ways, how much would costs be reduced?

What are the threats to biotechnology industry survival?

The biotechnology industry is critical to the orphan disease community as a developer of new treatments required for survival. Approximately 5,000 of the 6,000 orphan diseases are genetic disorders, and many will require enzyme, hormone, and protein therapies that are biologics, not traditional drugs. Yet today, most biotech companies are start-up firms that say they must charge very high prices for their products to recover a return on their costly investments. How can the nation nourish the growth of this vital sector while simultaneously improving access to their products?

Lack of competition in biologics may impede treatment advances.

If biotechnology companies are able to continue their monopolies without competition from generic manufacturers, they may have little incentive to continue to innovate and make better and safer biologics.

The 1984 "Waxman-Hatch" Act has provided incentives to brand name drug manufacturers for improving on their older drugs. When a patent is about to expire, many brand name companies do what they do best-they innovate. They devise long-acting versions of their old drugs, they make oral versions of old injectable drugs, or they develop skin patches instead of pills, etc. These improvements benefit consumers and manufacturers alike. But without a pathway for competitive biologics, what is the incentive for biotechnology manufacturers to develop improved versions of their old injectable or intravenous biologic treatments?

Science must address the feasibility of generic biologics.

Can therapeutically equivalent biologics be developed? Does the scientific feasibility vary with the type of biologic entity? Scientists have been silent on this critical issue, and we desperately need them to devote their expertise to addressing these questions.

Some scientists claim that it is not scientifically possible to develop "therapeutically equivalent" biologics. Minor differences between products can result in major differences that affect a product's safety and efficacy.

Other scientists claim that it is possible to make "therapeutically equivalent" biologics. They point to multiple brands of human growth hormone, insulin, estrogen, interferon, etc., and they tell us that FDA is planning to accept abbreviated applications for generic versions of some of these products, which, because of a legal loophole, were initially approved as "drugs," rather than biologics. Moreover, generic biologics are available in eastern Europe and Asia. Apparently, these products are safe, effective, and less expensive than the originator products in those countries. The scientific topics of bioequivalence are the most important in the current dialogue, and we applaud the U.S. Pharmacopoeia (USP), which will be holding a conference this fall to focus on these critical scientific issues.

Can and Will the FDA Develop a Generic Biologics Regulatory Pathway?

The scientific inquiry relates directly to the question of whether FDA will develop an explicit marketing approval pathway for therapeutic equivalents. Experts tell us the FDA has no apparent regulatory process to approve copies of biologics. The agency says that all biologics are "different" and that their efficacy and safety depend upon how they interact with the body.

In the past, the FDA Center for Biologics Evaluation and Research (CBER), which had jurisdiction over therapeutic biologics, said that each manufacturer must perform all clinical research necessary for any new biologic. This approach differs from regulatory approval of generic drugs, which do not have to undergo extensive clinical testing. What degree of clinical testing will be necessary to demonstrate therapeutic equivalency of biologics? Will this degree vary by type of biologic? How will these questions be scientifically addressed? Obviously, it is less expensive to develop a generic copy of a pharmaceutical compound than it would be to copy a biologic, because generic drugs require relatively little clinical verification (only bioequivalence testing). Thus, there is a less expensive "abbreviated" pathway for generic pharmaceuticals.

Because some degree of clinical testing may be necessary to establish therapeutic equivalency of generic biologics, what would this likely add to costs?

In a few instances, there have been multiple brand manufacturers of a particular biologic treatment, such as human growth hormone, the interferons, insulin, or growth factors. However, the FDA has determined that because each biologic is "different," each brand has to be fully tested as if it were an entirely new product. The 1984 "Waxman-Hatch" generic drug law does not apply to biologics, so FDA says it is legally prevented from accepting "abbreviated" applications for generic biologics, as it does for generic drugs. But a related FDA response, described below, seems to contradict this.

NORD® does not have the answers. Rather, we raise the questions to compel the experts to help us think through the answers. In this way, we and others can be informed participants in the debate that needs to occur.

We are confused by FDA's response about therapeutically equivalent orphan biologics:

Under the *Food, Drug and Cosmetic Act,* all biologics are "different" and every sponsor must file a Biologic License Application (BLA) for each biologic. But under the *Orphan Drug Act,* all "similar" biologics are the "same" as the originally approved orphan product, unless competitors can *prove* that their products are "different." These seem to be disparate

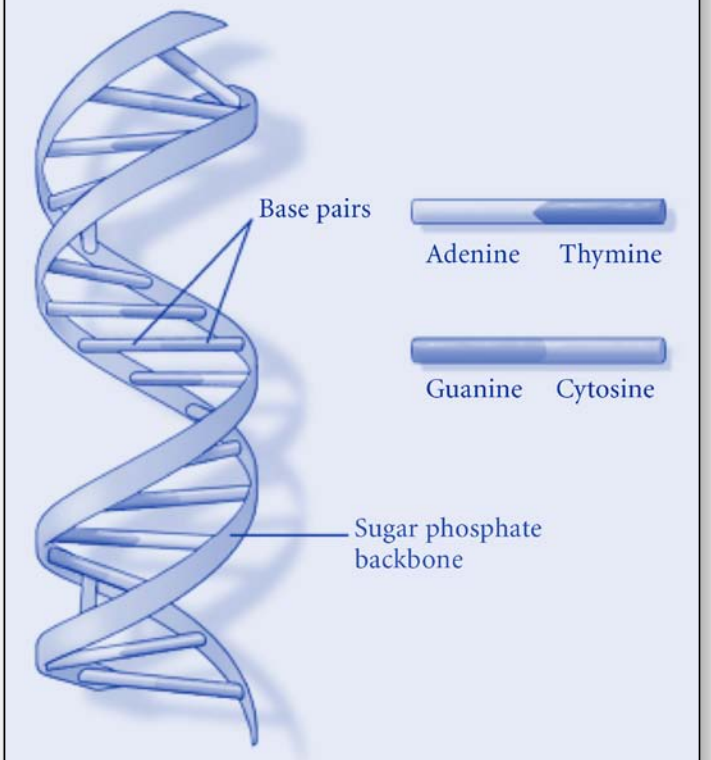
points of view. We need regulatory experts to tell us *whether there is a current regulatory pathway* for generic biologics, and if not, what mechanisms are needed to create such a pathway.

Based on the scientific and regulatory discussions, we also need to hear from economists about the financial implications. In the case of the multiple manufacturers of human growth hormone, or interferons, or growth factors, each manufacturer's price has been similar to the innovator's price. Thus, even though there are multiple versions of one biologic on the market, there are no cost savings to patients or their insurers. Would the cost for generic biologics be significantly lower than the cost for the innovator biologic if abbreviated applications are never acceptable to the FDA? What factors would lower costs to consumers?

NORD® does not have the answers. Rather, we raise the questions to compel the experts to help us think through the answers. In this way, we and others can be informed participants in the debate that needs to occur. In fact, we must face these issues now for the sake of the future: access, safety, availability, efficacy, costs, and free market competition.

LET THE DEBATE BEGIN.

MODEL OF DNA



SOURCE: ADAPTED FROM *NATURE*, APRIL 25, 1953

II.
The Science

Advances Hold Promise for Biologics

ALAN GUTTMACHER, M.D.
Deputy Director of the National Human Genome Research Institute of NIH and Director of the Office of Policy, Planning and Communications.

Background

The evolving fields of genomics (mapping and understanding the human genome) and proteomics (identifying proteins that genes produce to carry out their directions) hold tremendous promise for preventing and treating diseases. Moreover, these scientific advances are likely to bring about the ability to target highly specific biologic and drug therapies to small subsets of people with common diseases. These developments will create new groups of "orphan" diseases that affect fewer than 200,000 people in the U.S. Aided by information technology and the computer, scientists will work in these fields analyzing genetic data with unfathomable speed, learning about the microscopic puzzle pieces that make individuals unique, comprehending why people react differently to the same medication, and harnessing infinitesimally small parts of cells to fight against disease.

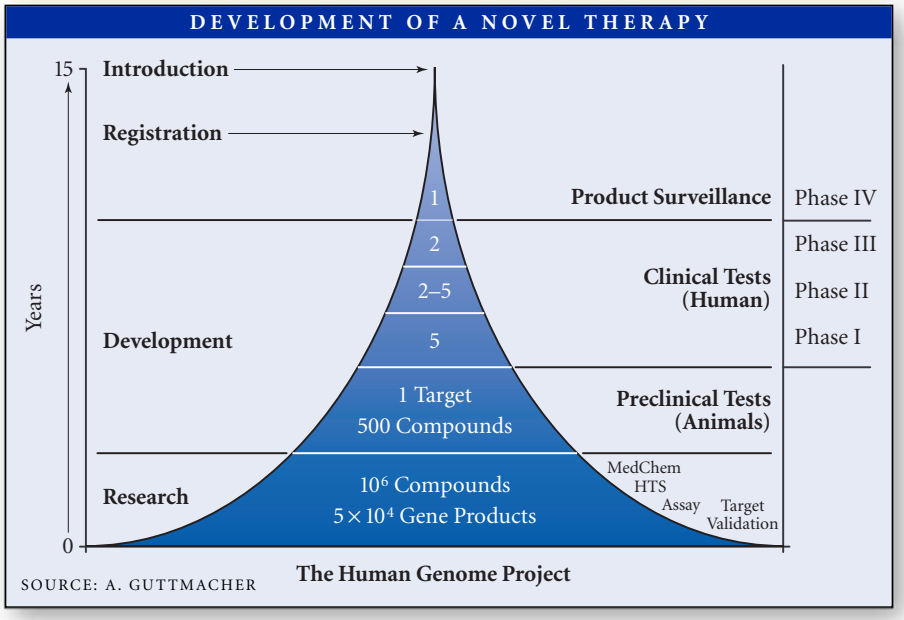
As Alan Guttmacher, M.D., Deputy Director of the National Human Genome Research Institute at NIH, has stressed, the first draft of the human genome project is completed. Scientists have sequenced the human genome; that is, they have determined the order of the 3 billion chemical "base pairs" that comprise the structure of DNA (deoxyribonucleic acid) found in each human cell. These "base pairs are A (Adenine), C (Cytosine), G (Guanine), and T (Thymine). The base pairs are like the rungs in a ladder connecting the two sides of DNA's double helix.

The human genome sequence, or the potential arrangement of the base pairs, is so huge that if it were published in the Washington, DC, phone book, it would take *150,000 pages to print the sequence of a single person.* Among those pages, for each individual there will be tens of thousands of mistakes, most of which are innocuous. Nonetheless, a variation (mistake) in the DNA sequence sometimes can signify the propensity for disease. These variations are the keys to why some people develop certain diseases and why individuals

respond differently to the same medicines. In fact, disease and drug response are often caused by a single variation.

Variation, in short, offers the potential for therapeutics development and disease control. Variation determines individuals'

- Propensity for heritable diseases,
- Different responses to various drugs and biologics used to treat diseases, and
- Potential for individually tailored, gene-based health promotion.



Variation is one reason that genomics and proteomics have the potential to drive drug and biologic innovations. Through the endless possibility of variation and combination, these sciences can help researchers identify genetic contributions to disease and therapeutic response, identify variants that contribute to good health and disease resistance, predict disease susceptibility, detect illness early, and create new approaches to designing drugs and biologics, based on an improved understanding of biology at the molecular and cellular levels. This new knowledge is leading to more precise definitions of specific diseases, identification of individual drug and biologic responses to treatment, and development of ways to target therapies for treatment and prevention.

The source for innovation, however, lies not in finding "bad genes" or mutations for "illness" but rather in discovering mutations that protect us. For example, people whose ancestors survived the plague in northern Europe may have one or two mutations on specific genes that are protective against the plague.

We estimate that there are about 30,000 genes, but many are as yet unidentified; many genes are proving to be suitable targets for drugs and biologics. The source for innovation, however, lies not in finding "bad genes" or mutations for "illness" but rather in discovering mutations that protect us. For example, people whose ancestors survived the plague in northern Europe may have one or two mutations on specific genes that are protective against the plague. These genes also can slow or prevent people infected with HIV from developing AIDS. Researchers are also testing the applicability of these genetic mutations to developing a possible AIDS vaccine. Other researchers are testing a gene that is protective against breast cancer. The fundamental approach is to understand genetic pathways and use them to identify novel targets for new drugs and biologics.

What Do These Advances Mean for Biologics and for Potential Development of Generic Versions of Biologics?

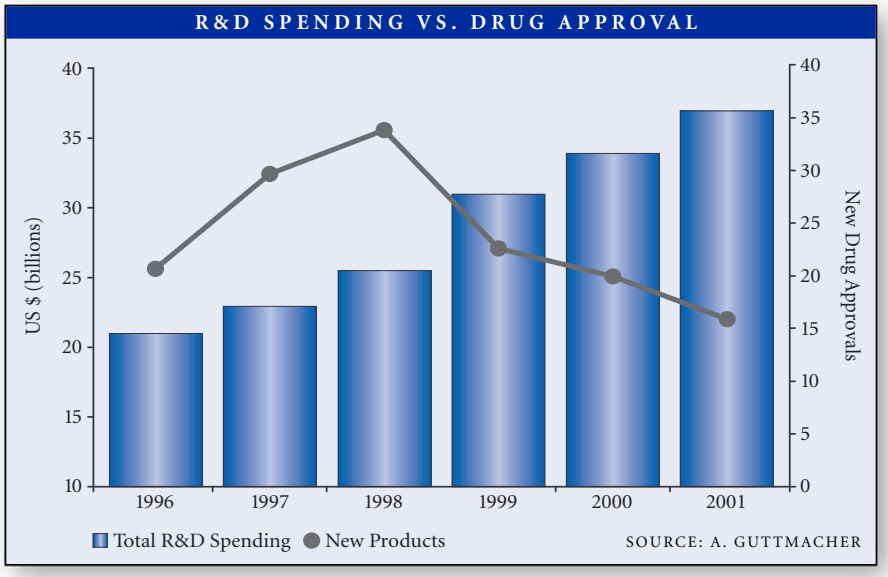
Guttmacher sees several implications for the future development of drugs and biologics that may lower the costs of product development, including the costs of large-scale human clinical trials, which are the largest expense in product development. In the development phase, for instance, advances in bioinformatics point to a day when cellular interactions will be modeled in computers rather than in basic research labs. Second, because genomics and proteomics are likely to lead to development of more targeted drugs and biologics with fewer adverse effects, clinical trials should be able to determine effectiveness and relative safety more quickly.

Third, in the future, scientists should be able to use enzyme tests to predict how a person's body will interact with the experimental agent. The body's metabolic response to an experimental agent is critical to determining that agent's safety and efficacy. Dr. Guttmacher predicts that such enzyme tests will be common in 10 years. These enzyme tests and other genomics advances should help to identify patients who, because they are likely to have adverse effects, will not

be candidates for clinical trials or use of certain approved products. In aggregate, these three factors have the potential to lower significantly the costs of clinical testing.

Computer modeling and genetic data may add to the value by reducing the time and cost required to produce the products. This might be the case especially for drugs and biologics intended to prevent disease in people with a genetic risk for developing a particular disease.

Additionally, genomic advances may produce highly targeted, smaller markets for a specific product, which are valuable to manufacturers because of their long pattern of patient use. Computer modeling and genetic data may add to the value by reducing the time and cost required to produce the products. This might be the case especially for drugs and biologics intended to prevent disease in people with a genetic risk for developing a particular disease. The elongated timeframes of long-term preventive agents might create prime candidates for generic versions of biologics, if these can be shown to be equivalently safe and effective. But safety determinations for biologics used in prevention may be even more difficult than for short-term use biologics, since the bar of proof needs to be much higher: preventive therapies are used in people who do not have the disease. This is an issue that manufacturers of original biologics, as well as generic manufacturers, would need to address.



III. *Regulatory Considerations*

FDA's Consolidation of Certain Products from CBER to CDER Has No Direct Implications for "Generic Biologics"

MURRAY M. LUMPKIN, M.D., M.SC.
Principal Associate Commissioner,
Food and Drug Administration (FDA)

Background

Regulatory authority for biologic medical products differs from that for drugs. Drugs are regulated under several specific sections of the Federal Food, Drug and Cosmetic Act, *which, since the 1984 amendments, has provided for the specific regulation of generic versions of some of these drugs. In the 1984 amendments, Congress deemed that generic copies of drug products, which had no further patent or exclusivity protection, only had to establish that, from a clinical prospective, they were "bioequivalent" to the innovator product. Having only to establish "bioequivalence" and not having to re-establish clinical safety and efficacy with a full clinical development program, substantially reduces generic manufacturers' development costs, and these lowered development costs contribute to the lower prices charged for generic drugs.*

Biologic medical products are generally regulated under the Public Health Service Act. *This Act currently has no explicit provisions for regulating generic equivalents of these products in the same context as exists for certain drugs regulated under the Federal* Food, Drug and Cosmetic Act.

Whenever the possibility of "generic" biologics is discussed, people express concern about the scientific and legal feasibility of developing such products using a development paradigm similar to that used for generic drug products. Much of the science that underlies any determination of "bioequivalence" regarding two biologic products is yet to be developed and agreed upon. Concerns about impact of manufacturing changes, antigenicity, and overall safety, efficacy, and quality of the products remain unanswered. In addition, the legal

framework for such products remains a topic of much debate. There is, nonetheless, in many communities, intense interest in the possibility of "generic" biologics due to the number of biologic products that are used today as primary treatments of a variety of diseases and the escalating costs associated with many of those products.

With the recent consolidation of certain products from CBER to CDER, the question of the impact of this consolidation on potential development of generic biologic medical products has been raised. FDA has made clear from the initial announcement of this consolidation that the change in management oversight of these products does not change their legal status or the scientific concerns that have been raised regarding "bioequivalence" between two biologic medical products. Products previously regulated under the Public Health Service Act *will continue to be regulated under that Act. CDER has the authority to approve BLAs just as CBER has the authority to approve NDAs (of which there are a number of specific examples). In addition, until the science issues are adequately addressed, the legal framework issues remain a less immediate issue for resolution.*

The Present Status of the Consolidation

In early 2003, FDA announced a reorganization of the management oversight of certain biologic products, with responsibility for most therapeutic biologics being transferred from CBER to CDER. This process is ongoing, and Murray M. Lumpkin, M.D., Principal Associate Commissioner of the FDA, provided an update of the consolidation process. According to Lumpkin, this initiative has just now reached Phase 3 and is on schedule for implementation on June 30, 2003. In addition, he stated that the process of this product consolidation is guided by three major goals related primarily to improving the efficiency of product review within the limitations of FDA resources. The guiding principle of the consolidation, Lumpkin indicated, is to effect a fundamental integration of like functions under a single management umbrella, preserving the science base in both centers and the resources to focus on Agency mission-critical issues. The three goals outlined by Lumpkin are to:

- *Improve the consistency of therapeutic product clinical oversight.* FDA wants these products to be overseen using the same management approach as similarly used products by merging the best scientific and procedural practices presently used by CBER and CDER. The management objective is to organize the review processes for all of these products primarily around the disease being treated, emphasizing patient-centered, science-based, clinical decision-making.
- *Improve the efficiency of resource utilization*, avoiding duplication of expertise in both the drug and biologic centers.
- *Provide CBER with the resources and time necessary to concentrate on its remaining responsibilities to regulate biologics*, especially those relating to national security, blood safety and emerging diseases, and cutting-edge medical technology areas, including gene therapy and certain cellular therapies, blood products, and vaccines.

[T]he process of this product consolidation is guided by three major goals related primarily to improving the efficiency of product review within the limitations of FDA resources.

Several specific classes of biologics are being consolidated under the CDER management umbrella. (These include peptides, non-glycosylated proteins, glycosylated proteins, monoclonal antibodies, cytokines, growth factors, interferons [including recombinant versions], and certain proteins intended for therapeutic use that come from animals or microorganisms.) CBER will continue to oversee cellular and tissue-based therapies, gene therapies, blood and blood components, products from human or animal cells, and tissues. FDA officials have not yet decided which center will have oversight of therapeutic vaccines, which also have been characterized as "immunotherapies." According to Lumpkin, the change in management oversight does not change the legal status of a product. If a product is regulated under the Federal *Food, Drug and Cosmetic Act,* CDER will use its New Drug Application (NDA) authorities to oversee the product. If the product is regulated under the *Public Health Service Act,* CDER will use its Biologic License Application (BLA) authorities to oversee the product. All FDA centers have the authority to use whatever regulatory framework is appropriate for a given product. For years, CBER has approved NDAs (drugs) and 510ks (medical devices) when products it oversees are subject to those provisions of the law. So having CDER use other than NDA authorities is not a new regulatory concept for the FDA.

Implications for Generic Biologics Not Directly Related to Consolidation

According to Lumpkin, FDA cannot make a decision on the proper pathway for bioequivalence in isolation from the legal and scientific concerns. "There are scientific and legal issues and concerns that have to be addressed and answered," he noted, adding he thought part of the process would require stakeholders being involved in discussing and providing ideas on how to address the scientific and legal concerns around this topic. "This will push the debate," he said. "The scientific concerns need addressing first; and we need to engage the various communities affected by this issue to help us figure out the right science and public policy to follow at this point." While Lumpkin reiterated that the consolidation of these products and the issue of "generic biologics" are not "linked," he did again ask for communities with an interest in the science, law, and public policy of "generic" biologics to inform FDA about their interest and perspectives so that they can be included in any specific FDA process that will consider the issue in the future.

IV.
Legal and Regulatory Factors

FRANK J. SASINOWSKI, J.D., M.S., M.P.H., *and*
KURT R. KARST, ESQ., *Hyman, Phelps, and McNamara, P.C.*

Under *The Public Health Service (PHS) Act*, the licensure of a Biologics License Application (BLA) is contingent upon two requirements. The first requirement is demonstrating that a product is safe, pure, and potent. The sponsor of a BLA generally meets this requirement by collecting safety and effectiveness data from adequate and well-controlled clinical studies. The second requirement is that the facility in which the product is manufactured, processed, packed, or held meets standards designed to assure that the product *continues to be* safe, pure, and potent. Determining whether this requirement is met is generally based on FDA's inspection of the manufacturing facility. Neither the PHS Act nor the FDC Act provides explicit statutory authority for the approval of second generation or follow-on biologics.

However, according to Frank Sasinowski and his associate Kurt Karst, attorneys at Hyman, Phelps & McNamara, *FDA has recognized that it may exercise administrative discretion in determining whether the sufficient quantity and quality of data necessary for biologic products has been presented.* Sasinowski and Karst observe that CBER's public statements implying that the term "generic biologic" is an oxymoron are the result of the long-held position taken by CBER that a biological product is defined in essence by the process by which it is created. Thus, according to CBER, two biological products created by different manufacturing processes cannot be the same. However, the speakers noted that CBER "has exercised administrative creativity" in approving biologics with either less than the conventional quantity or quality of *clinical trial* information otherwise generally required, or on the basis of products made by processes that were not the same as those on which the pivotal clinical trials had been conducted. These administrative decisions, the speakers suggested, have important implications for the future of follow-on or second generation biologics.

Because active ingredients in biologics are larger and more complex than those in drugs derived through chemical processes, it is scientifically challenging to determine the "sameness" of biologically active products.

The speakers indicated that FDA or Congress may consider past Agency actions as precedents upon which to guide future administrative actions or lawmaking efforts: "Either administrative discretion or legislation has the ability to draw on regulatory precedents and policies to create a system capable of yielding a biologic that is *comparable* to the originator biologic and whose approval likely is based primarily on a single clinical trial." This observation was drawn from an evolutionary assessment of FDA's previous approval decisions concerning biologics.

Because active ingredients in biologics are larger and more complex than those in drugs derived through chemical processes, it is scientifically challenging to determine the "sameness" of biologically active products. Prior to 1996, CBER defined a biologic by its manufacturing process, according to Sasinowski and Karst. This position had been validated in the finding in 1993 that two different manufacturing processes for a specific biologic (Activase®) had

resulted in different potencies. This supported CBER's position that the "process is the product." But not long thereafter, FDA departed from this long-held position by accepting bioequivalence data for the approval of a biologic (Verluma®) when the manufacturer and manufacturing site changed during product development.

Prior to 1996, CBER defined a biologic by its manufacturing process…FDA departed from this long-held position by accepting bioequivalence data for the approval of a biologic…when the manufacturer and manufacturing site changed during product development.

Then in 1996, FDA issued a guidance document titled *"FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products,"* which permits sponsors to *rely on clinical data from a "precursor product" if there is evidence of comparability.* According to Sasinowski and Karst, FDA's introduction of the comparability concept expressed for the first time the view that different processes could, in fact, produce the same biological product. FDA used the Comparability Guidance as a basis to approve Avonex® (beta interferon) produced by Biogen. FDA allowed Biogen to rely upon data from its pivotal clinical study even though the beta interferon product studied in that trial had been made at a different site with a substantially different manufacturing process from the proposed commercial product.

In effect, CBER's regulation of biologics has changed over time, according to Sasinowski and Karst. Historically, CBER defined biologics by the process by which they were created. A sea change occurred with the FDA's *1996 Comparability Guidance,* which permitted reliance on clinical data from a precursor product if there is evidence of comparability. For the first time, FDA recognized that different processes could produce the same biological product. The result: the process is not necessarily the product; the end product is the product.

The implications of this change, which permitted FDA to approve Biogen's beta interferon product based on comparability data, introduced another element of uncertainty. The decision indicated that a company making a biological product by a different or revised, even improved, process might not necessarily have to submit the complete battery of preclinical and clinical testing that had in the past been generally required by CBER. Instead, a company may only have to demonstrate to FDA's satisfaction that its product is comparable to an earlier version of the product. In the Biogen case, that company had been one of the two joint partners working on the clinical trials of the initial product; these data were then used to secure marketing approval of a product made by a different process at a different site. But, what if one company relied upon another company's data? This raises the thorny issue of who may legally access an innovator's data.

The characteristics of a "typical" biological product (most often a proteinaceous active moiety) include a complex, three-dimensional structure essential to the product's function, chains of several hundred or thousand amino acids, and specific glycosylation patterns. These characteristics are difficult to measure with current science, and significantly complicate a determination that two products are the "same." Several factors may influence FDA's judgment on whether active ingredients are the same in one product versus another. The CBER Comparability Guidance does not explicitly state that determining sameness requires access to the preclinical and clinical data of the precursor product. Some have suggested that the FDA could use the 505(b)(2) application process created for drugs (not biologics) by the *1984 "Waxman-Hatch" Act.* Under section 505(b)(2) of the FDC Act, a company, in seeking review and approval of a similar product, can rely upon studies to which it does not have a right of reference and did not conduct. Some have suggested that this pathway might be used for follow-on or second generation biologics, while critics contend that this approach is tantamount to intellectual property theft. (FDA has not answered a long pending citizen petition filed by Pfizer on this point.) This key question of legal access to these data remains an open issue.[1]

In addition to these administrative decisions and precedents, Congress has evidenced some interest in addressing the issue of generic biologics. Section §123(f) of the 1997 FDAMA law directed FDA to "take measures to minimize differences in the review and approval of products required to have

1 Subsequent to this talk, European drug regulatory authorities have announced a favorable decision on a Novartis human growth hormone product. The decision relies in part on information to which Novartis does not have legal access, that is, information in the scientific literature. See EMEA, Committee for Proprietary Medicinal Products Summary of Opinion for OMNITROP, (June 16, 2003).

approved biologics license applications…and products required to have approved new drug applications."

Additional expressions of interest have been contained in bills that have not passed. This includes H.R. 5231 (*Pharmaceutical Reform Act of 2000*) introduced by Representative Alan Mollohan (D-WV), which would have expressed the sense of Congress that section *351(j) of the PHS Act* authorizes the submission of abbreviated applications for approval of biologic products under the FDC Act. Senator Jay Rockefeller (D-WV) introduced a bill into the 107th Congress, which would have directed the Institute of Medicine to consider the feasibility of producing generic biologics and asked the FDA to develop procedures for approving these products within three years. Additionally, each of the sponsors of the *1984 Waxman-Hatch Act* has expressed an interest in exploring follow-on or second generation biologics. Representative Henry Waxman (D-CA) indicated an interest in pursuing the issue, and Senator Orin Hatch (R-UT) urged scientists to address the issue of feasibility.

US Pharmacopeia (USP) Creates Process to Consider the Science of Equivalence for Biologics and Biotechnology Ingredients and Products

ROGER WILLIAMS, M.D.
Executive Vice President and Chief Executive Officer, USP

The USP was formed in 1820 by physicians who wished to standardize the recipes used to prepare medications and give them clear, useful names. With the rise in modern pharmaceutical manufacturing, this role has changed so that the modern pharmacopeia now provides standards for therapeutic ingredients and products.

SOURCE: R. WILLIAMS

These are termed articles (as in articles of commerce) in the *Food, Drug and Cosmetic Act* and in the *United States Pharmacopeia* and the *National Formulary (USP-NF)*. These articles include biologics drawn from nature or by means of recombinant (rDNA) technology, chemically synthesized drugs,

REFERENCE STANDARDS TODAY

SOURCE: R. WILLIAMS

excipients, dietary supplements, and some devices. Standards are expressed in over 4000 ingredient and product monographs in the *USP-NF*. The standards in a monograph include the article's definition, e.g., its chemical name and structure, and description, brief packaging, storage and labeling statements, and its specification. The specification consists of the tests, procedures, and acceptance criteria that help assure the strength, quality, and purity of the article. A monograph is unambiguous so that any individual or body, with the requisite training and equipment, can conduct the tests in the monograph. If a tested article meets the stipulations of the monograph, the identity of the named article is established. A small number of recipes for preparations used in modern pharmacy compounding reflect the intent of the early pharmacopeia.

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At the direction of its Board of Trustees, USP publishes *USP-NF* annually with two supplements. While *USP-NF* are named as official compendia of the United States in the *Food, Drug and Cosmetic Act,* and also are referenced in other US laws, USP is a private, non-profit corporation whose governing bodies (Convention members and Board of Trustees) as well as its standard-setting bodies (Expert Committees of

the Council of Experts) are composed entirely of volunteers drawn from the pharmaceutical community. USP is thus unique among the pharmacopeias of the world in that it is separate from government or supragovernmental bodies. Its mission is:

> *…to promote the public health by establishing and disseminating these officially recognized standards of quality and authoritative information on the use of medicines and other health care technologies by health professionals, patients, and consumers.*
>
> *At its 2000 Quinquennial meeting, Convention delegates adopted the following resolution:*
>
> *Explore the feasibility and advisability of developing guidance on principles and approaches to assure equivalence of complex active ingredients (including botanicals and dietary supplements) recognizing the special issues associated with agents of biologic/biotechnological origin including their regulatory control.*

The issue of determining equivalence or lack thereof has been a core theme of USP since its founding in 1820. Therapeutic products that are equivalent—that have the same therapeutic outcome—should bear the same names. Therapeutic products that are not equivalent should bear different names.

Determining whether things are the same or different is a continuing facet of modern life. Consumers frequently make judgments that one car, or one house, or one cup of coffee is about the same as another. Or they may decide that they are not the same and may be willing to pay more for a certain car, house, or cup of coffee.

In making these judgments, consumers use implicit or explicit criteria to allow a comparison, e.g., a better house has more rooms and is better located. The general approach is similar to making judgments about whether one biologic drug (e.g., the first entry or pioneer drug) is the same as another biologic drug (e.g., the follow-on or generic drug) when the two are obtained from different manufacturers using different manufacturing processes. First, scientists must decide what criteria should be used for making comparisons between the two biologic drugs. These may be positive (blood pressure lowering, rise in blood count, time to survival) or negative (headache, fatigue) therapeutic outcomes based on clinical studies in patients. Or they may rely on non-clinical pharmacology/toxicology studies in animals. Scientists will also rely on physical and chemical measurements of the two biologic drugs—just as a purchaser in a grocery store would measure two apples by weight, color, and consistency.

Modern statistical approaches to equivalence assume that two biologics are not equivalent. Scientists wishing to determine equivalence then conduct clinical, non-clinical, and physical and chemical studies comparing the two biologics.

Whereas a consumer doesn't need to rely so much on statistics to make comparisons (although sometimes it would be helpful!), statistics plays an important role in making judgments of equivalence between two biologics, according to Dr. Williams. Modern statistical approaches to equivalence assume that two biologics are not equivalent. Scientists wishing to determine equivalence then conduct clinical, non-clinical, and physical and chemical studies comparing the two biologics. Depending on the outcome of the experiments, they may determine that the two biologics are in fact equivalent in all important measurements. In this setting, the hypothesis of non-equivalence is rejected and the two biologics are declared equivalent. In making this determination, it is important to understand how much of a difference is important. This difference is formally called an equivalence limit and sometimes informally a "goalpost." Just as a car purchaser has some idea of how fast a car must be to be considered faster than another, the scientist making an equivalence determination must have some idea of what an important difference is, to make an equivalence judgment. The clinical, non-clinical, physical and chemical studies needed to determine equivalence are called characterization studies.

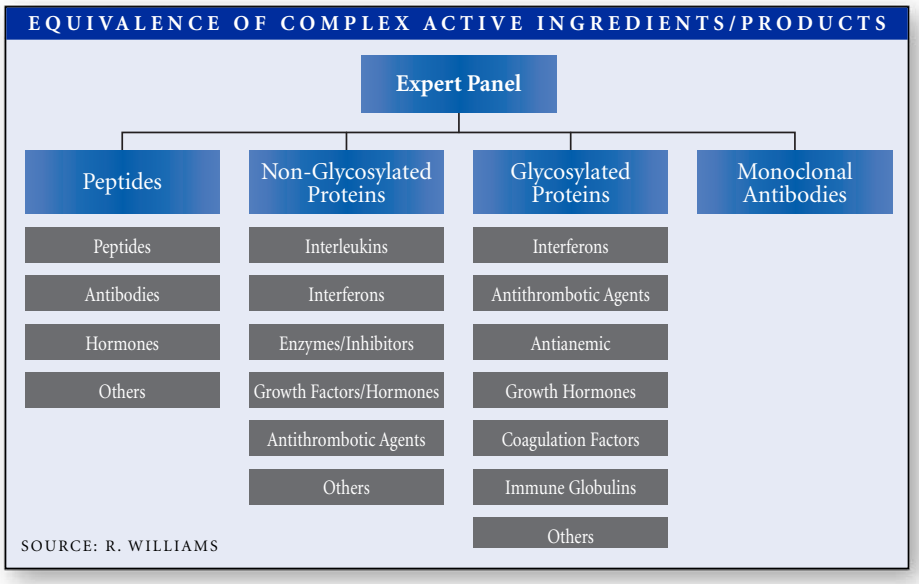
In assessing equivalence between two biologics drawn from different sources, a key question is how much additional characterization data are needed beyond the tests in a *USP-NF* monograph. USP is working to make its monographs more complete and flexible, to account for different routes of synthesis and different impurity profiles. Nonetheless,

the additional studies needed to confirm equivalence for two biologics drawn from different sources may require comparative clinical and non-clinical studies. These studies are beyond the scope of a pharmacopeial monograph. To understand the boundaries between a *USP-NF* monograph and the additional characterization studies needed to document equivalence, USP formed an Expert Panel in December 2002 composed of leading authorities on ingredient and product testing of biologicals. USP will convene a conference entitled "Biological and Biotechnological Drug Substances and Products" November 18–21, 2003, at the Crystal Gateway Marriott, that will include a discussion of the deliberations of the Expert Panel. Additionally, USP will convene a Biologics and Biotechnology Stakeholder Forum December 12, 2003, at the Rockville DoubleTree Hotel.

Via the standards-setting activities of the Council of Experts, USP will continue to address compendial approaches for natural source and rDNA biologics that include:

- Peptides, Proteins, Antibodies
- Gene Therapy, Cell Therapy, and Tissue Engineering;
- Vaccines, Virology, and Immunology;
- Blood and Blood Products

USP has completed a Guideline that provides information to sponsors of ingredient and product monographs for these articles. USP welcomes Requests for Revisions to USP-NF for biological ingredients and products, which are achieved via an open approach that respects trade secret information in conformance to US law.



V. *Marketplace*

PLIVA, a Croation Company, Shows the Way to Generic Biologic Manufacturing

ZDRAVKA KNEZEVIC, M.S.
Director of Development, PLIVA, d.d.

NEDILIJKO PAVLOVIC, M.S.
Deputy Director of Biotechnology, PLIVA, d.d.

Cost to Patients is Compelling Rationale

Background

PLIVA is an experienced, global, specialty pharmaceutical company founded in Croatia in 1921. The company is one of only a few whose R&D investments contemplate developing both proprietary and generic drugs and biologics. *PLIVA has successfully developed and marketed innovator products, such as Azithromycin, generic biologics, such as recombinant human Erythropoietin (EPO)—which is in advanced development—and many generic drugs.*

Complex But Feasible

According to PLIVA representatives Zdravka Knezevic and Nedilijko Pavlovic, the company, which is present in 7 out of 11 key pharmaceutical markets, has a global R&D organization with proven competencies (e.g. the discovery of Azithromycin). PLIVA is applying an active regulatory approach in Europe in the area of biologics, making PLIVA's experience an important model for U.S. policymakers. Manufacturing generic biologics is complex and requires a dedication to science, quality-based manufacturing, and quality assessment, as well as a supportive national structure, Knezevic and Pavlovic said. Knezevic added that innovation and research are as necessary for generic biologics as they are for innovative products, because in addition to quality, safety, and efficacy, other manufacturers have to address and implement strategies for numerous innovator patents and applications.

EQUIVALENT BIOLOGICS: CURRENT CONSIDERATIONS

- **The lack of an explicit legal/regulatory pathway is a significant barrier for entrance of equivalent biologicals**
- **FDA to establish procedure; EMEA/CMPM is starting to recognize this field in Note for guidance on biotech-derived proteins**
- **There are strong socioeconomic reasons for the introduction of equivalent biologics**
- **The technology is available**

SOURCE: PLIVA D.D. RESEARCH & DEVELOPMENT

Both innovator and generic biologics are complex, according to Knezevic and Pavlovic. Biologics are therapeutic proteins derived from living cells through recombinant DNA technology. Both the development and manufacturing and the quality systems are complex also. *An equivalent biologic is a biotechnology-derived product that has the "equivalent quality, safety and efficacy, and is interchangeable with a previously approved product,"* according to Knezevic. "While this is a relatively straightforward task when dealing with generics for small molecule (chemical) products, there are additional tests and questions and an additional line of criteria" that must be met, Knezevic said. These include abridged preclinical and clinical testing and demonstration of bioequivalence and bioavailability.

The company's experience demonstrates that equivalent biologics are technologically possible, Knezevic and Pavlovic concluded.

The PLIVA representatives described methods used to control potential contamination of biologics, to validate virus clearance, to characterize purity, identity, and potency. They also described the stepwise approach used to compare the generic to the originator biologic in terms of molecular structure, biologic activity, pharmokinetics, and safety and efficacy in humans. The company's experience demonstrates that equivalent biologics are technologically possible, Knezevic and Pavlovic concluded.

Scientific Considerations

As Pavlovic explained, the scientific goal is to develop and utilize technologies that will produce therapeutically equivalent biologics. These biologics will need to have profiles of quality, safety, and efficacy that are equivalent to innovators' products and that can be used interchangeably for those innovators' products that have been previously approved. Comparability needs to be proved in terms of molecular structure and of biological activity in living systems as well as in the laboratory. Equivalent biologics are technologically possible, Knezevic stated, if the biologic substance and product are known and well characterized, and if abbreviated and carefully designed pre-clinical and clinical testing demonstrates specific safety and efficacy.

Knezevic indicated that the European Medicine Evaluation Agency (EMEA), the European Union's drug regulatory body, issued a note for guidance on comparability of medical products that contain biotechnology-derived proteins as the biologic's substance. This document, she indicated, recognizes the existence of multi-source biologic products. The EMEA guidance calls for an extensive comparability "exercise." The extent of the pre-clinical or clinical "bridging" studies is dependent upon the nature of the substance and formulation, the complexity of the molecule, and the possible differences with the reference product. Although the guidance is general, she said, manufacturers have the ability to receive feedback from the agency concerning the adequacy of their generic development programs. (In August 2003, the EMEA approved a generic version of human growth hormone.)

Pavlovic described the process PLIVA used to develop its comparable version of EPO. Erythropoietin is a glycoprotein, a medium-sized biologic. It is glycosylated, having four glyco (carbohydrate) chains and sialic acid at the end of these chains, making it a complex molecule. It is actually a family of molecules in one product, consisting of isoforms. (These are proteins that have identical structures of core molecule coded by a single human gene incorporated in the genome of the host cell, in contrast to glycosylation, which is controlled by the host genome.) PLIVA scientists demonstrate that the isoforms are identical by using an isoelectric technique and a newly established method called capillary electrophoresis. PLIVA uses a cell culture technology based on recombinant technology, which can guarantee that the core molecule, the glycosylation pattern, and the proper folding of the protein can be expressed for this molecule.

PLIVA then uses working cell banks for the molecule's development and thereafter for its production. The three production cycles include cell cultivation, product recovery, and product purification. According to Pavlovic, product

purification controls the product's quality. It consists of five steps, including removal of any potential viral contaminants.

Viral contamination is a safety risk factor in developing biologics, and PLIVA addresses this contamination concern throughout the process, according to Pavlovic. To do so, the company uses an extensive master cell bank characterization to prove microbiological purity or sterility and identity. As additional proof of viral clearance, PLIVA also performs tests on end-of-production cell samples, the bulk product material, and individual assays to test for retroviruses. The bulk product is fully characterized to prove purity, identity and potency.

PLIVA compares its generic product to the innovator's biologic on several factors to demonstrate comparability. These factors include comparable molecular structure, biological activity in living systems, and, in the laboratory, pre-clinical safety and pharmacokinetics (absorption and metabolic processes), and safety and efficacy in human patients.

PLIVA compares its generic product to the innovator's biologic on several factors to demonstrate comparability. These factors include comparable molecular structure, biological activity in living systems, and, in the laboratory, pre-clinical safety and pharmacokinetics (absorption and metabolic processes), and safety and efficacy in human patients. PLIVA has a list, according to Pavlovic, of classical physical methods and of highly scientific methods to demonstrate that the primary, secondary, and tertiary structure is comparable and equivalent.

For demonstrating pre-clinical comparability of their EPO product, according to Knezevic, PLIVA undertook several studies using animal models, and correlated the results with human data. All studies are performed in comparison to the reference product. For the last step, demonstrating that PLIVA's generic is comparable to the innovator's biologic in terms of safety and efficacy in humans, PLIVA undertook "bridging" clinical studies. This includes using surrogate markers of specific biologic activity as endpoints for demonstrating efficacy, and showing that patients did not develop immunogenic responses to the product. PLIVA is now preparing for post-marketing safety surveillance, although it is not clear whether there is agreement with the EMEA on how to track immunogenicity of products.

Making affordable drugs, according to Knezevic, is the main driver for producing generic versions of biologic products. For example, Erythropoietin can cost individual patients up to $6,000 a year and alpha interferon can cost each patient $20,000 a year in the United States. Further, other biologics like factor VIII for hemophilia, PEG-ADA for Severe Combined immune deficiency, and Cerezyme for Gaucher's disease can cost each patient more than $100,000 per year (prices for use in children may be lower). In Croatia, these costs are beyond individual means, so biotech products are given sporadically and sometimes only in urgent cases. The result is that only one of 25 patients is appropriately treated. In addition, patents have expired or will expire soon for many key indications and therapeutic areas—"all are life-threatening."

Manufacturers of brand biologics all have secured additional patents (such as those covering manufacturing processes and formulations), that effectively extend the period of market protection for the biologic. The most creative and technologically advanced generic companies will find ways to address these additional barriers to market entry, without infringing on these additional components of patent protection.

VI.
Economic Considerations

Economic Factors: Current Marketing Dynamics for Generics

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Background

Scientists and regulators must determine what processes will be necessary for demonstrating equivalent safety and efficacy before they can resolve development and testing issues that will directly influence the total cost and price of generic biologics. Nonetheless, according to MIT economics professor Ernst Berndt, Ph.D., the likely "downstream" economic implications of generic biologics entering the market can be explored.

Can Lessons from Brand and Generic Drugs Provide Useful Insights for the Possible Success of Biogeneric Entrants?

Biologics and small molecule drugs behave very differently from one another in the economic market. To predict the margins and pricing behavior if and when generic biologics enter the market, Berndt suggests, it may be useful to consult standards other than the classic economic model. These factors will come into play in 2005 when a large number of biologics go off patent.

The Classic Model

In the classic economic model, generic versions of pharmaceuticals enter the market when a typical blockbuster drug's patent expires. This process produces changes in both the brand and generic markets over time. A generic manufacturer will file an abbreviated new drug application (ANDA) with FDA. Generic manufacturers follow the brand manufacturer's chemical "recipe" for the drug, so little clinical testing is required. This significantly reduces the generic manufacturer's cost. If FDA determines that the generic is comparable to the brand drug, the agency gives the generic an "A–B" rating. With this rating, the drug can be covered and reimbursed by insurers or public payers (Medicare and Medicaid). Initially, the brand drug's sale price will be maintained or rise, and the market share will fall, often to as little as fifty percent. The generic's price to the retailer will be about one-half the price of the brand drug. But when additional generic versions enter the market, this competition produces lower generic prices, which often comes to less than one-third of the brand drug's price.

For instance, according to Berndt, when Zantac (the world's highest selling drug) went off patent in 1997, prices followed this classic path. Zantac's price remained stable while its market share immediately dropped to 50 percent, as two generic products entered at 35 percent below Zantac's price. Two years later, Zantac's price had risen slightly while its market share had dropped to 10 percent, amid competition from 15 generic versions.

Generic Biologics May Differ from This Classic Model

Berndt predicted that these common economic models are likely to work differently for the entry of "generic" versions of biologics, due to four factors.

First, because biologics primarily are produced in intravenous or injectable forms, they are generally administered to patients by physicians in a hospital, clinic, or physician's office. Doctors and their patients would have to *perceive* that generic biologics are as safe and effective as the originator brand. Second, administration of biologics in healthcare settings adds to costs, so it is unclear how much cost-saving a generic version would provide. Third, because biologics interact with the patient's body, intensive post-marketing surveillance of the biologic's use and effects is needed. This also adds to costs. Finally, demonstrating generic comparability of biologics could be extremely complex since brand manufacturers are increasingly bundling the biologic and its delivery system as the "product." Berndt illustrated those four factors that may affect the economics of generic biologics, using examples from somewhat atypical generic drug situations that may nonetheless be quite applicable to generic biologics.

1. **Will doctors and patients perceive generic biologics as equivalent to the original product?** As an example of this potential situation for biologics, Berndt cited the anticoagulant Coumadin®. This blood thinner has a narrow therapeutic index, meaning that the optimal and lethal doses are not far apart; product administration requires careful physician titration and monitoring. While

TEN BIOLOGICS FACING POTENTIAL PATENT EXPIRATION

Brand	Generic	Indications	2001 Sales*	Dosing/Delivery
Epogen, Procrit	Epoetin Alfa	Anemia	$5,772	2×/week, INJ
Novolin	Human Insulin	Diabetes	$1,829	Need, INJ
Neupogen	Filgrastin	Neutropenia	$1,533	Daily, INJ
Humulin	Human Insulin	Diabetes	$1,061	Need, INJ
Avonex	Interferon beta-1a	MS	$ 972	Weekly, INJ
Intron-A	Interferon alpha-2b	Leukemia, others	$ 700	3×/week, INJ
Cerezyme, Ceredase	Alglucerase	Gaucher's Disease	$ 570	Bi-weekly, IV
Humatrope	Somatropin	Growth Failure	$ 311	Daily, INJ
Activase	Alteplase	Heart Attack, Stroke	$ 276	≤3 hours in ER/hosp., IV
Nutropin	Somatropin	Growth Failure	$ 250	Daily, INJ

*GLOBAL SALES, IN $M

SOURCE: *CHEMICAL & ENGINEERING NEWS*, COVER STORY, 9/23/02. PP. 61–65.

FDA gave the two generic versions of Coumadin® an A–B rating, the brand drug maintained close to 90 percent of the total market share. *Presumably, shaky confidence by physicians and their patients in the generic versions, given this thin line between the optimal and the lethal dosage, prompted doctors and patients to stay with Coumadin®. Similarly, physician confidence in generic versions of biologics may be a major obstacle to their use.*

2. **As is the case for some generic drugs, will the need to administer generic biologics in health care settings reduce their potential savings?** According to Berndt, it is unclear whether health professionals will change their reliance on the brand product when it comes to complex biologics. One question for the future of biologics is whether they can be designed to be more "user-friendly," more easily administered. For instance, Gleevec® is a *solid form* biologic that inhibits a specific enzyme in chronic myeloid leukemia, a relatively rare form of leukemia. It remains to be seen whether the economic benefits will appear largely in these easier to administer forms and if these forms will be more common in the future.

3. **What will be the impact of the non-trivial costs of intensive, post-market surveillance that will be needed for generic biologics?** The generic drug illustration of this issue cited by Berndt concerned the generic form of the antipsychotic drug Clozaril®. Because the drug can have a rare, but potentially fatal side effect of decreasing white blood cell count, the FDA required pharmacists to repeatedly obtain confirmation of recent favorable lab tests of patients prior to dispensing the drug to them. This required the generic as well as the brand manufacturers to bear the cost of building and maintaining information networks to link laboratory test results with the prescribing physician and dispensing pharmacist. In view of this requirement, only one generic product initially entered the market (approved by FDA in the beginning of 1998, with marketing beginning in 1999), and Clozaril® maintained 90 percent of market share. By 2000, two additional generics were available, yet Clozaril® lost only an additional 20 percent of market share. *Similar post-marketing surveillance of generic biologics is likely to be required if the biologic has potentially serious side effects, requiring manufacturers to include these costs of maintaining surveillance databases in their decision calculations.*

4. **The final issue, the practice of "bundling" both the substance and the delivery system as the brand biologic, would require the generic manufacturer to demonstrate that both the substance and its delivery system are comparable to the originator product. An illustration is the drug Cardizem®, a treatment for hypertension and angina.** The product was reissued in different delivery systems with different dosages and time-release systems. When the patent expired in 1995, two generic versions sought to enter the market, but their delivery systems differed from Cardizem's®. FDA, therefore, was unable to establish that the generic versions were therapeutically equivalent to Cardizem® and gave the generics a "BC" rather than "AB" rating. Because most state Medicaid programs that require mandatory generic substitution do not cover generics with a BC rating, many Medicaid and other patients have continued to use Cardizem®, which has maintained a 70 percent market share. *Biologics tend*

to have more complicated delivery systems than drugs, so this bundling of product and delivery mechanism could be a major issue for generic biologics. The additional question arises: will successively better delivery systems become barriers to generic entry, making first generation generic biologics obsolete?

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According to Berndt, these are all important issues, particularly when the estimated development cost to *manufacturers of generic biologics* is likely to be substantially greater than the estimated $2 to $5 million cost to manufacturers of *generic drugs*. Generic biologics manufacturers would need to calculate the additional costs that will be generated by analytical characterization of the biologic and to gain FDA approval by demonstrating therapeutic equivalence. The clinical testing that is likely to be required to demonstrate equivalence will be more extensive, and expensive, than for generic drugs.

In addition, generic biologics manufacturers would need to include the costs of training health care professionals to administer the product (in cases where the generic biologic is not an oral solid), persuading physicians that the products are comparable, setting up distribution and marketing systems to hospitals and other health care delivery sites in place of the customary retail pharmacy channel, and supporting post-launch surveillance.

Berndt also said he expects that if availability of generic biologics were facilitated in the U.S., branded companies would heavily litigate against generic biologic companies that attempt to enter the U.S. market. This is particularly the case, Berndt surmises, because the extensive entry cost barriers will extend the effective product life cycle of branded non-oral solid biologics beyond that of small molecule pharmaceuticals. Still, Berndt maintains, because many of these biologics are truly blockbusters, they will attract a number of generic competitors and open up niche markets.

VII.
Panelists Revisit Economics

Economic Factors were Discussed Further by an Expert Panel

STEPHEN SCHONDELMEYER, PHARM.D., PH.D.
Professor of Pharmaceutical Economics and Head of Department of Pharmaceutical Care and Health Systems, University of Minnesota

MARVIN SAMSON
President and CEO, Sicor, a vertically integrated pharmaceutical company that manufactures generic biologics

JAMES GREEN, PH.D., D.A.B.T.
Vice President of Clinical and Preclinical Development Sciences, Biogen

ANTHONY BARRUETA, J.D.
Senior Counsel, Government Relations, Kaiser Foundation Health Plan

Stephen Schondelmeyer, Pharm.D, Ph.D., professor of Pharmaceutical Economics at the University of Minnesota, said it is important to focus on advocating and looking for new pathways for generic biologics. For instance, he noted that while science issues are paramount, manufacturers should avoid being mired in "science obstruction" issues. Schondelmeyer cited Coumadin®, which, as Berndt had pointed out, has a narrow margin between therapeutic and lethal doses. But, according to Schondelmeyer, while FDA recognizes generic versions of this drug as equivalent, a number of states have laws that treat such "narrow therapeutic index" drugs differently, and many physicians are concerned about using the drug. Schondelmeyer said he considers these to be problems of *science obstruction* and urged that decisions instead be based on evidence-based medicine, for generic biologics as well as generic drugs.

A second problem is uncertainty, according to Schondelmeyer. He said even if some say there may be "quasi-legal" ways to approve equivalent biologics—(please see the section on Legal and Regulatory Factors)—uncertainty about likely FDA approval will limit the number of firms that are willing to risk developing generic biologics. He urged clarity of policy to minimize uncertainty and to enable decisions to be made based on true economic factors. Additionally, since

prices are significantly lowered only when there are multiple generic versions of a product, he stressed the importance of establishing procedures that will facilitate multiple generic versions of biologics.

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The payment system is a third problem, Schondelmeyer said. Medicare and Medicaid tend to reimburse biologics in a much higher proportion than they do traditional oral medications. He said that the federal government became so frustrated with the access and price of Epogen®, a biologic to treat anemia in patients undergoing kidney dialysis, that it placed limits on doses and payment per dose. This was, he said, an example of government regulating price. A product that is not affordable, he added, does not improve a patient's health.

The Importance of Market Competition

Written comments provided by Marvin Samson, B.S., president and CEO of Sicor, emphasized the positive effect on branded companies that results when prices are set by competition and other market forces, rather than by government controls. Sicor is a vertically integrated, multinational specialty pharmaceutical company that develops, manufactures, and markets active pharmaceutical ingredients, generic injectable finished dosage forms, and generic biopharmaceuticals. Samson explained that Sicor decided to enter the generic biologics market because the firm has the ability to produce difficult-to-manufacture products and to provide them in user-friendly packages. Biogenerics is seen as Sicor's next frontier, and its subsidiary in Lithuania has been selling the biologics human growth hormone and interferon alpha 2B in the Baltic countries and other developing nations for 12 years.

Samson stressed that while the pharmaceutical industry warned at the time of the 1984 *Drug Price Competition Act* that innovation might be compromised if generic drugs were to achieve significant market share, some evidence suggests that major pharmaceutical companies are increasingly reliant on newer generation drugs. While in 1997 the average contribution of sales from new drugs launched in the previous five years was 14 percent of total sales for major companies, by 2000 the average contribution of sales from new drugs had risen to 21 percent. This paralleled the growth in generic drug entries. Thus, he concluded, generic drugs indirectly motivated pharmaceutical companies to innovate. Samson saw no reason for the dynamics to be any different with research-intensive biopharmaceutical companies. A strong biogenerics industry will provide value to all constituencies, including the general population, which gains through the cost advantages obtained by competition, Samson added.

Safety Issues Are Profound Challenge

According to James Green, Ph.D., D.A.B.T., vice president of Pre-clinical and Clinical Development Sciences at Biogen, safety issues have profound implications for potential manufacturers of generic biologics. Determining that a follow-on biologic is safe and ready for therapeutic use and widespread application presents major scientific challenges that translate into major economic challenges as well.

Biologics are not pure substances, he emphasized. They are heterogeneous mixtures. The manufacturing process used to make the biologic contributes to the safety profile. Product life cycles differ between biologics and small molecule drugs, as Dr. Berndt pointed out. A biologic begins its life at the pre-IND (early discovery) stage, often as one form, and works through a number of process iterations until the final product is commercialized. During this life cycle, the manufacturing process usually evolves dramatically; multiple changes occur during this evolutionary process. These include changes in formulation, fermentation conditions, product, purification, and sometimes, expression systems. Different regulatory requirements are expected.

Development, Green said, will cost more than for small molecule generic programs. The absolute dollar cost has yet to be realized. He questioned what the cost savings would be in such a capital- and manufacturing-intensive business. Extensive facility requirements, testing to assure the maintenance of important and product-specific attributes of product quality, and extensive product comparability programs

could bring the total investment to somewhere between $50 million and $400 million. He cautioned that experienced manufacturers have had extensive product comparability programs in place and despite that have observed unexpected changes in safety and immunogenicity. Green predicted that a generic biologic manufacturer, starting from a new process, would have only a low to moderate probability of achieving technical success in matching the brand product's specifications for key elements of the product. The more differences observed, the more work would need to be done in costly clinical assessments, he said.

Perspective from a Major Health Plan

Anthony Barrueta, J.D., Kaiser Foundation Health Plan senior counsel, spoke on behalf of the Kaiser Permanente. From the standpoint of a health plan with a closely cooperating medical group, he said, the organization's 11,000 physicians have as their primary concern the safety and efficacy of generic drugs. Kaiser Permanente physicians prescribe and Kaiser Pharmacies dispense generic drugs more widely than any other plan. A new and growing concern of Kaiser Permanente's pharmacy managers is the cost effect of the lack of generic biologics, he said. Over the past five years, the costs of prescription drugs generally have nearly doubled, according to Barrueta. During that same time, the costs of biologics in the plan have more than tripled. Kaiser expects its biologics costs to double again in the next two years.

Barrueta said that while biologic costs are still a relatively small proportion of Kaiser's overall drug budget, the costs are growing rapidly and becoming an increasing concern. Kaiser anticipated that paying for prescription drugs and biologicals would reduce the need for hospitalizations and repeat physician visits, but data supporting this supposition are quite poor for most drugs, he added. Drug coverage is eroding, certainly in public payment programs, and employers are resisting increases in drug premiums, he said. Kaiser is increasingly facing a market in which employer purchasers are asking for drug plan products that are less comprehensive.

In this environment, Barrueta said, plans and providers share several principles. First, for generic biologics, the science really needs to drive the decisions. Second, the economics for drug markets needs to be nurtured. Markets should work to achieve the appropriate price-quality value point for society. If we do not get generic biologics relatively soon, he speculated, there will be no market option because drug benefits cannot sustain the current increases in drug costs, and biologic costs are increasing much faster than drug costs overall. He concluded that it is in everybody's interests that there be generic biologics, because they will help the market set realistic prices.

In addition to strong intellectual property protection, there also has to be a timely end to intellectual property rights and market exclusivity. Without both of these elements, Barrueta said, manufacturers do not have a maximum incentive to invest in meaningful innovation.

The third principle is that clear intellectual property rules are critical to protecting and promoting innovation. In addition to strong intellectual property protection, there also has to be a timely end to intellectual property rights and market exclusivity. Without both of these elements, he said, manufacturers do not have a maximum incentive to invest in meaningful innovation

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