



Federal Strategies for Promoting Affordable Biologics: Follow-On Biologic Competition

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Conference Report

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The Health Industry Forum is based at Brandeis University, chaired by Professor Stuart Altman, and directed by Robert Mechanic. The Forum brings together public policy experts and senior executives from leading healthcare organizations to address challenging health policy issues. The Forum conducts independent, objective policy analysis and provides neutral venues where stakeholders work together to develop practical, actionable strategies to improve the quality and value of the US healthcare system.

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Key Themes

Context

Biologic therapies save lives and advance the standard of care for many patients, but their increasing use and high prices have created concerns for Medicare, private payers, and consumers. A key question is whether strategies can be developed that slow the growth of spending for biologics while still providing manufacturers with sufficient incentive to innovate and bring new products to market.

On June 11, 2009, the Health Industry Forum brought together current and former federal officials, representatives from the biotechnology industry, academics, and other policy analysts to discuss strategies for enhancing competition in the biologics market.

Key Themes

- **Introduction of generic competition in the U.S. has helped reduce the growth in prescription drug costs.**

The 1984 Hatch-Waxman Act created an abbreviated U.S. Food and Drug Administration (FDA) approval pathway for generic drugs, allowing manufacturers to introduce new bioequivalent products once the patent period for branded drugs expires, without a requirement for costly new clinical trials. Since Hatch-Waxman, many generic drugs have entered the market at prices well below competing branded drugs, significantly reducing spending growth in certain product categories. Currently, there is no FDA abbreviated approval pathway for biosimilar products. Therefore, innovator biologics frequently can monopolize the market long after their patents have expired.

- **As science has evolved, experts believe that the FDA can establish a safe and effective abbreviated approval pathway for generic equivalents of biologics, known as biosimilars or follow-on biologics.**

Initially, there was concern that the FDA could not ensure that biosimilar products would be safe and effective without clinical trials; however, the FDA's practices for licensing and approval of biologics has evolved over time. Specifically, the FDA learned that recombinant DNA proteins are more easily characterized than earlier biologics, which allowed the FDA to update its regulations related to "comparability." This allowed streamlined FDA approvals of manufacturing process changes based on physical chemical demonstrations of product comparability. This has proven successful for regulating changes in manufacturing processes for approved products, and establishes the FDA's capacity to evaluate inter-manufacturer comparability. It also sets the stage for an abbreviated approval pathway for biosimilars using data from a comparable reference biologic.

However, officials believe that to ensure a safe and effective abbreviated approval pathway for biosimilars, the FDA must be allowed to use current science to evaluate efficacy and safety without legislative barriers. The science behind biologics is

constantly evolving, and the FDA should be able to use current scientific knowledge without constraints.

- **Competition from biosimilars will drive lower prices for reference biologic products but the impact will be more limited than what has occurred with generic drugs.**

Establishing an accelerated approval pathway for biosimilars in the U.S. could create downward pressure on the cost of biologics, although most participants in this Forum agreed that the impact would be less than what has occurred with generic drugs. This is due to the cost and complexity of developing biosimilars which limits the number of companies that can develop competing products. More limited competition would enable the innovator firms to maintain reasonably high prices even when competing with biosimilars.

- **Medicare needs new authority to benefit from enhanced competition among biologic therapies.**

Medicare would require authority to modify current reimbursement practices in order to benefit from enhanced competition. Possible changes include allowing CMS to assign similar drugs into a single reimbursement code, using least costly alternative pricing, and establishing Part B formularies. Another strategy to take advantage of competing products is paying for episodes of care that bundle payment for medical treatments and biologics. Today, Medicare reimburses doctors for biologics based on the average sales price plus a markup, which incents use of more expensive drugs. Bundling would increase physician financial incentives to select the most cost-effective products available. However, bundling would need to be combined with safeguards to ensure quality and safety under this type of financial arrangement. Several participants viewed the bundling option as unlikely to gain political support, particularly for cancer therapies.

- **Data exclusivity is at the epicenter of the biosimilar policy debate.**

Biologic manufacturers want to protect their investments and make sufficient returns so investors will continue to support development of new products. They agree with Henry Grabowski's analysis that 12-14 years of data exclusivity is necessary. In contrast, many consumers, payers, providers, and biosimilar companies support the data exclusivity period of 7 years established by the Hatch-Waxman Act for generic drugs. A recent Federal Trade Commission (FTC) report concluded that competition between biosimilars and branded biologics will be similar to competition between two branded drugs which historically has resulted in more modest price discounting. The FTC recommends that no data exclusivity period is necessary because they concluded that patent law, along with market-based pricing, provides sufficient protection for innovators' investments. Although most agree that establishing an abbreviated FDA approval pathway is a good policy direction, the period of data exclusivity remains the most divisive issue among stakeholders.

Promoting Access to Affordable Biologic Therapies in Medicare

Presenter: **Peter Bach, M.D., M.A.P.P.**, Associate Attending Physician, Memorial Sloan-Kettering Cancer Center

Overview

The cost of cancer drugs has increased dramatically, growing much faster than total healthcare costs. High drug costs are attributable to the inability of Medicare and private payers to influence either prices or utilization. Medicare's current rules and state mandates imposed on private payers effectively allow manufacturers to charge whatever they want. One potential solution is to allow Medicare to implement reimbursement strategies that create financial incentives to prescribe lower cost drugs where appropriate. These include blended, bundled, and lowest cost alternative pricing. Allowing entry of generic biologics (biosimilars) would increase the number of substitutable products, making these reimbursement methods more effective. These strategies could lower costs and encourage innovation as manufacturers would have stronger incentives to develop unique drugs with superior performance that have no substitutes.

Context

Dr. Bach discussed factors driving the rising cost of cancer drugs and potential options that Medicare, with additional authority, could consider to control these costs.

Key Takeaways

- **Rising cancer drug costs can be attributed to Medicare's limited ability to influence prices or utilization.**

Over the past forty years, the price and cost of cancer drugs has increased dramatically, maybe faster than in any other area of healthcare. These high costs are partially due to the limited ability of Medicare and private payers to influence prices or utilization. The result: manufacturers can essentially charge any price they want.

"Medicare and private payers have very limited ability to hold down either prices or utilization."

— Peter Bach

Medicare is constrained for several reasons. It can no longer use blended reimbursement methods to force similar drugs to compete on price, and it is prohibited from using competitive acquisition or other bidding approaches. It cannot limit coverage based on lack of evidence, and it cannot use bundled payments.

Private payers face similar challenges. In the states that have 74% of the American population, state laws mandate that payers must cover all cancer drugs. Dr. Bach concluded that the current situation requires policy changes.

- **One solution: Empower Medicare to do more.**

Addressing the Medicare drug costs is possible through Congressional action that would allow Medicare to do more; specifically, substitutability and bundling.

Substitutability

There are a variety of strategies for controlling the cost of drugs that are determined to be substitutable. One is establishing blended reimbursement codes. A second approach would be setting payment based on the price of the "least costly alternative (LCA)." Another approach is to establish formularies. Under any of these payment strategies, "generic biologics" (biosimilars) could play a role.

As Dr. Bach wrote in the February 5, 2009 New England Journal of Medicine, "Blended reimbursement is an example of the application of a reimbursement formula to groups of interchangeable drugs in order to obtain lower prices. Under this approach, Medicare reimburses for the use of a particular drug on the basis average of prices for that drug and other similar drugs, with the weighting linked to the sales volume of each drug."

In July 2007, Medicare implemented blended-price reimbursement for two drugs that were deemed "clinically equivalent" and thus interchangeable (branded levalbuterol and generic albuterol). At the time, the reimbursement for levalbuterol was \$3.84 per unit versus \$0.20 per unit for albuterol. The blended rate was set at \$0.525 per unit, causing the market to quickly shift to albuterol. This shift lowered the blended rate (because it is based on the sales volume), which reduced Medicare's cost significantly.

A similar approach could be used for many cancer drugs, particularly combinations of drugs. For cancers such as metastatic breast cancer and adjuvant colon cancer, several combinations of drugs are presented in the practice guidelines as having the same clinical outcomes. Yet these different combinations have dramatically different costs. For breast cancer, five comparable drug combinations range in cost from \$2,230 to \$19,132 for a 12-week cycle.

While attractive, substitutability has the following challenges:

- *Determination of substitutability.* Someone within the government will need to determine which drugs are substitutable.

- *Different indications.* Cancer drugs used to treat a specific condition often don't have identical indications. This makes substitutability determination more complex.

—*Reimbursement through different parts of Medicare.* Even though drugs may be substitutable, one drug may be administered intravenously (IV) and another orally, which means that one is within Part B and the other is in Part D. This adds further complexity to implementing substitutability since oral and IV drugs fall under different reimbursement rules.

Bundling

Bundling would shift from the current model where each drug and service is reimbursed separately, to payment based on “episodes.” An episode would cover a discrete period of treatment and could include visits, labs, administration fees, and drugs. Episodes could also be expanded to cover related ancillary services such as imaging tests, radiation therapy, and surgery.

Bundled payments would create strong incentives for doctors to pay attention to drug costs. If bundled payments are constructed based on clinical guidelines, they would encourage quality, and could yield significant cost savings.

Under the current system, doctors are reimbursed for the cost of drugs plus a percentage of the cost (e.g., average sales price – ASP - plus 6%). The “markup” that is added to the cost of a drug provides an incentive for doctors to prescribe higher-priced drugs and more of them.

Financial motivations definitely affect physicians’ drug choices. This can be seen when a lower-priced generic drug is introduced, because Medicare calculation of average sales price has a lag of about six months. For the next few quarters, there is a large spread between Medicare reimbursement and the cost of the generic drugs. Doctors shift rapidly to the generic but are paid at the old, higher rate (essentially gaming the system). Eventually, reimbursement catches up, the spread disappears, and doctors go back to prescribing the higher-priced drug, where they make more profit.

With bundled payment, a single payment would cover all patient care for a defined episode of illness, including drugs. As a result, physicians have strong motivation to prescribe less expensive alternatives if they are equally effective.

*“The cost savings potential [of bundling] is large.
That’s why we are talking about this.”*
— Peter Bach

With bundling (as with capitation), a key concern is that physicians may withhold effective services. Therefore, mechanisms to ensure quality should accompany bundled payments. One approach would be to make reimbursement contingent on oncologists’ certification that they are following an approved regimen/protocol.

■ **Another solution: allowing entry of competitor generic biologics (biosimilars).**

The reimbursement strategies described above require substitutable products in order to achieve savings. Allowing

generic biologics would create a much broader range of substitutable products. This has certainly been the case with small-molecule drugs, and would counterbalance the ability of manufacturers to charge whatever they want.

At the same time, allowing competitor generic biologics could spur innovation. To avoid substitutability, manufacturers would have an incentive to develop better drugs and show superiority. This would encourage head-to-head clinical trials and personalization. Manufacturers would also seek to demonstrate superiority for narrower indications.

This would focus competition on therapeutic benefits rather than marketing. If there were no clear superiority, then comparable regimens would compete on price. As a result, allowing generic biologics could lower costs, lead to greater value, and drive creation of better drugs.

Dr. Bach could envision potential exceptions. For example, there might be situations (like orphan diseases) where a model of price controls with a guaranteed return would be appropriate.

Participant Discussion

- **Safety of generic biologics.** Safety is one area of concern around biosimilars. But this concern can often be addressed. A participant noted that his company has sold a biosimilar in Europe since January 2008. During the European approval process, the product went through numerous safety and efficacy requirements that proved it was as safe as the innovator drug.
- **Bundled payment systems and incrementally better regimens.** Tarceva, a drug for pancreatic cancer, provides on average nine additional days of life for patients at a cost of \$60K. However, most patients don’t conform to the average. The drug provides great benefit for some and none for others. A participant questioned whether bundled payment systems fail with these types of drugs that provide incremental improvement.

Dr. Bach agreed that bundled payments are not the solution in all situations. If a drug is truly better than the alternatives and is therefore not substitutable, the market price should be paid. In the case of pancreatic cancer, a huge market exists. Innovators will enter and compete with Tarceva, providing equivalent or additional benefits. In this scenario, society wins.

- **Bundled payment systems vs. changing the ASP-based reimbursement structure.** Participants believe it will be a long time before a bundled payment system can be implemented. There will be considerable political battles about what is included in bundles. One participant suggested that changes could be made more quickly to the ASP structure. For example, a greater percentage reimbursement could be provided when generics are prescribed (giving physicians higher margins on generics).

Dr. Bach responded that there are challenges in regulating ASP reimbursements. It is undesirable for ASP reimbursement formulas to be legislated because it limits CMS flexibility. In

addition, it would be onerous to create reimbursement formulas on a drug-by-drug basis.

- **Cancer treatments and orphan drugs.** Stuart Altman noted that cancer treatments seem to be dominated by orphan drugs. Meaning, for some cancers there is only one drug that works. This makes bundling difficult as each one needs to be defined separately. Manufacturers and advocates will strongly push different drugs. At some point, the regulators will give up and say that they can't implement a bundled system.

Dr. Bach acknowledged that there will be challenges to moving towards bundled reimbursement. However, he believes that government can negotiate these problems, as long as there is a theory behind the new system. In the end, the doctor should still be the principal decision maker.

Biosimilars and the FDA Approval Process

Presenter: **William Egan, Ph.D.**, Vice President, PharmaNet Consulting

Responder: **Jonca Bull, M.D.**, Vice President, Drug Regulatory Affairs, Novartis Pharmaceuticals Corporation

Overview

The FDA has been regulating recombinant DNA (rDNA) protein products for more than 25 years, with the majority being regulated as biologics and some, primarily hormones, as drugs. For early biologics, which were often complex mixtures not readily amenable to molecular characterization as many other pharmaceuticals are, a great emphasis was placed on the manufacturing process to ensure product consistency; hence the paradigm, "The product is the process." Equating the product with the process, however, made process changes difficult, often requiring clinical studies before process changes were approved.

This understanding changed over time as the agency recognized that rDNA proteins were more amenable to molecular characterization than earlier biologics. In response, the FDA updated the manner in which recombinant proteins and monoclonal antibodies were regulated and established a formal product comparability process. This streamlined manufacturing process changes by allowing approvals to be based on physical chemical demonstration of product comparability.

By streamlining approvals for manufacturing changes, the comparability process has resulted in many benefits, such as increased purity, yields, and more stable formulations. Experience suggests that this process may now be extended to determine product comparability from different manufacturers. This would set the stage for the licensure of follow-on protein products. According to the experts on this panel, the FDA has the experience and expertise to determine both efficacy and safety of biosimilar products.

Context

Dr. Egan discussed how the FDA's approach to evaluating rDNA protein products and its processes for determining product comparability have evolved. Dr. Bull commented on the FDA's depth of knowledge in the area of biotechnology products and the flexibility of the current regulations. Participants shared their perspectives on post-marketing data gathering and the need for follow-on biologics (biosimilar) legislation in the United States.

Key Takeaways (Egan)

- **The FDA has been regulating rDNA biological products for more than 25 years. Most of these products are regulated as biologics under the Public Health Service Act, but some, primarily hormones, are regulated as drugs under the Federal Food, Drug, and Cosmetic Act.**

In 1986, the Food and Drug Administration (FDA) published a notice in the Federal Register that licensing and approval of rDNA

protein products were required even if they were believed to be identical to a natural product or existing product. Two different statutes approve or license rDNA protein products.

—*The Federal Food, Drug, and Cosmetic (FD&C) Act*. Some therapeutic biotech products, primarily hormones, are approved under Section 505 of the FD&C Act. The FDA's Center for Drug Evaluation and Research (CDER) primarily handles the regulation of these products.

—*The Public Health Service (PHS) Act*. In contrast, most therapeutic biotech products including interferons, G-CSF, EPO, t-PA, and monoclonal antibodies, as well as blood products, vaccines, cell and gene therapies, are approved under Section 351 of the PHS Act. Initially, the FDA's Center for Biologics Evaluation and Research (CBER) handled the regulation of these products. In 2003, CDER assumed regulatory responsibility for most therapeutic biotech protein products.

The biologics license application process allowed a great deal of flexibility. While the regulations indicated what needed to be done to obtain licensure, they did not define how it should be done, allowing the FDA to use its expertise and apply new developments in both science and technology.

- **Because rDNA protein products are generally purer and more readily characterized at the molecular level than are the earlier biologics, the FDA changed its procedures as to how these products were regulated and, in 1996, published a guidance on establishing product comparability following manufacturing changes.**

Earlier biological products, since they are naturally sourced, were often complex molecular mixtures that were not amenable to detailed product characterization at the molecular level. As a result, these biologics relied on exact repeatability of the manufacturing process to assure product comparability and lot-to-lot consistency. This led to the biologics paradigm of "The product is the process." Unfortunately, equating the product with the process presented barriers to implementing changes to the manufacturing process. When process changes were proposed, clinical trials were often required to demonstrate product comparability.

In contrast, rDNA proteins are highly pure and are more readily characterized at the molecular level. In response, the FDA changed the way these "well-characterized" biologics were regulated. These included modifications to the licensing application, lot-release requirements, and changes in the basis for implementing post-approval manufacturing changes for already approved rDNA protein products.

—*FDA Guidance Concerning Demonstration of Comparability of Human Biologic Products, including Therapeutic Biotechnology-derived Products*. In 1996, the FDA issued guidance that

formalized a pathway to allow manufacturing process changes to be made without clinical studies for specified products. Comparability can instead be established through a combination of analytical and pre-clinical studies. However, if comparability could not be satisfactorily established through physical-chemical studies, clinical studies would be needed.

—*International Conference on Harmonisation (ICH) Guideline Q5E – Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.* A guideline on comparability was also added to the ICH process stipulating that quality attributes of pre- and post- change products do not need to be identical. Instead, differences can occur when existing knowledge suggests that they will not cause any adverse impact on safety or efficacy.

- **The new policies on comparability generate many benefits and may be applied to products from different manufacturers.**

In addition to risks associated with the comparability policy, there are numerous benefits to reducing barriers to making beneficial changes in production processes. For example, increased purity leads to potentially safer products; increased yields can increase availability and decrease costs; and improved formulations enhance safety and offer greater stability.

The comparability policy has proven highly successful for regulating changes within a single manufacturer's operations. The question is whether the scientific process for comparability can be extended to products from different manufacturers. Dr. Egan believes that an inter-manufacturer comparability process can work.

With inter-manufacturer comparability, what matters is the comparison of the product; not the manufacturing process. More than one pathway may exist to manufacturing a given product. Each manufacturer must, however, have validated manufacturing processes that result in a consistent product.

- **The licensure of follow-on protein products (biosimilars) is an extension of the comparability policy.**

The FDA defines follow-on protein products (biosimilars) as proteins and peptides that are intended to be sufficiently similar to an already approved or licensed product such that existing scientific knowledge about safety and effectiveness can be used to obtain approval. Dr. Egan noted that the definition of these products does not have interchangeability built in, and he raised the question of whether interchangeability is a necessary part of the definition.

Comparability evaluations for follow-on protein products are based on a number of factors, including:

—*Chemical, biological, and clinical characterization.* As molecular complexity increases, separation and characterization to determine comparability become more difficult. Complexity may be a function of the overall size of a protein, the number of glycosylation sites, the number of potential modifying sugars at any site, and the number of post-translational

modifications, as well as product-related impurities (degradants). Although a protein may be highly complex, the scientific principles used to assess inter-manufacturer comparability are the same as those that have been used to assess intra-manufacturer comparability. However, as molecular complexity increases, the demonstration of comparability becomes more difficult; additionally, the definition of comparable becomes increasingly difficult.

—*Clinical experience and knowledge of the disease and treatment.* These factors provide a contextual framework for comparability evaluations. Key considerations include the extent of use, adverse event history, and therapeutic index for the product.

—*Process experience and knowledge.* Process knowledge provides an assurance of product consistency. This knowledge helps determine the potential for different process steps to affect protein quality and in what manner. The FDA's Quality by Design initiative is one way that companies can build quality, safety, and efficacy into biologics products.

—*Safety and efficacy.* Efficacy is a function of the drug substance. As a result, efficacy is easier to establish through comparability studies than safety. Safety issues are often associated with process and product impurities. Examples of impurities include immunogenicity and altered specificity of minor species. Dr. Egan noted that immunogenicity is primarily a problem with molecular aggregates.

"Everyone can think of all the reasons why we can't do this—all the 'what-ifs'. But you can be paralyzed by that. Cardinal Newman said it well: 'Nothing would be done at all if one waited until one could do it so well that no one could find fault with it.'"

— William Egan

- **With protein products, orphan exclusivity is only possible when minor changes to a molecule show clinical significance.**

Currently, the FDA grants seven years of exclusivity to orphan drugs based on legislation set by Congress. When protein products were first licensed for orphan indications, a concern was that manufacturers would try to break orphan exclusivity by making minor product changes (e.g., conservative amino acid substitutions). However, the FDA has put into regulation that such changes can break orphan exclusivity only if those changes show a clinically significant benefit. From a regulatory standpoint, minor differences in amino acid sequences and glycosylation do not necessarily alter the safety and efficacy of a protein product, and therefore, do not break orphan exclusivity.

The FDA has established clinical significance as an important factor in maintaining data exclusivity periods that could be applied to biosimilars when legislation allows licensure in the U.S.

Key Takeaways (Bull)

- **The entire product lifecycle must be considered as the pharmaceutical industry develops safe licensure pathways for biologics.**

With biologic products, a lifecycle approach to safety evaluation is necessary. A study issued by the FDA's Office of Surveillance and Epidemiology examined whether there were any points in the product lifecycle assessment that were not necessary. It found no point in time where safety evaluations can be eliminated. Safety profiles for all biologic products evolve over time, and it is necessary to put patient safety first.

"In all aspects of safety, we need to put our patients first, and ensure that the highest standards of clinical practice are adhered to."

— Dr. Jonca Bull

- **The FDA team ensures that high scientific standards are applied to biologic products.**

Dr. Bull commented that she is not worried about the oversight of the science that is used to produce biosimilars. The FDA's Office of Biotechnology Products (OBP) has significant depth and breadth of experience with current and past issues related to biologics. In addition, they have tremendous knowledge across manufacturers. The FDA team is knowledgeable about what works and what doesn't in drug and biologic development. The FDA ensures that the same manufacturing standards and processes that an innovator uses are also used by makers of biosimilars.

The frameworks of current regulations are flexible and have served the FDA and the public well. Dr. Bull feels that the agency has the tools it needs to effectively manage biosimilars as soon as legislation is enacted.

Participant Discussion

- **Post-marketing product evaluations.** Dr. Altman asked whether post-marketing studies should be required for biologic and biosimilar products.

Dr. Bull commented that the FDA Amendments Act of 2007 greatly expanded the agency's authority to collect safety data. Reports made to the FDA about efficacy and safety inform how the agency looks at drugs.

Dr. Egan also noted that there has been a marked increase in the number of post-marketing and post-licensure studies that have been required and funded by drug manufacturers.

Participants from Hospira discussed how they were the first U.S. company to register a biosimilar product in the E.U. The approval process included a significant risk-management program that was reviewed by governmental agencies. In addition, 1,500 patients are being followed to evaluate any significant adverse

effects or lack of efficacy. All data from the study must be provided to the government.

In the U.S., Hospira feels that the FDA is best positioned to evaluate the post-marketing safety of complex molecules on a case-by-case basis. It would not be desirable for requirements to be put into legislation. That would lead to higher drug prices and reduced competition.

- **Follow-on biologics legislation.** One participant noted that without legislation there is no path for follow-on biologics in the U.S. Lack of legislation is the missing piece. The FDA is unwilling to have a dialogue about these drugs because there is not legislation in place to allow licensure. The science is there, comparability is possible, and there are systems in place to ensure a safe and efficacious product. But, there is no legislation.
- **Comparable biologics and Medicare.** Mr. Mechanic asked how Medicare reimbursement policy would be affected if Congress enacts a pathway for follow-on biologics and the FDA classified certain cancer drugs as comparable.

Dr. Bach responded that it depends on the exact terms that the FDA uses to describe the drugs. Lower drug prices are only likely if Medicare can get drugs classified into the same payment code.

Potential Impacts of Biosimilars in the U.S. Market

Speaker: **Paul Heldman**, Senior Health Policy Analyst, Potomac Research Group

Discussant: **Steven Miller, M.D.**, Senior Vice President & Chief Medical Officer, Express Scripts, Inc.

Overview

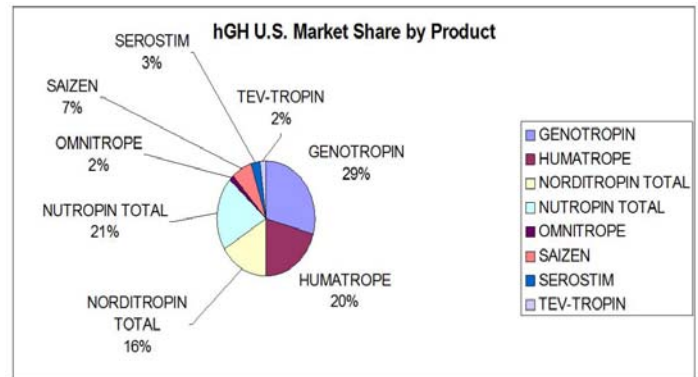
Early experience with biosimilars in Europe and the U.S. offers important lessons about pricing, product quality, and the potential for enhanced price competition through biosimilars. Equivalent or "bio-better" drugs are the key to success.

Some biopharmaceutical companies argue that biosimilars will weaken the incentives for them to develop new therapies; however, the high market prices brand-name biologics currently earn weakens this argument considerably.

Biologics and biosimilars are motivating payers, including Medicare, to re-examine how they reimburse for these products. Some private insurer incentives are already in place to promote the use of lower-cost substitute products, but additional reimbursement reforms are needed.

"You can't penetrate a market with just discounted prices. Quality matters."

— Paul Heldman



Source: IMS Health

Context

Mr. Heldman described the potential for biosimilars to reduce drug prices in the U.S. market and emphasized the need for changes in Medicare reimbursement and coding policies. Dr. Miller discussed the linkage between biosimilar product quality and market success.

Key Takeaways (Heldman)

- **A market exists for lower-cost biosimilars, but discounts alone won't drive market penetration.**

If Congress approves a pathway for biosimilars, there will clearly be a U.S. market for biosimilars. However, the experience of Sandoz's human growth hormone (hGH), Omnitrope, suggests that discounts alone will not drive market penetration.

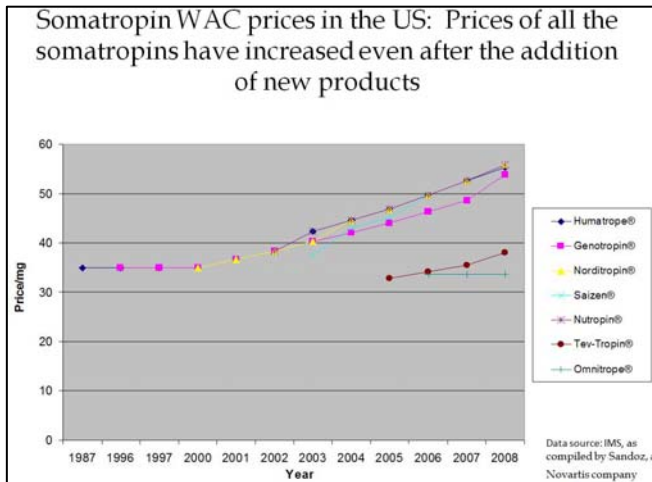
Sandoz was the first pharmaceutical company to win FDA approval for a follow-on biotech product, using abbreviated clinical data. This product, Omnitrope, was launched in the U.S. in early 2007 at a discount to competitor products. The drug gained some market share following launch; however, sales were limited because the initial version used an inferior delivery mechanism in comparison to the reference product, Genotropin. Only in 2008, after the FDA approved an improved delivery system and a more popular 10mg cartridge, did sales increase.

Today, Omnitrope has just a 2% market share. At the time of launch, the hGH market was already saturated, and doctors did not have a compelling reason to use alternatives that were not fully substitutable. This suggests that in a crowded market, product quality matters, and brand loyalty may limit penetration.

- **Although the first biosimilars in Europe and the U.S. generated price discounts, the opportunity is more modest than for small-molecule generics.**

The experience with erythropoiesis-stimulating agents (ESAs) in Germany demonstrates that biosimilars can trigger price reductions. Before and after the entry of biosimilars, brand-name competitors reduced ESA prices. This helped branded products retain market share. Aranesp, for example, experienced an initial dip in market share after the introduction of biosimilars. However, it cut prices 13-16% in early 2008 and maintained its market share. Less than a year after introduction, biosimilar ESAs attained 18% penetration in Germany. Research suggests that ESA biosimilars in Germany are priced at a 25% discount to innovator products, a discount that is more modest than for small molecule generics.

In the U.S., the hGH market has seen increases in wholesale acquisition cost (WAC) prices over time, even after the entry of new biosimilar products. Omnitrope, for example, was selling at a 40% discount to the reference product. Yet, the WAC of other products continued to increase.



▪ **The high cost of biologics is causing policymakers to consider reforms in the Medicare Part B and D programs.**

Today, biologics represent a significant percentage of Medicare Part B reimbursement costs. Six of the top ten biotech drugs in dollar sales account for 43% of Medicare Part B drug costs. In addition, Medicare reimbursement for drugs under Part B encourages the use of higher-cost medications.

Mr. Heldman proposed two options for changing Medicare Part B and another option that could be considered for Medicare Part D reimbursement that would promote the use of biosimilars.

—*Reference pricing of Part B drugs.* This would give Medicare the authority to set a reference price for Part B drugs at the price of the least costly alternative. Medicare successfully used reference pricing for Lupron. However, it failed with Xopenex and generic albuterol. The Congressional Budget Office has specifically suggested least costly alternative as a potential source of savings.

—*Collapse similar drugs into the same reimbursement code.* This “blended” pricing option would create strong incentives for physicians to use the less costly drugs. But it would also create patient safety concerns if the drugs are not completely interchangeable. One solution would be making blended pricing contingent on FDA determination of interchangeability, and giving the Secretary of Health and Human Services discretion to determine clinical appropriateness.

—*Changing policies around catastrophic benefit coverage.* By 2018, Medicare Part D is expected to account for 30% of the retail drug market, as compared to 2% prior to 2006. Biotech drugs are the fastest-growing component of Medicare Part D costs. In 2007, biologics accounted for 6% of Part D spending, but between 2006 and 2007, they grew 14% faster than other drug segments. The expense of biotech drugs is so high that most Medicare Part D patients move almost immediately to the catastrophic coverage category. Under this coverage, the government covers 80% of drug costs. MedPAC has recommended that government reimburse a lower percentage

of the cost for expensive innovator drugs and a higher percentage for less expensive biosimilars.

CMS, private payers, and states have implemented a limited number of payment incentives that would promote the use of biosimilars, once legislation is passed.

—*Dialysis bundling.* In 2008, Congress mandated bundled payments for dialysis. This policy will be phased in starting in 2011. Bundled payments incent dialysis centers to use biosimilar drugs to save money.

—*Insurance plan formularies.* Many insurance plans already use specialty tiers and step therapies.

—*Medicaid preferred drug lists.* In 2008, 42 states had preferred drug lists and prior authorization requirements. These could be used to encourage the use of biosimilars.

▪ **Expansion of incentives for orphan drug development is a tough sell.**

About 20% of orphan drugs are biotech products and have a seven-year exclusivity period. Some brand-name drug companies argue that biosimilars would weaken the incentive to develop orphan drugs. However, high prices currently paid for orphan drugs may make it hard for this argument to gain traction.

Key Takeaways (Miller)

▪ **To succeed, biosimilar products must be equivalent to or better than the innovator product.**

Lower prices alone won't guarantee that biosimilars will gain market share, as Omnitrope proved. Success requires an equivalent or better product and requires effective marketing. While Omnitrope was priced lower, the product was inferior and was not actively marketed.

In contrast, Hospira launched a great product to compete with EPO in Europe with a lower price and a strong marketing force. As a result, it captured 25% of the market.

The German market illustrates the effect that would be expected for biosimilars in the U.S.—lower prices.

“The United States is a much more aggressive market. I anticipate that the U.S. biosimilars market will be like Germany on steroids.”

— Steven Miller

▪ **Regulatory and statutory changes are needed to reform Medicare reimbursement for biosimilars.**

Potential mechanisms for payment reform include bundled payments, J-code sharing (e.g., blended rates), and electronic prescribing. In some cases, bundling will work well. For example, bundled payments for dialysis will make a huge difference. Electronic prescribing also offers significant benefits by putting visibility about cost differences in the hands of the doctor at the time of prescribing. Medicare now provides incentives for doctors

to electronically prescribe medications. The Federal definition of electronic prescribing includes a formulary and benefit check; not just electronic transmission of the prescriptions.

- **Technological advances are enabling new tools that will aid in the creation of biosimilars.**

Express Scripts has an enormous database with pharmacy and medical history. Using this data, it will be possible to develop revolutionary tools to compare protocols, manage drugs, and tie drug usage to outcomes. The opportunities are tremendous, and if an abbreviated pathway is chosen by Congress for follow-on biologics, it is critical that the law allow for the changing scientific and technology landscape.

Participant Discussion

- **Who benefits from lower drug prices?** Is it the government, the patient, or physicians? Mr. Heldman responded that price reductions from biosimilars will benefit both patients and taxpayers. Dr. Miller commented that for generic drugs, about 25% of the savings goes to the patient and 75% to the payer (either the government or the employer). For higher-priced biologics, however, the savings are less clear. The patient pays only about 2% of the total cost of biologics today, as compared to 22% of the cost of pharmaceuticals.
- **Changing consumer behavior through communications.** When it comes to prescription drug coverage, Dr. Miller noted that many consumers are motivated more by communications

than by co-pay amounts. For example, Express Scripts worked with Lowe's on a program where employees are automatically enrolled in the mail-order pharmacy benefit. They must opt out to purchase drugs through a regular pharmacy. This program has saved Lowe's \$3 million per year, and did not require any change in the benefit program.

- **The Hatch-Waxman Act and the pharmaceutical industry.**

The group had differing views about the effect of the Hatch-Waxman Act on the drug industry. Dr. Miller suggested that the legislation stimulated pharmaceutical innovations, provided savings for patients, and did not harm the industry. Stuart Altman, in contrast, felt that the Act had suppressed investment in pharmaceuticals. He indicated that venture capitalists are no longer investing in strict pharmaceutical projects, and are instead focusing on biologics.

- **Medicare Part B and Part D.** Dr. Altman noted that Medicare Part D has worked better than expected. However, high-cost biologics raise questions about the effectiveness of the program. If high drug costs aren't addressed, the viability of Part D may become an issue. Dr. Miller commented that in Medicare Part B, there is little data available to help manage drug costs. Prices are obscured, and data is not available in real time. It is easier to track costs on the pharmacy side, due to real-time information processing. As a result, payers are pushing to get drugs to the pharmacy side where tools like co-insurance, step therapies, formularies, tiered pricing, and prior authorization can help control costs.

Options for Follow-On Biologic Competition in the U.S.

Presenter: **Tara Koslov**, Attorney-Advisor, Federal Trade Commission (FTC)

Panelists: **Alex Brill**, Research Fellow, American Enterprise Institute for Public Policy Research
Henry G. Grabowski, Ph.D., Professor, Duke University
Cole Pinnow, Vice President, Global Specialty Pharmaceuticals, Hospira Inc.

Overview

The FTC recently issued a report on follow-on biologic (FOB) drug competition, concluding that the market will be similar to competition between branded drugs. The Commission believes that the same incentives that motivate branded biologics will also foster FOB competition. The FTC does not recommend any data exclusivity period because their evaluation concluded that patent law plus market-based pricing provide sufficient protection for the innovator's investments.

Some participants questioned the FTC's analysis, asserting that data exclusivity is more important for biologics than for small-molecule drugs, and that patent law alone is insufficient to protect the innovator's investment. Participants also discussed the importance of relying on science to determine the safety and efficacy of FOBs, arguing that the FDA's expertise is necessary to evaluate the changing scientific landscape in production of biologics and FOBs. This suggests that legislation should provide the FDA with flexibility to act based on science.

Context

Ms. Koslov, speaking on behalf of FTC Commissioner Pamela Jones Harbour, summarized the FTC report "Follow-on Biologic Drug Competition," which can be found on their website at <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf>, and outlined the Commission's recommendations for U.S. policy towards follow-on biologics. A panel responded to the report's findings, offering opposing and supporting views. Participants then shared their perspectives on the biologics market in the U.S. and Europe.

Key Takeaways (Koslov)

- **The FTC concluded that competition between pioneer biologics and FOBs is likely to look like competition between branded drugs.**

The FTC believes that FOB competition will be similar to competition between two branded, small-molecule drugs, and less like the competition between branded and generic drugs. There are four reasons for this conclusion:

—*Entry costs and time.* In contrast to generic drugs, the cost and time to develop an FOB will limit the number of competitors. The steep cost will also limit the discounts that an FOB can offer in relation to pioneer biologic prices.

—*Pioneers will retain significant market share.* In the small-molecule space, when generics enter, branded firms soon

lose much of their share. However, in biologics, a pioneer is likely to retain significant market share after FOB entry. This is due to first-mover advantage, the lack of interchangeability, no automatic substitution, and smaller price discounts. In addition, safety and efficacy concerns may prevent doctors from switching current patients to an FOB. This may limit FOB market opportunities to newly diagnosed patients.

—*Specialty pharmaceutical characteristics.* Specialty drugs are often injected or infused, and are combined with medical services that require specialized training. These factors will make it more difficult to switch from a pioneer to an FOB alternative.

—*Payment issues.* Because biologics are administered in clinic settings as part of medical treatments, they are not purchased and reimbursed in the same way as small-molecule drugs. Payers cannot employ the same strategies that encourage consumers to seek generic drugs.

- **Elements of the Hatch-Waxman Act provide a model for follow-on biologics, but it is not a perfect template for legislation.**

While biologics provide important benefits, they are expensive. One way to reduce the cost of biologics is to permit market entry of FOBs, once a biologic's patents expire.

Today, there is no statutory or regulatory pathway that allows abbreviated FOB entry without duplication of clinical trials. In the small-molecule drug market, the Hatch-Waxman Act does not require generic drug applicants to repeat clinical testing of branded drugs. It was noted that elements of this Act may offer a model for reducing FOB entry costs.

Under Hatch-Waxman, a generic applicant must show that its product is "bioequivalent" to the branded drug. This has three implications.

1. Bioequivalence is less expensive to demonstrate than full clinical testing.
2. If a generic is deemed equivalent to the branded drug, it can be safely substituted and will be equally effective. Consequently, two drugs can compete head-to-head in the marketplace.
3. Because substitution is possible, many states allow pharmacists to automatically substitute a generic for a branded drug. This ensures that the generic gains market share at the branded drug's expense.

Hatch-Waxman, however, is not a perfect template for FOB legislation. Biologic products cannot be perfectly duplicated today. Even minor differences can trigger dangerous immune responses. Given the high risk of adverse effects, patients cannot switch freely between a pioneer biologic and an FOB. This will directly impact the market limiting competition between FOB products and brand biologic products.

▪ **FOB manufacturers will be attracted to large markets, offer smaller discounts than generics, and capture market share slowly.**

The FTC predicts that FOB markets will develop with the following characteristics.

- FOB entry is unlikely in biologic markets with less than \$250 million in annual sales.
- Only two or three FOB manufacturers will attempt entry in a particular pioneer biologic market.
- FOB manufacturers will not offer price discounts larger than 10% to 30% off the pioneer product's price. Although this discount is not as large as small-molecule generics, it represents millions of dollars in consumer savings.
- Pioneer manufacturers are expected to respond by offering competitive discounts to maintain their market share. This price competition likely will increase consumer access and further expand the market.
- Without automatic substitution, FOB market share acquisition will be slowed. Pioneer manufacturers likely will retain 70% to 90% of their market share. Pioneer firms will reap substantial profits for years, even after entry by an FOB.

▪ **The same incentives that motivate branded biologics are sufficient to foster FOB competition and ongoing biologics innovation.**

The primary incentives are patent protection and market-based pricing.

- Patent protection:* Through patent protection and the resulting exclusionary rights, biotech firms increase their expected profits from investments in R&D. Patents foster innovation that would not otherwise occur.
- Market-based pricing.* This allows firms to charge prices that reflect the products' value to consumers. By pricing at market rates, firms recoup their substantial investments in biologics. Prices also give firms accurate market signals about the value of developing particular biologic products.

▪ **The FTC's findings have significant implications for the design of an abbreviated approval system for FOBs.**

The FTC's conclusions have three implications for the design of an abbreviated approval system.

- Pioneers do not need additional incentives to innovate.* Beyond existing patent protection and market-based pricing, pioneer manufacturers will not need additional incentives to innovate in the face of FOB entry. The FTC believes that no

additional period of branded exclusivity is needed to spur development of new biologic products and that granting additional exclusivity would be inefficient. Exceptions could be made in situations where a molecule is in the public domain and not patentable, or where market-based pricing provides insufficient incentives.

- Special patent resolution procedures are unnecessary.* The Hatch-Waxman procedures to trigger an early start of patent litigation made sense in the generic drug context, where generics might not be able to pay post-entry patent infringement damages. In the case of biologics, special procedures are unlikely to resolve all pertinent patent issues prior to FDA approval. This is partially due to the fact that pioneer biologics are covered by more varied patents than small-molecule drugs. Special procedures might also result in competitive problems, such as the "pay for delay" settlements that have been seen in the Hatch-Waxman context.
- FOB manufacturers do not need additional incentives to develop interchangeable products.* A branded manufacturer does not receive any protection against market entry by another branded product. If FOBs closely resemble brand-to-brand competition, then incentives provided by market-based pricing should be sufficient, and there is no reason to risk delayed entry of subsequent FOBs that are ready for market.

Key Takeaways (Grabowski)

▪ **Data protection and patents play complementary roles, but data protection is more important for biologics than for small-molecule drugs.**

Data protection is designed to supplement patent systems. Data protection provides market exclusivity in two circumstances: when development is especially long and when biosimilars can circumvent the innovator's patents. If the criterion for biosimilars is similarity, not sameness, then circumvention of patents is possible. Consequently, data protection is more important for biologics than for small molecule drugs.

▪ **The economics supporting the FTC's conclusions on biosimilars are flawed.**

Dr. Grabowski noted several areas where he felt that the economics supporting the conclusions in the FTC's report were flawed.

- Barriers to entry.* The report suggests that there are major barriers to entry that will inhibit FOB manufacturers from entering the market. However, biologics is a global industry. R&D and manufacturing costs will come down over time and barriers to entry will diminish.
- Demand side factors.* On the demand side, comparability and the tools that can be brought to bear by insurers will result in a much more rapid loss of market share for pioneer manufacturers than is predicted by the FTC. For example, a

recently released MedPAC report indicates several ways in which Medicare can realize savings by encouraging utilization of biosimilars.

—*First mover advantage.* It is almost never the case that first movers in therapeutic markets keep 70-90% market share (as the FTC predicts), even when products are highly differentiated. It is unlikely that pioneer manufacturers will retain the level of market share that is predicted by the FTC, especially because products may not be very differentiated.

—*Data exclusivity periods.* Dr. Grabowski's model—which considers factors such as the cost of capital and contribution margins—suggests that innovation can take place with a seven-year data exclusivity period. However, longer periods promote even greater innovation. In contrast, the FTC report suggests that no data exclusivity periods are necessary. Dr. Grabowski feels the economics in the Commission's report could have been better developed and has written a letter to the FTC with accompanying documentation that provides a detailed response. See http://econ.duke.edu/~grabow/FDS/FullFTC_response.pdf.

- **Venture capital funding and partnerships are crucial in biologics.**

Venture capital-backed firms are estimated to have 40% of total employment in the biotech sector. Most ventures are early stage and small. Fewer than 10% have marketed products. The prospect of short data protection periods and rapid entry of biosimilars increases the risks associated with biotech investing, which could affect the flow of capital into this industry.

Key Takeaways (Brill)

- **The FTC's view that 12 years is too long a period for data exclusivity is correct but developing models for this issue still is a valid exercise.**

One of the Commission's concerns about Dr. Grabowski's model is the uncertainty of the assumptions. Small changes in the assumptions can lead to large differences in outcomes, and may limit the model's usefulness. While Mr. Brill agrees with this point, he believes that there is value in developing a model despite its limitations. Mr. Brill praised the FTC for expanding the model to incorporate the effects of price declines on the total size of the market and noted that this model confirms his views that seven years of data exclusivity is sufficient.

- **Patent protection alone may enable innovator drugs to recoup their costs, and data exclusivity needs to be understood as an additional protection for the innovator.**

Data exclusivity creates certainty and reduces risk for innovator companies. In an environment where the data exclusivity period is shortened or eliminated, the strength and effectiveness of the patent system becomes even more important. Existing modeling work on data exclusivity assumes

that only data exclusivity protects innovative drugs. In reality, seven, five, and zero years of data exclusivity are far more similar to each other than they are to 12 years. This is due to the natural delays in market entry by generics caused by R&D requirements and FDA approval process. Mr. Brill concluded that having a short data exclusivity period is sufficient for innovators to have the time and opportunity to recoup their costs.

- **The European experience with data exclusivity periods cannot be translated directly to the U.S.**

Caution must be used when applying European lessons about data exclusivity to the U.S. market. Pricing structures are not the same in these two markets. When price controls are in place, it is natural to look for longer data exclusivity periods. Since the U.S. market does not use price controls, shorter data exclusivity periods may be appropriate.

Key Takeaways (Pinnow)

- **The FDA must decide the safety and efficacy of FOBs on a case-by-case basis.**

Small-molecule drugs are very different from biologics. FOBs must be proven safe and efficacious before they are approved. The FDA should make these decisions on a case-by-case basis using their internal scientific expertise and should not rely on a mandate in legislation to determine if a product is safe.

- **Legislation for an abbreviated pathway needs to be flexible enough to allow for evolution.**

Science and technology are evolving rapidly, and the FDA must be able to use new information to assess and license products. Abbreviated pathway legislation must be flexible enough to allow the FDA to use new scientific knowledge and tools.

Participant Discussion

- **Reimbursement techniques for biologics.** If the FDA certifies that FOBs are interchangeable, then techniques like prior authorization or bundled pricing will probably expand for biologics. With health reform, payers and the government will be much less likely to pay for comparable products that are more expensive products.

- **Exclusivity periods and patent protection.** Dr. Altman questioned why Europe's exclusivity periods are longer than the U.S.'s. Dr. Grabowski suggested that Europe may want to become a stronger innovator in biopharmaceuticals. Ms. Koslov noted that longer European exclusivity periods may be due to a weaker European patent system. The premise of the FTC report is that patent protection is so strong in the U.S. that an additional exclusivity period is not necessary.

Mr. Bauer commented that in Hospira's experience, patents offer strong, broad protection. Innovators do a good job of getting broad protection for molecules. The complexity of

biopharmaceuticals presents opportunities to get additional patents that don't exist in the small-molecule space. These include patents on sequences (both the molecule and active sequences), process patents, cell lines, oscillation patterns, and mutations.

In Europe, the same exclusivity period applies to both small-molecule drugs and biologics. Mr. Bauer suggested that the same policy should be applied in the U.S.

- **Patent challenges and innovator drugs.** Mr. Mechanic inquired about the history of patent challenges to innovator drugs. Ms. Koslov indicated that generics have been quite successful with patent challenges. Mr. Bauer added that Amgen's suite of EPO patents has been asserted repeatedly in the courts successfully.
- **Uniqueness of the healthcare market.** Dr. Altman noted that the healthcare market is unique because for most patients, a third party insulates the consumer from the cost of the product. In recent years, third parties have had difficulty getting consumers and physicians to change behavior. Given these dynamics, healthcare providers and manufacturers have significant power. Consumers must get more involved in the market in order to see the benefits of lower prices.