Statement

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My comments will focus on how the market for follow-on biologics can be expected to evolve economically. Assuming a regulatory pathway is created by Congress, it is relevant to ask whether the economic impact will be the same as for generic drugs under Hatch-Waxman.

Biologics are typically more complex molecules than chemical drugs, and are not manufactured through chemical synthesis, but instead produced through biological processes involving manipulation of genetic material and large-scale cultures of living mammalian, microbial, or yeast cells. Biologics made in different cell lines or manufacturing plants might behave differently as medicines and exhibit unexpected adverse events *in vivo*. These fundamental differences between biological and chemical entities result in important differences in the economics conditions for follow-on biologics compared to generic drugs.

With a group of my colleagues, I have examined the differences between follow-on biologics and generic drugs from an economic perspective in two recent peer-reviewed studies. The first article, entitled "The Market for Follow-On

Biologicals," co-authored by Iain Cockburn and Genia Long, was published in the September/October 2006 issue of *Health Affairs*. The second paper, entitled, "Entry and Competition in Generic Biologics," is in press for a forthcoming issue of *Managerial and Decision Economics*.

Based on our analyses, we conclude that the costs of entry will be significantly higher for follow-on biologics than generic drugs. As a consequence, we expect fewer firms will enter, and average prices will decline less than for follow-on biologics than generic drugs. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the government programs and other payors.

In designing a pathway for follow-on biologics, it is also very important that Congress balance price competition and innovation incentives. The process for discovering a new biologic is lengthy, costly and risky. Over the coming decade, biopharmaceutical innovation can provide major improvements in the duration and quality of human life. It is important to preserve the incentives for innovators through a data exclusivity period that takes into account the high costs and risks of developing new biological entities.

DIFFERENCES BETWEEN FOLLOW-ON BIOLOGICALS AND PHARMACEUTICALS

Clinical Trial Costs

Biologicals made with different cell lines or manufacturing facilities can exhibit significantly different efficacy and safety characteristics. If the U.S. follows a similar approach to Europe's, some clinical trial data demonstrating comparable efficacy and safety will be required for follow-on biologics on a case by case basis. New follow-on entrants may not have to repeat all the original sponsor's clinical steps or incur the costs associated with large patient phase III trials. However, even relatively small trials in biologics of several hundred patients are likely to generate development costs of tens of millions of dollars and take many years to complete. Furthermore, firms can expect to incur additional costs for immunogenicity tests and pharmacovigilance studies.

In the case of European approvals, some estimates from generic company presentations and interviews suggest a plausible range could be $10 to $40 million for pre-market clinical studies. The exact amount is likely to depend on how well-characterized the molecule is and other scientific and technological factors. This contrasts with the $1 - $2 million cost necessary to demonstrate bioequivalence for generic drugs.

Development Times

Estimates from generic firms indicate that development times for a follow-on biological are likely to range from five to eight years. This estimate is based on one to two years for cell biology, one year for process analysis, two to four years for clinical trials, and one year for approval. By comparison, generic drugs seldom require more than a few years to do bioequivalence tests and gain regulatory approval.

Manufacturing Cost and Risks

The required capital investment in property, plant, and equipment, and the costs of manufacturing are also likely to be higher for follow-on biologics than for generic drugs. Cell culture facilities require significant capital and labor investment, taking on average three to five years to construct and costing $250 - $450 million. Plant investment must often be made before drugs enter clinical testing.

An alternative to manufacturing in-house is contract manufacturing. Contract manufacturing of follow-on biologics will be more costly than for pharmaceuticals, due to higher variable costs of production. Contract manufacturers also typically capture a share of the potential profit, limiting the amount ultimately passed on to end users. Due to increased demand associated with the large number of new biological

introductions, contract manufacturers have considerable leverage in negotiations with client firms.

Distribution Structure and Market Acceptance by Physicians

Biologic and drug markets also differ in the structures of their distribution systems and in the economic incentives for participants in the value chain. Most drugs are oral agents distributed through retail and mail order pharmacies. Generic drug products are designated as therapeutically equivalent and interchangeable by the FDA. Strong financial incentives and systems favor rapid generic penetration.

In contrast, biologics include both injected or transfused agents delivered in a physician's office, clinic, or hospital, as well as self-injectible products dispensed through pharmacies. It is unlikely that most follow-on biologics will be designated as interchangeable by the FDA. Instead, they will be treated as therapeutic alternatives by health care providers. Omnithrope fits this categorization, as does the initial human growth hormone products approved in Europe.

We expect that physicians will initially be cautious with respect to the substitution of follow-on products. Health care providers and patients are likely to be wary until clinical experience has accumulated and demonstrated that a follow-on product is a satisfactory therapeutic alternative to the

original product. The perspectives of specialist physicians and organized patient groups in therapeutic areas with high biologic usage will be important in driving or limiting demand for follow-on products.

To overcome barriers to physician and patient acceptance, follow-on biologic entrants may find it necessary to establish "reputation bonds" with branded products to capture and maintain market share. In this environment, market access is facilitated through specialist education and detailing, as well as through contracts with major managed care plans and coordination with centralized formulary policies. Relative to generic drugs, companies may have to incur the added costs of professional detailing forces, perhaps comparable to those of specialty pharmaceutical and biotechnology companies (estimated elsewhere at 40 people).

ENTRY AND PRICE COMPETITION FOR FOLLOW-ON BIOLOGICALS

In the case of generic drugs, a key economic driver of lower prices is the number of generic entrants. A recent analysis published in 2005 that I performed with Atanu Saha and colleagues, "Generic Competition in the U.S. Pharmaceutical Industry," quantifies the dynamic effects of generic entry. As more competitors enter, prices decline and the share of the molecule captured by generics increases. Our analysis indicates

that 10 to 20 generics are likely to enter for large selling products. In these cases, prices are typically driven down to marginal costs of production within a period of months. Large savings to payors and consumers can result when this intensive price competition occurs.

However, we expect the economic dynamics in the case of follow-on biologics will be different. This is due to the higher fixed costs for clinical trials, high manufacturing barriers to entry, and the slower penetration associated with the reluctance of physicians initially to switch patients to follow-on biological products. This will constrain the number of entrants in this market. Entry is the key economic driver of lower prices.

In my research study with David Ridley and Kevin Schulman, we find that the number of entrants and the price discounts of follow-on biologics are highly sensitive to fixed costs. As a consequence, even very large selling biological products are likely to have only a few entrants. Accordingly, price discounts are expected to be moderate. For markets with only one to three entrants, we project that price discounts will be in the range of 10 to 25%. This is in accordance with the European experience to date.

It is also important to remember that the current rapid pace of generic entry and penetration that now characterizes

most large drug products when patents expire took many years to evolve. We expect that this also will be true for follow-on biologics. A more robust follow-on industry will likely emerge as regulatory standards, process engineering, and demand evolve, but this will take many years, even for well-characterized biologics.

Implications for Cost Savings

Given the higher costs of firm entry and the likelihood of demand-side constraints and learning effects for follow-on biologics, cost savings estimates cannot be based on the experiences of generic drug utilization and pricing. Savings estimates based on these assumptions, like those from Express Scripts, are subject to strong upward biases.

A correct economic analysis must take account of the significant economic differences between generic drugs and biologics enumerated above. As discussed, our analysis predicts fewer entrants, smaller price discounts, and lower overall market penetration in the case of follow-on biologicals. A more conservative approach for estimating cost savings is therefore warranted, in our view.

A correct savings analysis must also take account of the time necessary to promulgate FDA regulations and review applications for follow-on biologicals. Even if legislation is

passed in 2007, several years are likely to elapse before a follow-on product is approved and launched in the United States.

A correct economic analysis must also recognize that the sales distribution of existing biotechnology is highly skewed, and that a significant percentage of the largest selling products are currently patent protected over the next decade. In a dynamic market like biopharmaceuticals, improved new products also will be introduced that will replace some of the market for the products subject to patent expiration.

A correct accounting of all these factors would substantially lower the savings estimates in the Express Script and PCMA studies. As a consequence, most of the projected savings in these studies are unlikely to be realized in the ten year scoring window. A recent analysis by Avalere Health, that has very different assumptions in some important dimensions, finds much lower cost savings.

R&D Costs of Innovators are Increasing

Joseph DiMasi and I recently examined the R&D costs and development times for a new data set of recombinant proteins and monoclonal antibodies. We found that mean out-of-pocket R&D costs to discover and develop a new biological entity (including the costs of failures) totaled $559 million. When capitalized to date of marketing at a cost of capital of 11.5%, R&D costs

increased to $1.24 billion. Compared to new chemical entities, we found new biological entities had higher preclinical expenditures and longer clinical development times, but also experienced higher probabilities of success. When adjusted for the time periods analyzed, we found that overall costs for new biological entities were comparable to new chemical entities. Both have been increasing much more rapidly than inflation in recent years.

We also found that the development of biologics entails higher manufacturing costs than new chemical entities. This reflects the need to resolve novel manufacturing challenges at the R&D stage for products developed through fermentation or fragile mammalian cell cultures. By contrast, manufacturing issues in R&D are more straightforward for new clinical drugs. Process specifications and know-how will be important for regulators to consider in developing guidelines for follow-on biologics, and raise important intellectual property issues.

INTELLECTUAL PROPERTY PROVISIONS AND DATA EXCLUSIVITY

Given the entrepreneurial character of the biotech industry, it is especially important that Congress carefully consider the intellectual property provisions that will govern competition between innovators and imitators. In particular, Congress will have to consider whether to award market

exclusivity to the first follow-on biological to successfully challenge a patent. Second, it will also need to decide whether to award innovators a data exclusivity period. This determines the earliest point in time that follow-on biologics can enter, based on an abbreviated process that relies in whole or part on innovators' safety and efficacy data.

Intellectual property has been an important factor for investment in the lengthy risk R&D process for new biological entities, and especially to biotech startups in securing venture funding and partnerships with larger firms. Product life cycles for new medicines span decades and R&D decisions are made with long time horizons on future returns. Legislators may view the encouragement of patent challenges and attendant litigation as a good short-term mechanism for exposing more biologics to follow-on price competition. But increased uncertainty and IP litigation in biotech also would have significant negative incentive effects on capital market decisions for developing private and public biotech firms with promising pipelines. Most of these firms have few, if any, profitable products.

The EU has recently instituted a ten-year data exclusivity period for new medicines of chemical or biological origin, with provisions for additional exclusivity for the approval of new indications. This prevents patent challengers from filing abbreviated follow-on applications until at least ten years have

elapsed. The comparable period for pharmaceuticals under Hatch-Waxman in the United States is five years. The patents of all commercially significant drug products are now challenged in a competitive race by generic firms to gain 180 day exclusivity.

R&D costs have increased substantially since Hatch-Waxman was enacted over 20 years ago. Five years does not provide enough time for firms to recoup the high costs of discovering and developing a new medicine. Breakeven returns on R&D for the average new drug products typically take more than a decade.

I understand that H.R.1038/S.623 have no provisions for data exclusivity for biological innovators. In effect, patents would be subject to challenge as soon as a new biological entity is approved by the FDA. A ten year exclusivity period, like that currently exists in Europe, would help balance innovation incentives and price competition when instituting a new regulatory pathway for biologicals.

A significant data exclusivity period is also important in terms of encouraging investment in new indications for approved biologics. New indications for approved medicines have led to important advances in several disease areas, including cancer and other life-threatening diseases. If a product is subject to patent challenges and follow-on entry very early in its product life cycle, then innovative firms will have much less economic

incentive to invest in the costly and risky process to gain approval for these new indications.

SUMMARY

It is hard to think of many activities that have the potential to increase human welfare more than new biological entities, from both a preventive and therapeutic standpoint. Over the coming decades, biopharmaceutical innovation can truly revolutionize health care and the treatment of many life-threatening and disabling diseases. But the resulting advances could also exacerbate budgetary pressures for Medicare and other payors. In establishing a new regulatory pathway for follow-on biologics, it will fall to Congress and the FDA to balance the objectives of innovation incentives, patient safety, and price competition as was the case when Congress created the Hatch-Waxman program more than two decades ago.

In crafting this legislation it is important that Congress recognizes the significant differences between generic drugs and follow-on biologicals that will affect how the market evolves from an economic perspective. Over the ten year budgetary scoring period, it is reasonable to expect modest cost savings, given the higher cost of entry and demand side constraints affecting follow-on biologics.

Since this legislation will essentially define the terms of competition between innovators and imitators for decades to come, it is critical that it maintain strong incentives for R&D investment in new biopharmaceutical medicines. A data exclusivity period of at least ten years in length would recognize the high costs and risks of developing new biological entities, and deter patent challenges from occurring until a more mature phase of the product life cycle. This would also preserve incentives for the development of new indications, and harmonize United States law with that of the European Union.