Data Exclusivity Periods and Next Generation Improvements to Innovator Biologics: Key Issues

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I. Introduction

Context and Study Objectives

Congress is considering various legislative proposals to establish an abbreviated regulatory approval pathway for biosimilar versions of branded biologics, and continues to debate the issue.[1] In the United States, market entry for most biologics is regulated through the Public Health Service Act (PHS Act). At present, the PHS Act does not include an abbreviated pathway for biosimilars analogous to that which exists for generic drug entry for chemical entities through the 1984 *Drug Price Competition and Patent Term Restoration Act* (Hatch-Waxman Act). An abbreviated filing pathway would allow imitators to rely on the Food and Drug Administration (FDA) findings regarding safety and efficacy data submitted by the innovator for the reference drug in order to encourage lower cost entry and increase price competition. In designing the provisions of an abbreviated biosimilar approval pathway, Congress and FDA should balance the dual objectives of potential cost savings from biosimilar entry with continued strong incentives for investment in the development of novel biologic therapies.

A critical dimension of any biosimilar legislative proposal, and one of the most contentious issues being debated, is the duration and coverage of the data exclusivity period for a

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[1] Terminology for proposed abbreviated pathway biologics is evolving, and they are sometimes referred to in the literature as "biosimilars," "biogenerics," and "follow-on biologics" (FOBs). In this paper, we use the terms "biosimilars" and "follow-on biologics" interchangeably to mean biologic products introduced by other manufacturers that are similar enough to previously approved reference products according to FDA guidelines and the scientific evidence submitted that the safety and efficacy data for the reference product may be considered by the FDA in approving an abbreviated regulatory filing. In contrast, the term "biogenerics" suggests that a fully identical, AP-rated version of a biologic is currently possible. In a November, 2008 presentation to the Federal Trade Commission, Dr. Rachel Behrman, Associate Commissioner for Clinical Programs and Director of the Office of Critical Path Programs at the FDA stated that "[i]n most cases, at this time it will be impossible to establish that active ingredients are identical for follow-on biologics," (http://www.ftc.gov/bc/workshops/hcbio/docs/fob/rbehrman.pdf. Because the anticipated standard for FDA approval will be *similarity* rather than *identity*, the authors reject the use of the term "biogenerics."

novel biologic. Data exclusivity is the period of time between FDA approval of an innovator drug and the point at which an abbreviated filing for a biosimilar relying in whole or in part on the innovator's data on safety and efficacy can receive final marketing approval. It is an important form of protection for innovative pharmaceuticals and runs independently, but generally concurrently, with patent protection, beginning with the date of FDA marketing approval.[2] Data exclusivity is designed to preserve innovation incentives, and recognizes the significant investment required to finance the long and risky development process necessary to demonstrate a product's safety and efficacy and gain FDA marketing approval. The need for protection to safeguard the value of these investments in extensive clinical and other data developed in the course of the approval process is unique to products that need to obtain pre-market approval from a federal agency before launch, and in which other protections would be insufficient to maintain investment incentives.

Recent discussions have addressed several aspects of data exclusivity periods for biologics:

- The ***base level of data exclusivity*** applied to a new molecule, and whether the same base data exclusivity period should apply to all innovator firms' new biologic molecules, regardless of how closely related chemically they are to previously approved biologics (i.e., whether or not they are first or "next generation molecules").[3]
- The appropriate duration of ***extensions to the base data exclusivity period for new indications*** or other supplemental applications containing significant new clinical information; and

[2] Data exclusivity protection is sometimes referred to as "innovator exclusivity," in order to clearly distinguish it from the use of the term "market exclusivity", which some commentators define to encompass the 180-day period that first generic entrants enjoy under Hatch-Waxman.

[3] In this paper, we define "next generation molecules" as products that are closely related chemically to an earlier generation biologic produced by the same manufacturer, and might be marketed either as improvements to existing brands or as entirely new brands. An alternative definition used by others includes any new biologic product that is closely related to an earlier generation biologic product regardless of the manufacturer.

- The appropriate duration of other ***extensions to the base data exclusivity period for pediatric studies and orphan drug considerations***.

This paper outlines some economic considerations relevant to data exclusivity, focusing on the first of these questions, with the aim of informing policy makers in their continuing deliberations of this critical issue.

Clarifying Some Mischaracterizations

Some recent analyses mischaracterize next generation biologic molecules as a means of extending "monopoly" protection on existing biologics, and rely on this mischaracterization to support very limited, or no, data exclusivity periods for next generation molecules. This characterization is flawed for several reasons:

(1) ***It is incorrect to equate data exclusivity with monopoly protection.*** All biologic products are potentially subject to competition from therapeutic alternatives, and many face vigorous branded competition today, regardless of data exclusivity protections. In addition, data exclusivity does not prevent a potential competitor from entering the market with a complete application based on its own dossier of safety and efficacy data, without reference to the data developed by another. For example, in the case of the human growth hormone market, five out of six competing manufacturers producing somatropin-based human growth hormones received product approvals through full New Drug Applications (NDAs). Novartis's Omnitrope is the only drug that did not receive approval through a full NDA, and instead entered the market through an abbreviated process under Section 505(b)(2).

(2) ***Data exclusivity for a next generation improved biologic new molecule has no effect on FDA review and approval for a biosimilar of a preceding generation biologic (i.e., next generation biologic data exclusivity does not extend to the safety and efficacy data used in***

approval of the preceding generation biologic). An abbreviated pathway for biosimilar approval remains available for the preceding generation biologic.

(3) ***Next generation improved biologic new molecules will compete successfully with preceding generation biologics (including lesser-priced biosimilars) when they offer improvements in safety, efficacy, or convenience that are valued by physicians, patients, and payers and as such are valuable advances that should be encouraged.*** Demand for next generation new biologic molecules is determined by physician and patient demand for the benefit of these therapies, in comparison with alternative therapies (including future, presumably less expensive, biosimilar therapies with lower patient out-of-pocket costs), as well as payer pushback in the form of formulary, benefit and patient cost-sharing design features and utilization management techniques. Next generation new biologic molecules that do not offer significant improved benefits for patients and physicians will increasingly find their market shares limited by the normal competitive process. If next generation biologics offer no improvement over equally beneficial but less expensive alternatives, lack of demand and controls exerted by payers to encourage use of the less expensive alternatives will limit sales. Conversely, next generation new biologic molecules that offer significant improved benefits over existing therapies are likely to gain substantial market share from first-generation biologics, thereby reducing the size of the market available to biosimilars on those first-generation biologics. Policy makers should therefore focus on maximizing benefits to patients, including both price competition from biosimilars to existing products and value competition from newer next generation biologics, and not focus solely on maximizing sales of biosimilars per se.

(4) ***Next generation molecules are likely to require long, costly, and risky investments that would in many cases not be profitable, and therefore some next generation***

molecules may not be developed, in the absence of adequate innovation protections such as those offered by data exclusivity. As a result, data exclusivity for next generation improved new molecules is necessary to encourage investment in innovative advances for patients, as is the case for first-generation innovative biologics.

In addition, there is a fifth economic consideration that suggests limited, or no, data exclusivity period for next generation new molecules is problematic:

(5) ***Implementation of any "two-tiered" data exclusivity framework, where less, or no, data protection is extended to next generation new molecules than to first-generation molecules must consider the potential for inefficient distortions in investment incentives that would be created, as well as the practicality of such an approach.*** Determining whether or not a molecule constitutes a next generation or first generation molecule may require difficult subjective judgments, i.e., it will be necessary to determine *ex ante* the extent of differentiation in chemical structure required to designate a molecule as a first generation molecule, independent of the clinical significance of that difference or when the clinical significance of the difference may not be known.. Even greater degrees of subjective judgment and uncertainty are introduced if the determination is based not only on the degree of difference in chemical structure, but also based on differences in patient treatment outcomes or potential clinical impact, which may further be dependent on the population or sub-group studied. In many cases, the ultimate clinical impact would only be observable after launch, with potentially long delays until sufficient clinical experience has been gained or post-approval clinical studies have been completed. In contrast, a distinction based on whether or not a full BLA was filed would provide a clear "bright line" definition.

The level of data exclusivity could also depend on which manufacturer produces the molecule (assuming non-infringement of any process patents) and whether or not that manufacturer also produced the first-generation molecule.[4] If different data exclusivity periods were implemented for first- and next generation biologic molecules, then investment incentives may be inefficiently reduced due to uncertainty during the research and development process as to which data exclusivity period will ultimately apply to the resulting product; or investment may be inefficiently distorted to pursue products more likely to be classified as first-generation molecules (even if they are of lesser clinical value) in order to increase the likelihood of obtaining a longer data exclusivity period.

Conclusion

While the creation of an abbreviated biosimilar approval pathway is a desirable policy, it is important that it not deter innovation and the development of valuable new biologic therapies. The U.S. biopharmaceutical industry has been a global leader in biologic advances for more than two decades. Substantial new investment is necessary to maintain U.S. status as the leader in worldwide biologic development and a source of valuable new treatments for patients. In this respect, the potential cost savings from biosimilar entry must be balanced with continued incentives to invest in the development of new biologics, including next generation, improved new biologic molecules. From a public benefits perspective, the data exclusivity period should

[4] Alternatively, the determination of next-generation molecule status could be made independent of manufacturer (i.e., if any manufacturer's new biologic molecule has a similar chemical structure to any other manufacturer's existing biologics, then it would be classified as a next generation molecule). Under this alternative definition, a two-tiered data exclusivity approach could negatively impact competition and the number of new molecules launched. Where manufacturers are simultaneously advancing uncertain development programs in the same therapeutic area, they compete to be the first to gain FDA approval and to be the first-to-market their version of the therapy. With a two-tiered data exclusivity approach, if a manufacturer falls behind in the "development race", the possibility of receiving a shorter data exclusivity period would be a further investment disincentive, and could lead to abandonment of the development program. This would reduce treatment options for patients and reduce brand-brand competition.

be long enough to encourage the development of new biologics, but not so long that it unnecessarily delays the entry of biosimilars and their associated potential cost savings.

An appropriate data exclusivity period for next generation biologics is necessary to maintain investment incentives and to continue to make new and improved therapies available to patients. The length of the data exclusivity period should, therefore, reflect the significant costs of developing next generation molecules and the risks that many research ventures will fail in development. Even those next generation molecules that advance to launch will face greater commercial challenges in the future as the entry of potentially lower-priced biosimilars for the first-generation biologic molecule become possible and more prevalent. Third-party payers already exert access and utilization restrictions on biologics, and are likely to implement stronger control and influence over biologic choice in the future, particularly as biosimilars become available. Increasingly, payers will require that next generation biologic new molecules demonstrate significant advances for physicians and patients to justify any cost differences relative to first-generation and biosimilar products.

Successful next generation biologic new molecules may generate high levels of sales, and these sales may in part reflect lower sales for first-generation products and smaller market potential for biosimilars. In these cases, the potentially smaller market for first-generation products, and therefore for biosimilars, may limit potential payer cost savings from biosimilar entry. At the same time, however, patient benefits from improved therapies in cancer, autoimmune disease, and other areas with substantial remaining unmet medical need would be significant.

The remainder of this paper is organized as follows:

- **Section II** defines what is meant by a next generation biologic molecule and characterizes improvements into three broad classes (new indications, new forms of administration, and changes in molecular structure);
- **Section III** discusses the importance of data exclusivity to biologics generally, including why patents alone may be insufficient to provide protection and incentives for biologics;
- **Section IV** describes the potential research and development activities associated with bringing a next generation biologic new molecule to market;
- **Section V** reviews the dynamic nature of competition and research in biologic markets;
- **Section VI** discusses the incentives for bringing next generation biologic new molecules to market, the fact that the extent of commercial success will reflect the level of improvements offered in a given therapeutic area, and the potential for successful next generation new molecules to improve patient welfare;
- **Section VII** provides a qualitative assessment of appropriate data exclusivity periods for next generation biologic molecules; and
- **Section VIII** summarizes our conclusions.

II. What Are Next Generation Molecules?

Improvements to existing biologic products can take many forms, often reflecting investment costs and risks consistent with the development of an entirely new biologic. To clarify the analysis and discussion of the appropriate data exclusivity treatment of next generation molecules, we identify and consider three broad classes of biologic improvements:

(1) A ***new indication*** for an existing biologic product, which would involve clinical trials in new patient populations.[5]

(2) A ***new form of administration*** of the same product (e.g., intravenous, subcutaneous, pen, inhalation).

(3) A ***change in molecular structure*** of the previous generation biologic (i.e., changes to the molecule such as pegylation and glycosolation, with the aim of improving some efficacy, safety, or patient convenience performance characteristic such as the release profile over time).

Table 1 summarizes the three categories of biologic improvements, identifies the potential FDA requirements for marketing approval based on the type of improvement, and summarizes how the current bills for an abbreviated pathway for biosimilar entry treat these improvements with respect to data exclusivity periods. Following the practice with small molecule drugs regulated under Hatch-Waxman, improvements might receive additional data protection and economic incentives under the law, in order to recognize the investments required and to provide incentives for further therapeutic improvements that benefit patients. For instance, under current law, small molecule drugs receive three years of data exclusivity for any supplemental application containing new clinical investigations (other than bioavailability

[5] This may also include other label changes besides new indications, such as significant changes in dosage strength either in connection with a new indicated use, or an existing indication.

studies) essential to approval of the application. The three years of data exclusivity is only applied to the subject matter of the supplemental application (e.g., the specific new indication or new form of administration supported by the application), and begins at the time of approval of the supplemental application. In addition, small molecule drugs receive six months of data exclusivity for clinical evidence related to pediatric use. Several proposed biosimilar bills also recognize the need to extend data exclusivity to some of these situations. Depending on the bill, they provide for a one-time extension of 3 months to 2 years of additional data exclusivity for significant new indications requiring clinical evidence for approval, and 6 months for evidence related to pediatric use.[6]

Some recent discussions of data exclusivity periods and biologic improvements have mistakenly trivialized the nature of biologic improvements. For example, in an unpublished white paper, Kotlikoff (2008) argues that data exclusivity will lead to "evergreening" as innovators "stack" exclusivity terms by gaming the system with minor changes, such as the introduction of new dosage strengths.[7] As noted above, some of the bills allow for a one-time limited extension in data exclusivity for significant new indications or pediatric evidence, however none of the proposed bills provide additional data exclusivity for minor changes such as new dosage strengths. Data exclusivity extensions are an incentive mechanism to encourage further significant research and development ("R&D") investment on beneficial new uses for patients. Post-launch R&D plays an important role in extending the clinical evidence on biologics, as is evident by the fact that approximately half of the biologics licensed by the FDA between 1986 and 2006 experienced at least one post-launch additional FDA-approved

[6] Biosimilar legislation in Europe also provides for data exclusivity extensions related to significant new indications, with the EMEA extending the data exclusivity period by one year for new indications.
[7] Kotlikoff, L., "Stimulating Innovation in the Biologics Industry: A Balanced Approach to Marketing Exclusivity," unpublished manuscript, September 2008.

indication.[8] None of the bills in Congress would lead to "evergreening" in the manner alleged by Kotlikoff.

A final consideration in the appropriate framework for innovation incentives and intellectual property protections for biologics is that patients using biologic therapies typically suffer from very serious illnesses with substantial unmet need based on currently available therapies (e.g., cancer, hepatitis C, autoimmune disorders, multiple sclerosis). As a result of the extensive unmet patient needs in the disease states targeted by biologics, there exist significant opportunities for improvements to current-generation biologics to substantially enhance clinical effectiveness for those patient populations. Data exclusivity for next generation biologics is an important component of maintaining investment incentives to develop these valuable and necessary improvements.

This paper focuses on data exclusivity periods for the third category of improvements listed above, a change in molecular structure. Changes in molecular structure can have a significant impact on the action of the biologic within the body, and hence its safety, clinical effectiveness and value. As a result, products representing changes in molecular structure to previous generation biologics have historically generally required a full Biologic Licensing Application (BLA) to gain FDA approval, including substantial data from pre-clinical and clinical trials, with the sponsoring company performing a full battery of clinical tests.[9]

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[8] Said, M., Brouwers, C, and Tollman, P., "Continued Development of Approved Biological Drugs: A Quantitative Study of Additional Indications Approved Postlaunch in the United States," Boston Consulting Group, White Paper, December 2007.

[9] In some cases, the second category of improvements, changes in route or form of administration, may require a full BLA, with a correspondingly high level of investment in pre-clinical and clinical evidence. For example, a significant change in the form of administration, such as inhaled versions of a biologic (e.g., inhaled insulin) or an as yet undeveloped oral form of administration, resulting in substantial changes to the drug's safety/efficacy profile, would also require a complete BLA. Recent experience with inhaled insulin suggests that substantial and new changes in delivery mechanism may result in potential safety concerns, and therefore that significant clinical trial investments would be necessary for FDA approval. The first category of improvement, new indications, does not involve a modification to the molecule itself and, in the past, has required only a supplemental BLA. In either case,

An important "bright line" distinction exists between biologics approved through full BLAs and those approved through supplemental BLAs, with those approved through full BLAs typically facing higher expected approval costs, along with greater risks of failure. However, within those biologics approved through a full BLA there may be quite severe science and regulatory obstacles to developing a practical definition of exactly what constitutes a "next generation" product.

For purposes of illustration, Table 2 contains a list of some biologic therapies that reflect changes in molecular changes relative to an earlier generation drugs.[10] A number of different types emerge:

- ***Pegylation and other protein optimization techniques:*** In a number of cases, the molecular change is related to offering a longer-acting therapy compared to the previous generation biologic. One route to achieve improvements in release profile, half-life, and frequency of dosing and other features is through pegylation (the addition of a polyethylene glycol molecule(s)) of the previous generation biologic, such as in the case of Neulasta, allowing for fewer administrations as compared to the previous product Neupogen. PegIntron and Pegasys are other examples of pegylation of an existing molecule leading to next generation biologics. In all of these cases, pegylation led to the creation of a substantially new molecule and a full BLA was required for approval. While historically most proteins have been developed for immediate release, more sustained release biologics are in development and biotech

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the application would include clinical evidence regarding the safety and efficacy of the therapy in a new group of patients or for a new disease condition.

[10] In addition to the therapies reflected in Table 2, next generation biologics also include vaccines and biologics where the improvement is through the replacement of live cell product with recombinant DNA with the aim of reducing impurities and risk of infectious disease transmission (e.g., Kogenate compared to Koate, or Cerezyme compared to Ceredase). Data limitations in identifying all prior generation live cell products resulted in omitting these clinically important improvements from Table 2.

companies are investigating technologies to optimize the performance of their products, in order to improve safety, reduce immunogenicity and adverse events, and improve release and dosing profiles. Similarly, the introduction of basal insulin products, such as Levemir, allowed for once-daily insulin treatment for some patients with diabetes, not available through the previous-generation biologic, Novolin.

- ***Substitution of synthetic/recombinant proteins for naturally occurring proteins:*** Other examples of existing next generation biologic molecules include products that rely on a reduced level, or total elimination, of human and animal albumin, in order to increasing the level of safety and reducing immunogenicity-related adverse events as a result (e.g., insulin and blood factor products). Risk of immunogenic reactions has been reduced by substituting fully human recombinant antibodies.
- ***Biologic combinations:*** Table 2 also includes some combination therapies (e.g., Rebetron) and other molecular modifications.

As the biologics industry matures, the extent and nature of molecular modifications aimed at improving product attributes is likely to expand considerably. Section IV provides some example brief case studies of the advancements of treatment therapies and dynamic competition in the markets for insulin, TNF-inhibitors, and oncology biologics.

The innovator faces substantial costs and risks in terms of FDA approval and market acceptance for next generation biologics. If successful, changes in molecular structure can potentially result in significant improvements in patient treatment in terms of efficacy, safety, and convenience. Without a data exclusivity period for these types of next generation biologics, such costly and risky investments might not be made.

III. The Importance of Data Exclusivity to Biologics

Data exclusivity is a critical issue for the future of biologics, with different provisions for data exclusivity in recent legislative proposals ranging from 3 to 14 years. The Inslee (H.R. 1956) and Gregg (S. 1505) bills submitted in 2007 in the House and Senate, respectively, provide for fourteen years of effective data exclusivity (both permit biosimilar applications to be submitted twelve years after innovator approval). The Eshoo-Inslee-Barton bill (H.R. 1548)[11] submitted in 2009 and the Kennedy (S. 1695) bill submitted in 2007 allow for twelve years of effective data exclusivity (both permit biosimilar applications to be submitted four years after innovator approval). By contrast, the Waxman biologics bill in the House (H.R. 1427) and the Schumer bill in the Senate (S. 726) provide only 5 years of data exclusivity for some biologics and only 3 years for others.[12]

Patent protection and data exclusivity provide important intellectual property protections and incentives to maintain investment in new biologic innovations. The importance of patent and data exclusivity protection to maintaining investment incentives further depends on the speed and extent to which imitator products would divert sales from the innovative biologics, and thus erode the capacity of innovators to recover the uncertain and significant costs of developing new therapies. Data exclusivity periods are essential to compensate for some important limitations in patent protection for pharmaceuticals. Recent research presents a

[11] H.R. 1548 supersedes an earlier bill submitted by Eshoo and Barton in 2007 (H.R. 5629) that had similar data exclusivity provisions.

[12] Under H.R. 1427 and S. 726, a biologic receives 5 years of data exclusivity if it is determined, among other things, that "no major substance of the product, nor highly similar major substance, has been approved in any other application," that the application "did not rely on any clinical safety, purity, or potency study in any other [previously approved] application," and that it does not fall into any of several excluded categories. If the biologic does not qualify for 5 years of data exclusivity it could qualify for 3 years if it is determined, among other things, that the application "contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic studies) essential to approval," and if "the product represents a significant therapeutic advance." H.R. 1427 supersedes an earlier bill submitted by Representative Waxman (H.R. 1038) that did not contain a provision for a data exclusivity period.

structured model incorporating historical revenue and R&D cost data to help guide the analysis of the effects of different data exclusivity periods on the incentives faced by biotech investors (whether existing firms or venture-backed investors). Original model results appeared in *Nature Reviews Drug Discovery*, (Grabowski, 2008, henceforth referred to as the *Nature* article)[13], and were modified to explicitly consider entry by biosimilars in a Duke University Economics Department working paper "Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques" (Grabowski et al., 2008, henceforth referred to as the *Biosimilar Entry* paper).[14] Both papers present evidence supporting a data exclusivity period of between twelve and sixteen years, given a plausible set of input values on the economic factors affecting investment returns for biologics.

These findings reflect the distinctive economic characteristics of biologic drug development. For example, biologics require substantially more up-front investment in process engineering and manufacturing know-how than small-molecule drugs, while taking longer to develop. A substantial portion of the development of new biologics is also undertaken by venture-backed, research-oriented companies with no currently marketed products. These companies rely on funds from many sources at a high implied cost of capital. The funding of biologic drug development in these companies is very sensitive to expected risks and returns, and the risks associated with the adoption of a very short data exclusivity period may have a strong impact on these investment incentives. Authors advocating for significantly shorter periods fail

[13] Grabowski, H., "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Reviews Drug Discovery*, 7, 479 – 488 (2008).
[14] Grabowski, H,. Long, G., Mortimer, R., "Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques," Duke University Economics Department Whitepaper, No. 2008-10, December 22, 2008, available at http://www.econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf.

to take into account the unique economic characteristics of biologic drug development, discussed further below.[15,16]

Data exclusivity extends from the date of product approval, and this protection period runs independently, but generally concurrently, with any remaining patent term protection for the biologic. That is to say, data exclusivity provides additional protection to the innovator only to the extent that the patent is circumvented by a biosimilar, or that the remaining patent length is shorter than the data exclusivity period at the time of approval. For the reasons described below, patent protection alone is likely to be insufficient for biologics, thus increasing the importance of data exclusivity periods in ensuring that appropriate incentives exist for biotechnology investments.

Although each case exhibits a unique set of facts, it is generally believed that patents protecting biologics (particularly those representative of patents likely to protect biologics approved in the future) may be more susceptible to circumvention than traditional small-molecule drug patents for two primary reasons:

(1) Patent portfolios for biologics, in comparison with those for small molecule drugs, are often much more complex, and the patents protecting biologics tend to focus on very specific aspects of the protein or ways of producing the protein rather than on protecting the entire molecule or class of related molecular structures. While there is case-by-case variation

[15] For instance, Kotlikoff (2008) argues that a five year data exclusivity period has provided sufficient incentives for investment in the development of small molecule drugs, and mistakenly postulates that biologics are similar enough in terms of the economics of drug development so that five years should be sufficient for biologics as well. In fact, the minimum data exclusivity period for most small molecules takes into account stays on generic entry of two-and-a-half years when there are patent challenges in process, and is therefore actually seven-and-a-half years, rather than five years. More importantly, current rates of new product introductions have been sustained by de facto market exclusivity periods (i.e., the period between product launch and the first sale of a generic product) substantially longer than five years. The actual market exclusivity period for small molecules averages around twelve years.

[16] Similarly, in another unpublished white paper, Brill (2008) argues that the investment returns model developed in the *Nature* article can support a seven year data exclusivity period under alternative input values and assumptions. However, the *Biosimilar Entry* paper extends the original Nature analysis and corrects for certain problems in the Brill analysis, and confirms that under a broad range of economic scenarios, a data exclusivity period of twelve years or more for biologics may be necessary to make R&D investment attractive from a risk-return point of view.

and there are also some very broad patent portfolios and methods in the area, Manheim, Granahan, and Dow (2006) noted that, "because the number and types of biotech patents issued through the 1990s grew explosively, the scope of claims in patents covering recombinant protein products has generally become more narrowly drawn."[17] As noted by legal scholars, the greater reliance on process, rather than product, patents can create challenges: "The practical differences between product and process patents also routinely present vexing operational problems in terms of policing and enforcing the patent. Innovators have long preferred product protection to process protection due to such impediments. It is relatively simple to detect the unauthorized sale or presence of a patented product in the marketplace or to interdict such a product at the border. It is far more difficult to determine whether a particular product has been produced by the unauthorized practice of a patented process, or whether a patented process is otherwise in hidden use in a manufacturing facility."[18] When combined with evolving jurisprudence in the area, biologics innovators may face significant uncertainty regarding the likely degree of patent protection, which affects the risk profile associated with biotech investments.

(2) The standard for FDA approval of biosimilars is likely to be based on *similarity* rather than *sameness*, allowing for greater differences between the biosimilar and the reference product than are allowed between an AB-rated generic small-molecule drug and its reference product. As a result, development of a biosimilar may allow for greater deviations from the production process of the reference product, and greater opportunity to deviate slightly from the patented technology, thereby sidestepping patent infringement while still benefiting from an abbreviated FDA application process. Manheim, Granahan, and Dow (2006) suggest that the

[17] Manheim, B., Granahan, P., Dow, K., "'Follow-On Biologics': Ensuring Continued Innovation In The Biotechnology Industry," *Health Affairs*, Vol. 25 no. 2, pp. 394-404, (2006).
[18] Burk, D., "The Problem of Process in Biotechnology," *Houston Law Review*, Vol. 43, p. 561, (2006).

nature of biologic patents facilitates the potential ability of biosimilars to "innovate around" the innovator's patents.[19]

Data exclusivity provides investors with "insurance" against potential limitations on patent protection for biologics. To maintain incentives for investors to invest in the R&D process for new biologics, the anticipated discounted value of the future stream of profits must be sufficient to cover the cost of the initial R&D investment. If the future stream of discounted profits is insufficient, then the investment will not occur, and the potential new biologic will not be developed. As noted earlier, previous research (Grabowski, 2008; Grabowski et al., 2008) finds that data exclusivity periods of 12 to 16 years are necessary to maintain investment in new innovative biologics, based on a range of reasonable assumptions regarding the discounted present value of R&D costs, revenues for new innovative biologics, margins earned for new innovative biologics, and the price and share impacts of biosimilar entry. The portfolio of biologics relied upon to establish the cost and revenue assumptions in the *Nature* and *Biosimilar Entry* articles does not distinguish between first generation biologics and next generation improved biologics, as data are not available on their relative costs and probabilities of success. As discussed in Section IV, the costs and risks of developing next generation new biologic molecules may be substantial.

In addition to these results based on estimates for biologic R&D costs and margins, reported in the *Nature* and *Biosimilar Entry* articles, a 12 to 16 year data exclusivity period can be further benchmarked against recent evidence indicating that for small molecule drugs the time

[19] Manhiem, Granahan, and Dow cite Synagis (palivizumab), and Rituxan (rituximab) as examples of biologics that are protected, at least in part, by relatively narrow patents. The authors state that in the case of Synagis, the patent claim requires an infringing antibody to bind to the same specific binding site, or epitope, as the Synagis antibody; while in the case of Rituxan, the patent identified by the authors claims the use of a particular deposited cell line.

between launch and first generic entry is approximately 12 years on average.[20] Data exclusivity for small-molecule drugs is generally not the constraint on generic entry, whereas it is expected to be more determinative for biologics due to the differences in patent protection noted above. Hence, longer data exclusivity periods may be required in order to achieve a similar 12 year *effective patent life*, or the marketing period prior to biosimilar entry during which branded products can earn a sufficient return to cover investment costs and contribute to financing the many expensive development "dead ends," as discussed in Section IV.

To the degree that the patents protecting next generation biologics are limited as compared to those for first generation biologics, encouraging innovation through next generation changes in molecular structure that provide substantial advancement in patient care will depend even more heavily on a data exclusivity period.

[20] Grabowski, H. and Kyle, M., "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics*, 28: 491-502 (2007). For new molecular entities (NMEs) first experiencing generic entry in 2005, the most recent year analyzed in the Grabowski and Kyle paper, an average market exclusivity period of 13.1 years for all NMEs and 11.5 years for NMEs with brand sales greater than $100 million in the year prior to generic entry is calculated.

IV. Costs and Development of Next Generation Biologic Molecules

Previous analysis by the author(s) (in the *Nature* article and the *Biosimilar Entry* paper) propose that an appropriate framework for evaluating the impact of data exclusivity periods on investment incentives adopts the perspective of a potential investor weighing a portfolio of alternative investments, together with their expected risks, costs and returns. Under this framework, the data exclusivity period should be long enough to allow for a representative investment in the development of a biologic to cover the expected R&D, sales and marketing costs, together with the cost of capital in making these investments. Based on reasonable estimates of R&D and marketing costs, risks, cost of capital and subsequent revenue streams for development of a new biologic, these papers find that data exclusivity periods of 12 to 16 years are necessary to result in reasonable breakeven times for the representative portfolio of biologics (not distinguishing between first generation biologics and next generation molecules).

These models assume a capitalized cost for a representative new biologic entity of in excess of $1.2 billion, based on research by DiMasi and Grabowski (2007), with roughly half attributable to the pre-clinical stage of biologic development and half to the clinical stage.[21]

Average development cost and risk for a typical next generation molecule may be less than for a typical new first-generation molecule; however, there is insufficient data available to compare the two directly or to estimate average development costs for existing next generation molecules.[22] Information is also insufficient to estimate how development costs for possible

[21] DiMasi, J., and Grabowski, H., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, Vol. 28, Issue 4-5, pp. 469-479.

[22] While the data are not available to compare average development and approval costs for first and next generation biologics, next generation molecules are subjected to similar requirements for approval. Approval of next generation molecules depends on a complete data submission with the FDA independent of any data submitted for previous generation products, and representing preclinical and clinical studies along with separate manufacturing data.

future next generation molecules might differ from development costs for current or past next generation molecules.

While systematic information is not available, a review of development histories for selected next generation molecules suggests that the drug development programs for next generation molecules can be extensive, and cover many years. For example, Amgen's development of Aranesp (a next generation erythropoietin, or "EPO" biologic)[23] began over a decade prior to FDA approval, with basic research aimed at identifying the relationship between the carbohydrate structure and the in vivo activity of EPO.[24] Aranesp differs from first generation EPO biologics in that it contains 5 N-linked oligosaccharide chains rather than 3 chains. It was developed with the intention of increasing potency and providing an extended duration of action as compared to EPO, and is typically administered in fewer and less frequent injections than EPO. The development process required basic research aimed at supporting the hypothesis that increasing the number of N-linked chains would affect the dosing and serum half-life levels for EPO, including extensive animal studies in the early 1990s. Pharmacokinetic studies in humans were initiated in late 1996, and the studies included over 700 patients. Extensive clinical studies of efficacy and safety for use of Aranesp in patients with chronic renal failure and for patients receiving chemotherapy treatments were conducted for FDA approval. Seven clinical studies are included on the FDA label for Aranesp, and in total included approximately 2,500 patients. FDA approval was granted in September 2001.

Significant pharmacokinetic and clinical studies are described on the FDA labels of many next generation molecules, sometimes comparable to those undertaken for first generation

[23] First-generation EPO biologics include the brand drugs Epogen (Amgen) and Procrit (Johnson & Johnson), both of which are recombinant human EPO ("rHuEPO").
[24] Macdougall, I., "Darbepoetin Alfa: A New Therapeutic Agent for Renal Anemia," *Kidney International*, 61 (2002); and, Egrie, J., and Browne, J., "Development and Characterization of Novel Erythropoiesis Stimulating Protein (NESP)," *British Journal of Cancer*, 84 (Supplement 1) (2001).

products. By way of example, the tables and descriptions below summarize the clinical studies undertaken prior to FDA approval for two biologics that represent next generation molecules, and compare these studies to their first-generation counterparts. Neulasta (pegfilgrastim) is compared to the prior-generation biologic, Neupogen (filgrastim), and PegIntron (peginterferon alpha-2b) is compared to the prior-generation biologic, Intron A (interferon alpha-2b). Both Neulasta and PegIntron differ from their preceding generation biologics by incorporating a polyethylene glycol (PEG) molecule. The incorporation of the PEG molecule allows for the next generation biologic to be administered less frequently than the preceding generation.

	Neulasta **Next Generation Biologic**	**Neupogen** **First-Generation Biologic**
Number of Phase I, II, and III Clinical Trials	• Approximately 6 clinical trials -- label identifies 3 Phase III clinical trials, and the literature reflects at least an additional 3 Phase I and II clinical trials. *	• The FDA label identifies a total of 10 Phase I, II, and III clinical trials.
Total Number of Patients	• Approximately 1,400 patients (Phase III trials only)	• Over 1,200 patients (Phase I, II, and III trials)

* Source: PharmaProjects longitudinal data.

The FDA approved label for Neulasta indicates that pharmacokinetic studies were conducted involving hundreds of patients, and summarizes three Phase III clinical studies. The Phase III clinical studies were a mix of placebo-controlled studies and comparison studies between Neulasta and the prior generation biologic, filgrastim (Neupogen). In total, the three clinical studies included approximately 1,400 patients. In addition to the Phase III clinical

studies summarized on Neulasta's FDA approved label, there were at least three Phase I and Phase II trials, for a total of at least six Phase I, II, and III trials prior to FDA approval of Neulasta. By comparison, Neuopogen had approximately ten clinical trials (Phase I, II and III) prior to FDA approval that included a total of over 1,200 patients.

	PegIntron **Next Generation Biologic**	**Intron A** **First-Generation Biologic**
Number of Phase I, II, and III Clinical Trials	• 4 Phase III clinical trials for chronic hepatitis C • The trials ranged in duration from 6 months to 24 months	• 5 Phase III clinical trials for chronic hepatitis C • The trials ranged in duration from 6 months to 24 months
Total Number of Patients	• Over 7,500 patients	• Not available

The FDA-approved label for PegIntron, a pegylated version of interferon alpha-2b (Intron A), for the treatment of chronic hepatitis C, includes a summary of four Phase III clinical studies.[25] In the aggregate, the studies include over 7,500 patients and follow patients for between six months to two years. By comparison, the FDA-approved label for Intron A, describes five Phase III clinical trials for chronic hepatitis C, following patients for between six months and two years.[26]

Development of next generation molecules not only requires substantial investments, but also faces the risks of negative results. While the focus of this paper is on changes to molecular structure -- investments that are expected to carry substantially more risk than the pursuit of new indications for existing biologics -- it is useful to note that even with respect to new indications

[25] The clinical studies cover both monotherapy use of PegIntron and combination use of PegIntron and Rebetol.
[26] The number of patients included in the Intron A clinical studies is not available. Intron A is approved for several indications in addition to hepatitis C, and those additional indications required other clinical studies.

there is a significant chance of failure to obtain FDA approval. A recent survey analyzes FDA approvals and Phase III failures in the two-year period between January 2006 and December 2007. A failure is defined in this survey as a setback resulting from an FDA decision that can delay or cause a project's termination. This survey indicated that there were 17 Phase III failures associated with "line extension" applications (i.e., those submitted for new indications of drugs already approved) submitted by biotech companies or by biotech-pharma alliances, in comparison with 23 FDA approvals.[27] In comparison, for novel drugs and new chemical structures the corresponding figures were 47 Phase III failures and 14 approvals. Phase III failures represents a significant commercial risk.

For example, the TNF-inhibitor Enbrel has a number of FDA approved indications, including indications for rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. However, a clinical trial for the use of Enbrel for Crohn's disease failed to meet the study's endpoints, and Enbrel has not secured an indication for use for this disease. Crohn's disease is an FDA approved use for two other TNF-alphas, Humira and Remicade.

In addition to the risks related to FDA approval, next generation molecules also face risks in terms of market acceptance. For example, Pfizer developed Exubera, recombinant insulin that used an alternative delivery mechanism; it was inhaled rather than injected.[28] Development of

[27] Czerepak, E. and Ryser, S., "Drug Approvals and Failures: Implications for Alliances," *Nature Reviews Drug Discovery*, 7, 197-198 (2008). The survey in this paper is based on an analysis of approvals and Phase III setbacks as listed in quarterly *BioCentury* "Stock Wrap-Up" reports. The count of Phase III failures in the survey represents any FDA decision that is recorded as a setback to a Phase III trial on a quarterly basis in the *BioCentury* reports. There may be multiple Phase III failures for a given drug over the 2006 to 2007 time period of the survey, and these "failures" may be counted even if the biologic is ultimately successful in gaining FDA approval, for example based on new or modified Phase III trials. As a result, it is not appropriate to compare the count of Phase III failures to FDA approvals in order to arrive at a probability for a biologic progressing from Phase III trials to marketing approval.

[28] Exubera may not be considered a next generation biologic according to the definition used in this paper, as the prior-generation insulin products from which Exubera is derived were produced by other manufacturers. To some

Exubera was a long and costly process, but the product failed to gain market acceptance in part due to reluctance of payers to reimburse for its use, its relatively high price compared to the alternative injected recombinant insulins, and inadequate acceptance of the device features by patients. After Pfizer discontinued marketing Exubera, it was subsequently linked to a concern about increased risk of lung cancer. The potential safety issues associated with inhaled insulin underscores the fact that the FDA is likely to require extensive clinical testing to demonstrate safety and efficacy for future biologics that entail substantial changes in the form of administration.

From the perspective of an investor, the development of next generation molecules is a costly and risky investment. As a result, a data exclusivity period is an essential component of ensuring that incentives exist for investment in the development of next generation molecules. In the absence of sufficient data exclusivity periods, less investment in improvements to biologics would be undertaken, reducing the development of new therapies offering significant advances to patients.

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degree, this underscores the somewhat arbitrary nature of the distinction between same-manufacturer and other-manufacturer next generation products.

V. Biologics – Competition and Innovation

Some have mistakenly equated data exclusivity with monopoly protection or marketing exclusivity. Data exclusivity does not provide an innovator with either a monopoly or marketing exclusivity from competitors with therapeutic alternatives. Rather, data exclusivity is a more limited form of protection for innovators. As noted, it is the period of time before a biosimilar can enter the market relying on the innovator's data through an abbreviated regulatory filing pathway. Data exclusivity does not protect an innovator biologic from another firm that invests in its own clinical trials to demonstrate safety and efficacy entering the market with a biosimilar through a full BLA. In the case of human growth hormone (where products have typically received approval through NDAs), for example, there are currently six different manufacturers offering therapeutic alternatives based on the molecule somatropin, but only one manufacturer received approval for its product through an abbreviated filing (i.e., Novartis's Omnitrope, after extended litigation between Novartis and FDA).

Biologics face vigorous competition from other innovative firms with respect to the introduction of therapeutic alternatives and advances. Multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate target (e.g., a particular receptor or dysfunctional enzyme). For example, there are many targeted drugs currently in Phase II or III trials for breast cancer targeting the HER-2 receptor, and related proteins downstream from HER-2. Similar competition occurs in the TNF-inhibitors for rheumatoid arthritis and the angiogenesis-inhibiting drugs for cancer. Because the level of unmet medical need is so high in these categories, there is vigorous competition to demonstrate effectiveness that can translate into rapid changes in share of new patient prescribing behavior.

To illustrate the robust branded competition within biologic therapeutic classes, Table 3 provides a list of biologic approvals by therapeutic area, by date.[29] Even in the absence of a biosimilar pathway, biologic manufacturers have faced strong market incentives to develop new products that offer an efficacy, safety, or convenience advantage over existing therapeutic alternatives. The introduction of new biologics may target capturing sales from existing biologics produced by competing manufacturers, expanding the universe of sales by targeting new patients that are not adequately served by previous-generation biologics or other therapies, or both. The market for insulin, TNF-inhibitors, and oncology drugs all provide examples of this dynamic form of competition that characterizes biologic markets.

CASE STUDY: COMPETITION IN THE INSULIN MARKET

While human insulins have been available for many years, the introduction of fast-acting analog insulins in the mid 1990s represented major progress for diabetes patients, allowing them to take their medication as little as 10-15 minutes prior to meals. Humalog (Eli Lilly) was approved in 1996, followed by Novolog (Novo-Nordisk) in 2000 and Apidra (Sanofi-Aventis) in 2004. "Mix" products have since been introduced, combining short and long acting insulins for better management of blood glucose levels throughout the day: Humalog Mix50/50 and Mix75/25 (1999), Novolog Mix70/30 (2001) and Novolog Mix50/50 (2008).

In 2000, the launch of Lantus (Sanofi-Aventis), a long acting insulin analog, signified a next wave of product performance, as it permitted many diabetics to manage their condition with a once-daily treatment. This was achieved through mimicking the slow, steady (basal) secretion of insulin provided by the normal pancreas. Lantus has captured a significant share of the diabetes market, yet faces competition from Levemir (Novo-Nordisk), another long-acting once-daily insulin, approved in 2005. Many diabetic patients treated once-daily still need to supplement their treatment with fast-acting insulin around meal time. A search for the terms "diabetes", "basal" and "insulin" at clinicaltrials.gov yields 87 Phase III and IV trials since January 2005, suggesting a very active area of research and development.

Table 4 summarizes the competitive developments in the market for insulins since 1982.

[29] Table 3 excludes biologic approvals for purified live cell products.

CASE STUDY: COMPETITION AMONG TNF-INHIBITORS IN AUTOIMMUNE DISEASE

Enbrel (Amgen/Wyeth), Humira (Abbott), and Remicade (Centocor) are all TNF-inhibitors and compete against each other and with other therapies for the treatment of patients with various autoimmune diseases. Additional products with other modes of action also compete with these products (e.g., Orencia, Rituxan) or are under development (e.g., golimumab). Enbrel and Remicade were launched just a couple of months apart in 1998, while Humira was launched in late 2002.

Since launch, each manufacturer has invested significantly in clinical research into new indications and sub-population response, and pharmacoeconomic research into the payer and social impact of the use of these drugs. The new indications and other label changes provide physicians with substantial additional clinical evidence on the use of TNF-inhibitors in different patient populations and can lead to more effective treatment of patients suffering from autoimmune diseases. Table 5 provides a summary illustration of the timing of drug entry and the approval of new indications for each biologic. In addition to new indications, a variety of clinical and health economic data were made available through post-launch research. For example, Enbrel has been the focus of at least 10 post-approval clinical studies related to RA alone, and scores of health economic outcomes research publications.

CASE STUDY: COMPETITION IN COLORECTAL CANCER AGENTS

Avastin (Genentech), Erbitux (ImClone Systems) and Vectibix (Amgen) were originally approved for treatment of colorectal cancer (CRC). Both Avastin and Erbitux were approved in February 2004, while Vectibix was launched in September 2006. As demonstrated in Figure 1, the market for these products is large and growing. There are at least 4 additional products aiming to gain approval for use in CRC, which are currently in Phase III clinical trials: Afinitor (everolimus; Novartis), Recentin (cediranib; AstraZeneca), Sutent (sunitinib; Pfizer), and Aflibercept (VEGF-Trap; Regeneron/Sanofi-Aventis). Sutent is already approved for use in advanced renal cell carcinoma and in gastrointestinal stromal tumors, demonstrating that many of the oncology treatments have been found to be efficacious across a number of different cancers, creating an intense and dynamic competitive landscape.

Avastin and Erbitux, though originally approved for CRC, have since received approval for additional indications: Avastin for use in non-small cell lung cancer (October 2006) and breast cancer (February 2008); and Erbitux for use in certain forms of head and neck cancer (March 2006). Figure 1 suggests these new indications have contributed to their continued growth in sales. Given the unmet demand for efficacious oncology treatments, incentives are strong both for the development of new treatments, and for the extension of existing treatments to new indications.

The biotech industry embodies Schumpeter's model of dynamic competition, with innovative firm unable to simply rely on the status quo in the face of possible "game-changing" therapies developed by other competing innovative firms. Competition between innovators provides incentives for firms to continually invest in R&D aimed at improving their products. Vigorous competition spurred the R&D investment by innovative firms that has led to many therapeutic options and provided improvements in multiple therapeutic classes. There is currently a rich pipeline of product candidates in clinical testing, with over 600 biotechnology drugs currently under development in various therapeutic areas including over 250 biotechnology drugs alone under development for cancer.[30]

[30] PhRMA, "Medicines in Development," *Biotechnology 2008*.

VI. Next Generation Biologic Molecules – Market Pressure for Value

An important biotech innovation frontier is the development of next generation biologic molecules. In some cases, substantial advances in patient treatment reflect a series of underlying incremental improvements. For example, modifications to existing drugs that reduce side-effects or risks allow the therapeutic aspects of the biologic to be made available to a wider population of patients; similarly, modifications related to convenience (e.g., changes that require fewer administrations) could lead to better compliance and more effective treatment when taking "real world" considerations into account. Even changes in molecular structure that may *ex ante* appear to represent limited changes from previous-generation biologics may result in complex changes in drugs' activity, how they are metabolized, and their potential for significant changes in efficacy. As a result, it can be difficult to identify *ex ante* which improvements will prove to be the most significant contributors to patient welfare *ex post*.

As noted, the market for biologics is highly competitive, with innovators continually aiming to develop new biologics that offer advantages to patients and physician, allowing them to capture sales from existing biologics or to expand the market. The development of next generation molecules reflects this dynamic competition between biologic innovators.

Given the competitive nature of the market for biologics, next generation biologics must increasingly offer valuable therapeutic advances to be successful in the market. Entry of biosimilars may further spur the competitive incentives for innovators to develop next generation improved therapies, benefiting patients and physicians by making available new and better therapies. However, the development of valuable improvements through next generation biologics relies on the innovator being able to recoup the cost of its investment in developing the new biologic.

A. Next Generation Biologic Molecules Face Increasing Payer Pushback and Demands to Demonstrate their Value

The market potential for a next generation biologic molecule will depend on the degree of therapeutic efficacy, safety, or convenience advance that it offers patients and physicians over the existing standard of care. Next generation biologics will reflect a continuum of various degrees of improvement over first generation biologics, including significant improvements to patients, requiring substantial investments to develop and that are comparable to the investment required to develop an entirely new product. Improvements that offer limited therapeutic advantage will face obstacles to establishing more than a limited level of sales. However, those improvements that offer significant advantages may be able to gain a high level of sales, depending on the level of unmet need in the therapeutic area, the level of payer control exercised, and the cost difference over existing (first generation) therapies, among other factors.

The relatively high cost of biologic treatments means that health insurance plans have incentives to develop and implement means to control the uptake of biologics through formulary status and access restrictions where adequate therapeutic alternatives exist and a subset of therapies can be preferred. Health insurance plans will face increasing incentives to limit and manage the use of next generation molecules that fail to demonstrate substantial improvements over existing therapies for several reasons:

- Biologics tend to be relatively more expensive on a per patient basis and so increasingly are “on the radar screen” at plans.
- The population of patients receiving any individual biologic tends to be relatively small compared to small-molecule drugs, and thus easier to reach with tailored formulary and utilization management strategies.

- The population of physicians administering a biologic, generally specialists, may be small relative to small-molecule drugs, allowing third-party payers to better monitor and advise their use of biologics.

As a result of both the relatively high cost per patient and small patient population, third-party payers have an incentive to investigate use on a patient-by-patient basis to ensure necessity. As biosimilars of first generation biologics become available and potential cost differences increase, health plans may increasingly opt to impose access restrictions, such as prior authorization requirements, therapy step-edits, and differential coinsurance payment levels on more expensive therapies, unless there is strong evidence of patient benefit or value. The relatively small physician population administering biologics will further facilitate health plans' ability to ensure that the access restrictions are carried out.

Over the past decade, public and private health insurance plans have developed and begun putting into place medical management, network design, and benefit design strategies to control access to, and utilization of, biologic therapies. Medical management strategies include formulary design and preferred formulary positions for certain products, and access restrictions for others (e.g., differential prior authorization, step therapy requirements, quantity limits, other formulary restrictions); network design strategies include physician and distributor network limits (e.g., mandates that biologics must be prescribed by only certain specialties, voluntary or mandatory use of specialty pharmacy providers rather than physician "buy and bill" reimbursement); benefit design strategies include coinsurance, rather than copayment, and requirements for specialty and biologic drugs, with or without out-of-pocket payment limits. Some controls apply to all biologics within a therapeutic category; others are applied differentially to preferred and non-preferred products. Self-injectable, or other self administered,

biologic products are more often subject to the formulary restriction techniques developed for other pharmacy benefits, and infused agents and those that require physician administration (often still medical benefits) are more often subject to distribution and pricing-focused efforts. Over time, many plans may seek to migrate biologic treatments to the pharmacy benefit, where utilization and access control are well-established.

- A 2003-04 survey of thirty-eight Blue Cross and Blue Shield plans representing sixty-three million lives across twenty-five states revealed that roughly three-quarters of respondents had implemented a common approach to managing specialty pharmaceuticals that included four core strategies: prior authorization; formulary management/restrictions; utilization review; and claims review. 83% of respondents reported applying prior authorization requirements to specialty pharmaceuticals.[31] To the extent that there are multiple therapeutically comparable biologics in the same category, plans seek rebates from manufacturers in exchange for preferred formulary positions.
- A 2004 survey of commercial health insurance plans indicated that 45% of payers had preferred products in at least one specialty pharmacy therapeutic category.[32] Agents for rheumatoid arthritis (RA), multiple sclerosis (MS), growth hormone deficiency, or Hepatitis C (HCV), in which there are multiple therapeutic options available, increasingly compete on formularies that prefer one or more products.
- The level of formulary and medical management in Medicare Part D plans has often exceeded that in commercial plans and has increased over time. 82% of stand-alone

[31] Mullins, D., et al., "Health Plans' Strategies for Managing Outpatient Specialty Pharmaceuticals," *Health Affairs* 25 (2006): 1332-1339.
[32] Health Strategies Group, "MCO Trends in Specialty Pharmacy Management," 2004, as reported in Stern , D., "Specialty Pharmacy Cost Management Strategies of Private Health Care Payers," *Journal of Managed Care Pharmacy*, 2006; 12 (9): 736-44.

2009 Part D plan designs included a "Tier 4" specialty drug tier, for instance, and the average coinsurance rate for plans increased from 25% in 2006 to 33% in 2009 (2009 plan designs applied to 2008 plan enrollments in calculations.)[33] A separate Kaiser Family Foundation survey reports that 41 of 47 national Part D Prescription Drug Plans (PDPs) included a specialty tier, up from 21 in 2006.[34]

- Medicaid Preferred Drug Lists (PDLs) reflect preferred biologic products in a number of therapeutic categories – in a review of current Rheumatoid Arthritis (RA), Hepatitis C (HCV), and human growth hormone formularies in six of the largest states (Florida, Illinois, New York, Ohio, Pennsylvania and Texas), there were non-preferred agents in each state in each category. States preferred two or three RA agents (of six), one or two HCV agents (of five), and between two and five human growth hormones (of nine agents/forms).[35]

In addition to techniques that mirror those developed for small molecules, some plans are focusing increasing effort on the development or review of clinical protocols and guidelines, and extensive clinical and value review of biologics. Kaiser Permanente California, for instance, has charged a central multidisciplinary Biotechnology and Emerging Pharmaceutical Technology Assessment Committee with review of new biologics prior to any formal new product formulary review and action by its standing Pharmacy and Therapeutics (P&T) committee. Adoption of standardized evidence dossiers for all new products (such as Wellpoint's) has also raised the bar for the level of evidence of value, as well as effectiveness and safety, required for coverage.

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[33] Hoadley, J., "Medicare Part D Benefit Designs and Formularies, 2006-2009," December 5, 2008. Available at: http://www. medpac.gov/transcripts/MedPAC%20Formulary%20Presentation%20-%20Hoadley%2012-05-08%20revised.pdf.

[34] Hargrave, E., et al., "Medicare Part D 2008 Data Spotlight: Specialty Tiers," Kaiser Family Foundation, December 2007, available at: http://www.kff.org.

[35] Authors calculations, from on-line Preferred Drug Lists for Florida, Illinois, New York, Ohio, Pennsylvania and Texas.

Increasingly, third-party payers are likely to require substantial evidence of demonstrated value and cost-effectiveness for new next generation molecules, and may apply access restrictions and utilization controls to impose countervailing, market pressures limiting their uptake if such evidence is not available. Access restrictions are likely to become more prevalent and more aggressive as the use of biologics expands and as biologics grow as a share of pharmacy costs. As a result of these access restrictions, new next generation molecules that offer only minimal advantages compared to existing therapies are therefore increasingly likely to have limited market potential in the future, and limited impact on the sales of prior generation biologics or the market potential of biosimilars.

B. The Impact of Next Generation Biologics on Market Share for First Generation Products and Their Biosimilars

Next generation biologics that do offer a substantial advance may have fewer access restrictions imposed by third-party payers, and generate substantial sales despite any remaining access restrictions, as they are likely to be able to demonstrate that they better serve the unmet needs of a wider patient population. Some sales of next generation molecules will come from expanding total biologic therapy usage; some sales will reflect share gains from and therefore lower sales for previous generation products and smaller market potential for their biosimilars.

Even next generation molecules that achieve high sales will not necessarily limit the size of the market available to biosimilars to a degree that would impact biosimilar entry decisions. Recent examples of next generation biologic entry suggest that in a number of cases, a large portion of their sales reflects overall market growth rather than substitution of sales away from first-generation biologics within the same size market. For example, although Epogen and Procrit experienced a modest decline in sales following entry of the Aranesp, both products maintained substantial sales (see Figure 2). Similarly, Neupogen continued to have substantial

levels of sales following entry of the next-generation biologic Neulasta (see Figure 3). In other cases the next-generation biologic supplants some use of the previous generation biologic. For example, use of Intron A for patients with chronic hepatitis C declined substantially following introduction of the pegylated version PegIntron. PegIntron offers substantial improvements in patient convenience, requiring only once weekly administration compared to Intron A, which required administration three times per week.

VII. Appropriate Data Exclusivity Period for Next Generation Biologic Molecules

As scientific knowledge of underlying common mechanisms across diseases increases, next generation biologic molecules represent a key, and potential growing, component of competition in biologic markets and a valuable future source of therapy improvements for patients. To maintain investment incentives for the development and introduction of improved forms of biologics, legislation establishing an abbreviated pathway for biosimilars should not exclude next generation molecules from data protections extended to new biologic entities. An appropriate data exclusivity period for next generation molecules should incorporate the following two considerations:

(1) The length of the data exclusivity period should be sufficient to maintain investor incentives to invest in the development of new next generation molecules, and to make these valuable new therapies available to patients;

(2) The duration and scope of any data exclusivity period should be known to both investors and manufacturers in advance of investing in development of the biologic.

The costs and risks associated with developing next generation molecules may be substantial. Many next generation biologics reflect the culmination of lengthy development programs with uncertain outcomes during the development process. The data exclusivity period for next generation biologics should reflect the need to maintain investment incentives given these costs and risks.

Prior research described in both the *Nature* article and the *Biosimilar Entry* paper supports a data exclusivity period of 12 to 16 years for new biologic entities, given a plausible set of values for the economic factors affecting investment returns for biologics. Shorter data exclusivity periods are associated with reduced investment incentives for biologics, potentially

leading to the development of fewer biologic drugs and limiting the availability of valuable new therapies to patients. The findings in the *Nature* article and *Biosimilar Entry* paper provide a useful benchmark for data exclusivity periods for next generation molecules that require a full BLA for approval, given the often extensive costs and risks associated with developing these products.

A "two-tiered" data exclusivity period approach, with different data exclusivity periods for first generation and next generation molecules approved through full BLAs, may create significant uncertainty and inefficiencies that would deter investment in therapeutically valuable new biologics. Additional considerations for a two-tiered approach include:

(1) The data exclusivity tier applicable to a next generation biologic should be known to both investors and manufacturers in advance of investing in development of the biologic, and not subject to unpredictable subjective judgments by regulators;

(2) Any resulting inefficient distortions in investment incentives resulting from a two-tiered approach should be minimized.

Large differences in data exclusivity periods between first- and next generation biologic molecules could create substantial inefficient distortions in investment incentives. Reflective of these issues, the European Medicines Agency (EMEA) generally extends the same data exclusivity period to first and next generation molecules (including pegylated versions of older biologic products).[36] There would be a number of problems associated with a framework that applies very different data exclusivity periods to biologics approved through a new BLA process dependent on whether they are first-generation or next generation molecules:

[36] Horton, L., "The European Experience with Follow-on Biologics Legislation," Presentation, Federal Trade Commission Roundtable on Follow-on Biologic Drugs: Framework for Competition and Continued Innovation, November 21, 2008, available at http://www.ftc.gov/bc/workshops/hcbio/docs/fob/lhortonsv.pdf.

- ***The determination of whether a given molecule is a first-generation or next generation molecule may be subjective***. In some cases, the modifications to existing molecules may be extensive enough that it is not possible to establish an appropriate "bright line" between first generation and next generation molecules. Applying differentiated data exclusivity periods based on the degree of similarity in chemical structure between a new and existing molecule will require subjective judgment of what types and extent of molecular modifications constitutes a next generation molecule versus the creation of a new first generation molecule. It could also require complex subjective judgments related to the outcome of development programs that cannot be fully anticipated at the time of investment (i.e., the extent of therapeutic advance represented by the product). Such subjective determinations introduce a level of uncertainty that could negatively impact investment incentives and potentially deter the development of some valuable therapeutic advances, given the already high level of development risk inherent in the multi-year development of new biologics.
- ***The determination of whether a product is a first-generation or a next generation molecule may depend on the manufacturer, and differentiated data exclusivity periods could result in inefficient or sub-optimal investment incentives.*** For example, Lantus can be categorized as a first-generation insulin product for sanofi-aventis as it did not have a presence in the insulin market prior to launch. However, Levemir, developed by Novo Nordisk, might be characterized as a next generation biologic (Novolin being the first generation biologic) despite the fact that Levemir and Lantus are competing basal insulin products. Differentiating data exclusivity

periods for first generation and next generation molecules would mean that the applicable data exclusivity period would in some cases depend on who developed the biologic rather than the actual chemical composition of the biologic. Company-dependent data exclusivity periods could introduce a number of potential inefficiencies in biologic development incentives as companies strive to maximize data exclusivity periods.

- ***It may be possible to achieve comparable improvement to an existing biologic via several different approaches, some considered the development of a new first-generation biologic and some considered the development of a next generation biologic. In this case differentiated data exclusivity periods could result in inefficient investment incentives.*** For example, a biologic manufacturer may be interested in modifying an existing biologic to achieve certain target new features and benefits to patients. Some methods for achieving the improved features would modify the molecule to such an extent that it would they would be considered defining a new first generation molecule, while other feasible modifications would be less extensive and could conceivably result in what would be considered a next generation molecule. Longer data exclusivity periods for first-generation rather than next generation molecules would shift development incentives toward the methods and potential products that would result in a new first-generation biologic designation, and this greater incentive to pursue first-generation biologics might not reflect the relative underlying therapeutic value.

Economic analyses of the R&D costs and returns support a data exclusivity period for new biologics of 12 to 16 years, given a plausible range of assumptions, in order to maintain

investment incentives. These findings provide a useful benchmark for determining a data exclusivity period that is sufficient to maintain investment incentives for next generation molecules that require a full BLA submission for approval. Next generation molecules often face extensive costs and risks associated with development, approval, and market success. In addition, a two-tiered data exclusivity approach with different data exclusivity periods applied to first-generation and next generation molecules can introduce inefficient distortions in investment incentives. These distortions would be more pronounced the greater the differentiation in the length of data exclusivity periods for the different tiers. Given the importance of the biotechnology industry to the U.S. economy and, more importantly, the promise of therapeutic advances offered by new biologics, including next generation biologics, Congress should ensure that legislation establishing an abbreviated pathway for biosimilar approval include data exclusivity periods of sufficient length to maintain investment incentives.

Table 1
Categorization of Next Generation Biologics
FDA Requirements and Bill Provisions for Data Exclusivity
Congressional Bills Considered 2007 through 2009

Category of Improvement	Examples	Anticipated FDA Requirements for Approval	Data Exclusivity Period Offered by Bills
New Indications	Uses targeted to new diseases or patient populations	• Clinical trials to demonstrate efficacy and safety in new patient populations • Supplemental BLA in most instances	• 3 months (H.R. 1427) to 2 years (H.R. 1548) for new indications • 6 months for pediatric use
New Form of Administration	Additional intravenous, subcutaneous, pen administration, inhaled delivery forms	• Contingent on degree of change in form of administration and potential clinical implications and risks • Full or supplemental BLA	• 3 to 6 months (H.R. 1427) • Not specifically addressed (other bills)
Change in Molecular Structure	Pegylation, glycosylation	• Potentially a full set of clinical data on efficacy and safety necessary • Full BLA	• 0, 3, or 5 years (H.R. 1427) • Subject to same 12 to 14 year first-generation data exclusivity period (other bills)

Table 2
Next Generation Molecules
Changes in Molecular Structure

Brand Name	Company	FDA Approval	Disease	Predecessor Drug(s) - 1st Generation	Notes
Advate (Factor VIII [Recombinant])	Baxter Healthcare Corp.	July, 2003	Hemophilia	Recombinate (Antihemophiliac factor VIII [Recombinant])	Advate is a factor VIII blood product made without any added human or animal plasma proteins and albumin in the cell culture process, purification and final formulation, thereby eliminating the risk of infections caused by viruses that may be carried in these proteins, while maintaining the efficacy of Recombinate.
Aranesp (Darbepoetin alfa)	Amgen	September, 2001	Anemia	Epogen (Epoetin alpha)	Aranesp is derived from epoetin alpha, but contains 5 N-linked oligosaccharide chains rather than 3 chains. It was developed with the intention of increasing potency and providing an extended duration of action as compared to epoetin alfa. Aranesp is typically administered in fewer and less frequent injections than epoetin alpha.
Humalog (Insulin lispro)	Eli Lilly and Company	June, 1996	Diabetes	Humulin (Human insulin recombinant)	Rapid acting insulin. Humalog was engineered through recombinant DNA technology so that the penultimate lysine and proline residues on the C-terminal end of the B-chain were reversed, allowing larger amounts of active monomeric insulin to be available for postprandial (after meal) injections.
Levemir (Insulin detemir)	Novo Nordisk	June, 2005	Diabetes	Novolin (Human insulin recombinant)	Insulin detemir is a synthetic form of insulin. It may be used in combination with another type of insulin or with an oral diabetes medicine to keep blood sugar under control. The new formulation allows for once or twice daily administration.

Note:
Due to data limitations combination vaccines (e.g., Comvax, Twinrix, Pediarix) were excluded along with next generation biologics where the generational improvement was recombinant DNA (e.g., Kogenate, Humulin, Cerezyme).

Table 2 (Continued)
Next Generation Molecules
Changes in Molecular Structure

Brand Name	Company	FDA Approval	Disease	Predecessor Drug(s) - 1st Generation	Notes
Lucentis (Ranibizumab)	Genentech, Inc.	June, 2006	Wet age-related macular degeneration (AMD)	Avastin (Bevacizumab)	Both Lucentis and Avastin are recombinant monoclonal antibodies directed against the VEGF protein, though differ in their molecular weight. While Avastin is primarily used in oncology, Lucentis was developed for the treatment of AMD.
Luveris (Lutropin alfa)	Serono	October, 2004	Human Luteinizing Hormone	Gonal-F (Follitropin alfa)	Luveris is used in combination with Gonal-F (follitropin alfa for injection) to stimulate follicular development in infertile hypogonadotropic hypogonadal (HH) women with profound LH deficiency.
Neulasta (Pegfilgrastim)	Amgen	January, 2002	Febrile Neutropenia	Neupogen (Filgrastim)	Unlike Neupogen, Neulasta incorporates a polyethylene glycol molecule or "PEG" unit that enlarges the Filgrastim molecule, thereby extending its half-life and causing it to be removed more slowly from the body, allowing for administration in a single dose per chemotherapy cycle.
NovoLog (Insulin aspart)	Novo Nordisk	May, 2000	Diabetes	Novolin (Human insulin recombinant)	Rapid acting Insulin.
Nutropin Depot (Somatropin [rDNA origin])	Alkermes, Inc., and Genentech, Inc.	December, 1999	Growth Hormone Deficiency	Nutropin (Somatropin [rDNA origin])	Nutropin Depot is based on polymer microspheres, creating a long-acting form of Genentech's Nutropin using Alkermes' ProLease(R) injectable extended-release drug delivery system. This new formulation was designed to reduce the frequency of injections.

Note:
Due to data limitations combination vaccines (e.g., Comvax, Twinrix, Pediarix) were excluded along with next generation biologics where the generational improvement was recombinant DNA (e.g., Kogenate, Humulin, Cerezyme).

Table 2 (Continued)
Next Generation Molecules
Changes in Molecular Structure

Brand Name	Company	FDA Approval	Disease	Predecessor Drug(s) - 1st Generation	Notes
Pegasys (Peginterferon alpha-2b)	Roche, Inc.	October, 2002	Chronic Hepatitis C	Roferon A (Interferon alfa-2a)	Pegasys incorporates a PEG unit that enlarges the Interferon Alfa-2a molecule, thereby extending its half-life and causing it to be removed more slowly from the body.
PegIntron (Peginterferon alpha-2b)	Schering-Plough Corp.	January, 2001	Chronic Hepatitis C	Intron A (Interferon alfa-2b)	PegIntron incorporates a PEG unit that enlarges the Interferon Alfa-2b molecule, thereby extending its half-life and causing it to be removed more slowly from the body.
TNKase (Tenecteplase)	Genentech, Inc.	June, 2000	Acute Myocardial Infarction (AMI)	Activase (Alteplase)	TNKase is a bioengineered variant of Activase® (Alteplase, recombinant), which is a recombinant DNA-derived version of naturally occurring tissue plasminogen activator (t-PA). It is constructed with amino acid substitutions at three sites (the letters T, N and K represent the three regions changed from the natural t-PA protein). It is the first thrombolytic that can be administered in a single 5-second bolus, offering physicians the fastest administration of a thrombolytic to date in the treatment of heart attack.
Xyntha (Factor VIII)	Wyeth	Feb, 2008	Hemophilia	Refacto (Antihemophilic factor VIII [Recombinant])	Xyntha is a factor VIII blood product made without any added human or animal plasma proteins and albumin in the cell culture process, purification and final formulation, thereby eliminating the risk of infections caused by viruses that may be carried in these proteins, while maintaining the efficacy of Refacto.

Note:
Due to data limitations combination vaccines (e.g., Comvax, Twinrix, Pediarix) were excluded along with next generation biologics where the generational improvement was recombinant DNA (e.g., Kogenate, Humulin, Cerezyme).

Table 3
Timeline of Biologic Approvals by Therapeutic Area

Product	Company	FDA Approval	Approval Pathway
Blood Factor Products			
Recombinate® rAHF/ (antihemophilic factor VIII)	Baxter Healthcare Corp.	92-Feb	Unknown
Kogenate® /FS (antihemophilic factor VIII)	Bayer Corp.	93-Feb	BLA
Helixate® /FS (antihemophilic factor VIII)	Aventis Behring	94-Feb	BLA
Bioclate™ (antihemophilic factor VIII)	Aventis Behring	93-Dec	BLA
BeneFix™ (coagulation factor IX)	Wyeth	97-Feb	BLA
NovoSeven® (coagulation factor VIIa)	Novo Nordisk	99-Mar	BLA
ReFacto® (antihemophilic factor VIII)	Wyeth	00-Mar	BLA
Advate (antihemophilic factor VIII)	Baxter Healthcare Corp.	03-Jul	NDA
Xyntha (antihemophilic factor VIII)	Wyeth	08-Feb	BLA
Hormone Products			
Nutropin® (somatropin)	Genentech, Inc.	85-Oct	NDA
Protropin® (somatrem)	Genentech, Inc.	85-Oct	NDA
BioTropin™ / Tev-tropin (somatropin)	Biotech General	95-May	NDA
Norditropin®/Norditropin Nordiflex® (somatropin)	Novo Nordisk	95-May	NDA
GenoTropin® (somatropin)	Pharmacia	95-Aug	NDA
Zorbtive™ (Serostim®) (somatotropin)	Serono S.A.	96-Aug	NDA
Saizen® (somatropin)	Serono S.A.	96-Oct	NDA
Humatrope® (somatropin)	Eli Lilly and Company	96-Dec	NDA
Follistim™ (follitropin beta)	Organon (unit of Akzo Nobel)	97-Sep	NDA
Gonal-F® (follitropin alfa)	Serono S.A.	97-Sep	NDA
Thyrogen® (thyrotropin alfa)	Genzyme	98-Dec	NDA
Nutropin Depot™ (sustained-release formulation of somatropin)	Alkermes, Inc., and Genentech, Inc.	99-Dec	NDA
Omnitrope® (somatropin)	Novartis	06-May	NDA

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.
Kogenate is also sold under the brand name Helixate, produced by CSL Behring.

Table 3 (Continued)
Timeline of Biologic Approvals by Therapeutic Area

Product	Company	FDA Approval	Approval Pathway
Insulin Products			
Humulin® (insulin)	Eli Lilly And Company	82-Oct	NDA
Novolin® (insulin)	Novo Nordisk	82-Oct	NDA
Novolin L® (insulin; zinc suspension;)	Novo Nordisk	91-Jun	NDA
Novolin R® (insulin, regular;)	Novo Nordisk	91-Jun	NDA
Novolin N® (insulin; isophane suspension)	Novo Nordisk	91-Jul	NDA
Novolin® 70/30 (70% insulin isophane suspension and 30% regular insulin)	Novo Nordisk	91-Jun	NDA
Humalog® (insulin)	Eli Lilly and Company	96-Jun	NDA
Velosulin® BR (insulin; buffered formulation)	Novo Nordisk	99-Jul	NDA
Lantus® (insulin glargine)	Aventis	00-Apr	NDA
NovoLog® (insulin aspart)	Novo Nordisk	00-May	NDA
Apidra® (insulin glulisine recombinant)	Sanofi Aventis	04-Apr	NDA
Levemir® (insulin detemir injection)	Novo Nordisk	05-Jun	NDA
Anticoagulants			
Lovenox® (enoxaparin sodium)	Sanofi Aventis	93-Mar	NDA
Fragmin® (dalteparin sodium)	Pfizer	94-Dec	NDA
Innohep® (tinzaparin sodium)	Celgene Corp	00-Jul	NDA
Angiomax® (bivalirudin sodium)	Medicines Co	00-Dec	NDA
Arixtra® (fondaparinux sodium)	GlaxoSmithKline	01-Dec	NDA

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.
The list of anticoagulants excludes unfractionated heparin.

Table 3 (Continued)
Timeline of Biologic Approvals by Therapeutic Area

	Product	Company	FDA Approval	Approval Pathway
Transplant				
	Orthoclone OKT3® (muromomab-CD3)	Ortho Biotech, Inc. (subsidiary of Johnson & Johnson)	86-Jun	Unknown
	Zenapax® (daclizumab)	Hoffmann-La Roche, Inc., and Protein Design Labs	97-Dec	BLA
	Simulect® (basiliximab)	Novartis Pharmaceutical Corp.	98-May	BLA
Hepatitis-C				
	Rebetron™ (ribavirin and interferon alpha-2b)	Schering-Plough Corp.	98-Jun	Unknown
	PEG-Intron™ (peginterferon alfa-2b)	Enzon, Inc., and Schering-Plough Corp.	01-Jan	BLA
	Pegasys® (peginterferon alfa-2a)	Roche and Nektar Therapeutics, Inc.	02-Oct	BLA
	Pegpak (ribavirin and interferon alpha-2b)	Schering	08-Jun	BLA
Oncology				
	Intron A® (interferon alpha-2b)	Schering-Plough Corp.	86-Jun	BLA
	Roferon-A® (interferon alfa-2a)	Hoffmann-La Roche, Inc.	86-Jun	BLA
	Alferon N® (interferon alfa-N3, human leukocyte derived)	Interferon Sciences, Inc	89-Oct	BLA
	Proleukin, IL-2® (aldesleukin)	Chiron Corp.	92-May	BLA
	CEA-Scan® (acritumomab; technetium-99 labeled)	Immunomedics, Inc.	96-Jun	BLA
	ProstaScint® (indium In 111 capromab pendetide)	Cytogen Corp.	96-Oct	BLA
	Infergen® (interferon alfacon-1)	InterMune Pharmaceuticals, Inc., and Amgen	97-Oct	BLA
	Rituxan™ (rituximab)	Biogen Idec and Genentech, Inc.	97-Nov	BLA
	Herceptin® (trastuzumab)	Genentech, Inc.	98-Sep	BLA

Oncology - continued on the next page

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.

Table 3 (Continued)
Timeline of Biologic Approvals by Therapeutic Area

Product	Company	FDA Approval	Approval Pathway
Oncology - continued			
Mylotarg™ (gemtuzumab ozogamicin)	Celltech Pharmaceuticals and Wyeth	00-May	NDA
Campath® (alemtuzumab)	Ilex Oncology, Inc., Millennium Pharm., Inc., Genzyme and Berlex Lab., Inc.	01-May	BLA
Zevalin™ (ibritumomab tiuxetan)	Biogen Idec	02-Feb	BLA
Bexxar® (Tositumomab and I-131 tositumomab)	GlaxoSmithKline	03-Jun	BLA
Avastin™ (bevacizumab)	Genentech	04-Feb	BLA
Erbitux™ (cetuximab)	ImClone Systems Inc.	04-Feb	BLA
Vectibix (panitumumab)	Amgen	06-Sep	BLA
Anemia/Infection with Oncology			
Epogen® (epoetin alfa)	Amgen	89-Jun	BLA
Procrit® (epoetin alfa)	Ortho Biotech, Inc.	90-Dec	BLA
Neupogen® (filgrastim)	Amgen	91-Feb	BLA
Leukine®/Leukine® Liquid (sargramostim)	Berlex Laboratories	91-Mar	BLA
Neumega® (oprelvekin)	Wyeth	97-Nov	BLA
Aranesp™ (darbepoetin alfa)	Amgen	01-Sep	BLA
Neulasta™ (pegfilgrastim)	Amgen	02-Jan	BLA
Mircera (methoxy polyethylene glycol-epoetin beta)	Hoffman La-Roche	07-Nov	BLA

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.

Table 3 (Continued)
Timeline of Biologic Approvals by Therapeutic Area

Product	Company	FDA Approval	Approval Pathway
Rheumatoid arthritis and other autoimmune disorders			
Remicade® (infliximab)	Centocor, Inc. (subsidiary of Johnson & Johnson)	98-Aug	BLA
Enbrel® (etanercept)	Amgen and Wyeth	98-Nov	BLA
Kineret™ (anakinra)	Amgen	01-Nov	BLA
Humira™ (adalimumab)	Cambridge Antibody Technologies and Abbott Laboratories	02-Dec	BLA
Amevive® (Alefacept)	Biogen Idec	03-Jan	BLA
Xolair® (Omalizumab)	Genentech, Tanox, Inc. and Novartis Pharmaceuticals	03-Jun	BLA
Raptiva (Efalizumab)	Genentech	03-Oct	BLA
Orencia™ (abatacept, fully human soluable fusion protein)	Bristol-Myers Squibb Company	05-Dec	BLA
Arcalyst (rilonacept)	Regeneron	08-Feb	BLA
Cimzia (certolizumab pegol)	UCB	08-Apr	BLA
Nplate (romiplostim)	Amgen	08-Aug	BLA
Multiple Sclerosis			
Betaseron® (Interferon beta-1b)	Berlex Laboratories and Chiron Corp	93-Aug	BLA
Avonex® (interferon beta-1a; recombinant)	Biogen Idec	96-May	BLA
Copaxone® (glatiramer acetate for injection)	Teva	96-Dec	NDA
Rebif®/Rebif® Titration Pack (interferon beta 1-a)	Serono S.A., and Pfizer, Inc.	02-Mar	BLA
Tysabri® (formerly ANTEGREN®) (natalizumab)	Biogen Idec and Elan Corp.	04-Nov	BLA

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.

Table 3 (Continued)
Timeline of Biologic Approvals by Therapeutic Area

	Product	Company	FDA Approval	Approval Pathway
Other				
	Actimmune® (interferon gamma-1b)	InterMune Pharmaceuticals, Inc.	90-Dec	BLA
	Activase®/Cathflo® Activase® (alteplase)	Genentech, Inc.	87-Nov	BLA
	Aldurazyme® (laronidase)	BioMarin Pharmaceuticals Inc. and Genzyme	03-Apr	BLA
	Cerezyme® (imiglucerase)	Genzyme	94-May	NDA
	Elaprase (idursulfase)	Shire Human Genetic Therapies	06-Jul	BLA
	Elitek® (rasburicase)	Sanofi-Synthelabo	02-Jul	BLA
	Fabrazyme® (algasidase beta)	Genzyme	03-Apr	BLA
	Forteo® (teriparatide)	Eli Lilly and Company	02-Nov	NDA
	Fortical® Nasal Spray (calcitonin salmon)	Unigene Laboratories Inc.	05-Aug	NDA
	GEM 21S® (Growth-factor Enhanced Matrix)	BioMimetic Therapeutics Inc.	05-Nov	Unknown
	GlucaGen® (glucagon)	Novo Nordisk	98-Jun	NDA
	Hylenex™ (recombinant human hyaluronidase)	Halozyme Therapeutics Inc.	05-Dec	NDA
	Increlex™ (mecasermin)	Tercica Inc. Genentech Inc.	05-Aug	NDA
	Infuse™ Bone Graft/LT-CAGE™	Wyeth and Medtronic Sofamor Danek	02-Jul	Unknown
	Iplex™ (mecasermin rinfabate)	Insmed Inc.	05-Dec	NDA
	Kepivance (palifermin)	Amgen	04-Dec	BLA
	Lucentis (ranibizumab)	Genentech	06-Jun	BLA
	Luveris (lutropin alfa for injection)	Serono	04-Oct	NDA
	LYMErix™ (OspA lipoprotein)	SmithKline Beecham Biologicals (subsidiary of GlaxoSmithKline)	98-Dec	Unknown

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.

Table 3 (Continued)
Timeline of Biologic Approvals by Therapeutic Area

Product	Company	FDA Approval	Approval Pathway
Other - continued			
Myobloc™ (botulinum toxin type B)	Elan Corp.	00-Dec	BLA
Myozyme (alglucosidase alfa)	Genzyme	06-Apr	BLA
Naglazyme™ (galsulfase)	BioMarin Pharmaceuticals	05-May	BLA
Natrecor® (nesiritide)	Scios, Inc.	01-Aug	NDA
NeutroSpec™ (formerly LeuTech®) (Technetium fanolesomab)	Palatin Technologies and Mallinckrodt Imaging (Tyco Healthcare)	04-Jul	BLA
Ontak® (denileukin diftitox)	Ligand Pharmaceuticals, Inc.	99-Feb	BLA
Pulmozyme® (dornase alfa)	Genentech, Inc.	93-Dec	BLA
Refludan® (lepirudin)	Berlex Laboratories	98-Mar	NDA
Regranex® Gel (gel becaplermin)	Ortho-McNeil and Chiron Corp.	97-Dec	BLA
ReoPro™ (abciximab)	Centocor, Inc. (subsidiary of Johnson & Johnson) and Eli Lilly and Company	94-Dec	BLA
Retavase™ (reteplase)	Centocor, Inc. (subsidiary of Johnson & Johnson)	96-Oct	BLA
Soliris (eculizumab)	Alexion	07-Mar	BLA
Somavert® (pegvisomant)	Nektar Therapeutics and Pfizer, Inc.	03-Mar	NDA
Synagis™ (Palivizumab)	MedImmune, Inc.	98-Jun	BLA
TNKase™ (tenecteplase)	Genentech, Inc.	00-Jun	BLA
Xigris™ (drotrecogin alfa)	Eli Lilly and Company	01-Nov	BLA

Sources:
Approved Biotechnology Drugs, BIO
FDA Website, http://www.fda.gov/cder/rdmt/default.htm

Notes:
Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website.

Table 4

Therapeutic Developments in the Market for Insulins

FDA approval	Human Insulins	Insulin analogs	Long-acting, once-daily
1982	Humulin R (Oct) Humulin R Pen (Oct)		
1983			
1984			
1985			
1986			
1987			
1988			
1989	Humulin 70/30 (Apr) Humulin 70/30 Pen (Apr)		
1990			
1991	Novolin 70/30 (Jun) Novolin R (Jun) Novolin N (Jul)		
1992	Humulin 50/50 (Apr)		
1993			
1994			
1995			
1996		Humalog (Jun) Humalog Pen (Jun)	
1997			
1998			
1999		Humalog Mix50/50 (Dec) Humalog Mix75/25 (Dec)	
2000		Novolog (Jun) Novolog FlexPen (Jun)	Lantus (Apr) Lantus SoloStar (Apr)
2001		Novolog Mix70/30 (Nov) Novolog Mix70/30 FlexPen (Nov)	
2002			
2003			
2004		Apidra (Apr)	
2005			Levemir (Jun) Levemir FlexPen (Jun)
2006			
2007			
2008		Humalog KwikPen (Feb) Humalog Mix50/50 KwikPen (Feb) Humalog Mix75/25 KwikPen (Feb) Novolog Mix50/50 (Aug) Novolog Mix50/50 FlexPen (Aug)	

Source: Drugs@FDA

Notes: 1) Humulin and Humalog are produced by Eli Lilly; Novolin, Novolog and Levemir are produced by Novo-Nordisk; Lantus and Apidra are produced by sanofi-aventis.

2) Excludes discontinued products.

3) When the supplemental approval dates for a pen product is unavailable, NDA approval date is used.

Table 5

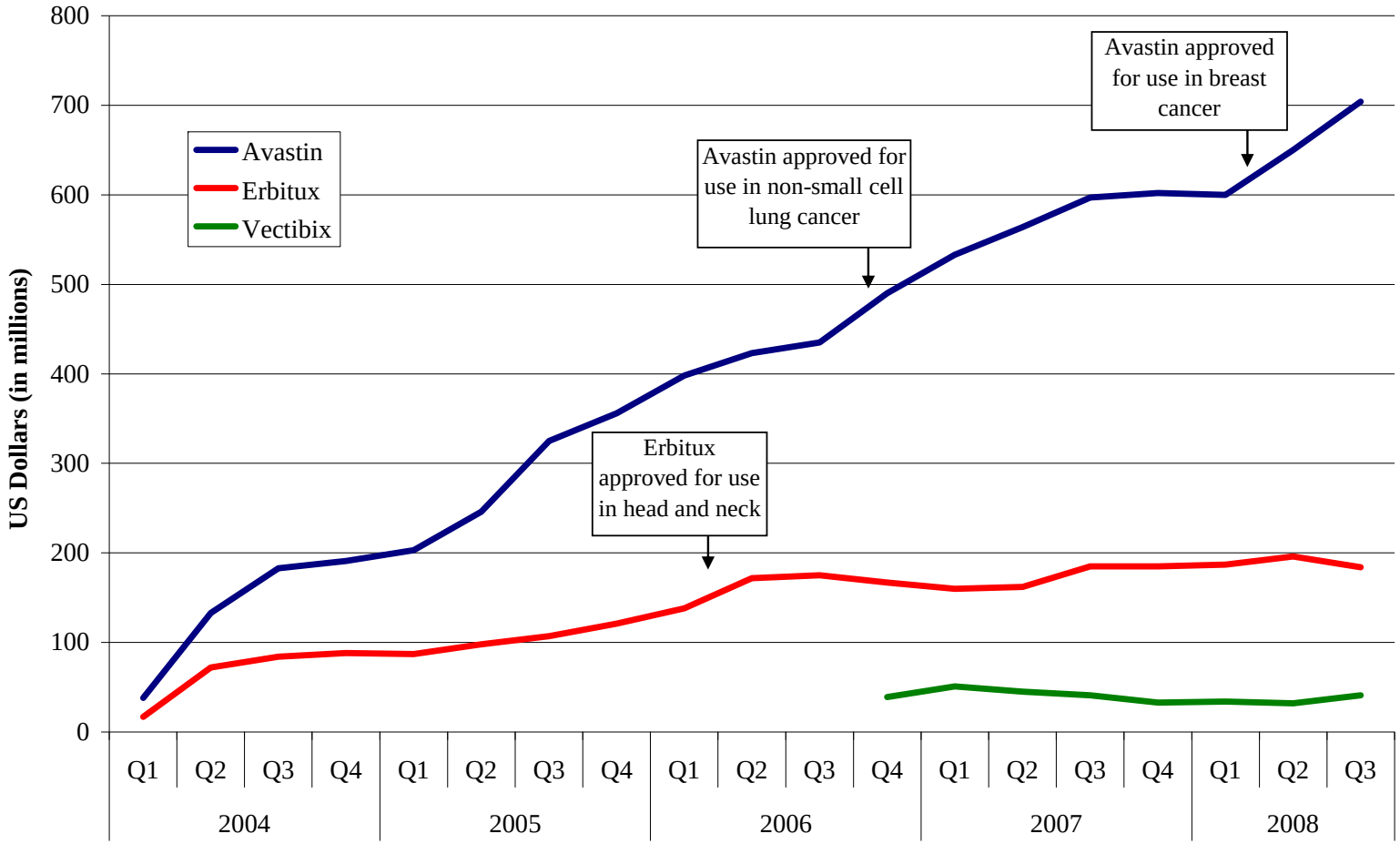
TNF Inhibitors: New Indications and Approval Dates

	Remicade (Centocor)	Enbrel (Amgen/Wyeth)	Humira (Abbott)
1998	**FDA approval**: Crohn's disease, treatment	**FDA approval**: RA, second-line therapy	
1999	Rheumatoid arthritis (RA), second-line therapy	Juvenile RA, second-line therapy	
2000	RA, inhibit structural damage second-line therapy	RA, first-line therapy RA, inhibit structural damage	
2001			
2002	RA, improve physical function second-line therapy Crohn's disease, maintenance second-line therapy	Psoriatic arthritis	**FDA approval:** RA, treatment and inhibit structural damage, second-line therapy
2003	Crohn's disease, reduce and maintain closure of fistulas	Ankylosing spondylitis RA, improve physical function Psoriatic arthritis, inhibit structural damage	
2004	RA, first-line therapy Ankylosing spondylitis	Plaque psoriasis RA, induction and first-line concomitant with methotrexate	RA, improve physical function, second-line therapy
2005	Psoriatic arthritis Ulcerative colitis, second-line therapy	Psoriatic arthritis, improve physical function	RA, first-line therapy Psoriatic arthritis
2006	Crohn's disease, pediatric patients Psoriatic arthritis, inhibit structural damage / improve function Chronic plaque psoriasis Ulcerative colitis, maintenance, second-line therapy		Ankylosing spondylitis Psoriatic arthritis, inhibit structural damage / improve physical function
2007			Crohn's disease
2008			Plaque psoriasis, patients who are candidates for systemic therapy or phototherapy Juvenile idiopathic arthritis

Sources: Drugs@fda

Figure 1

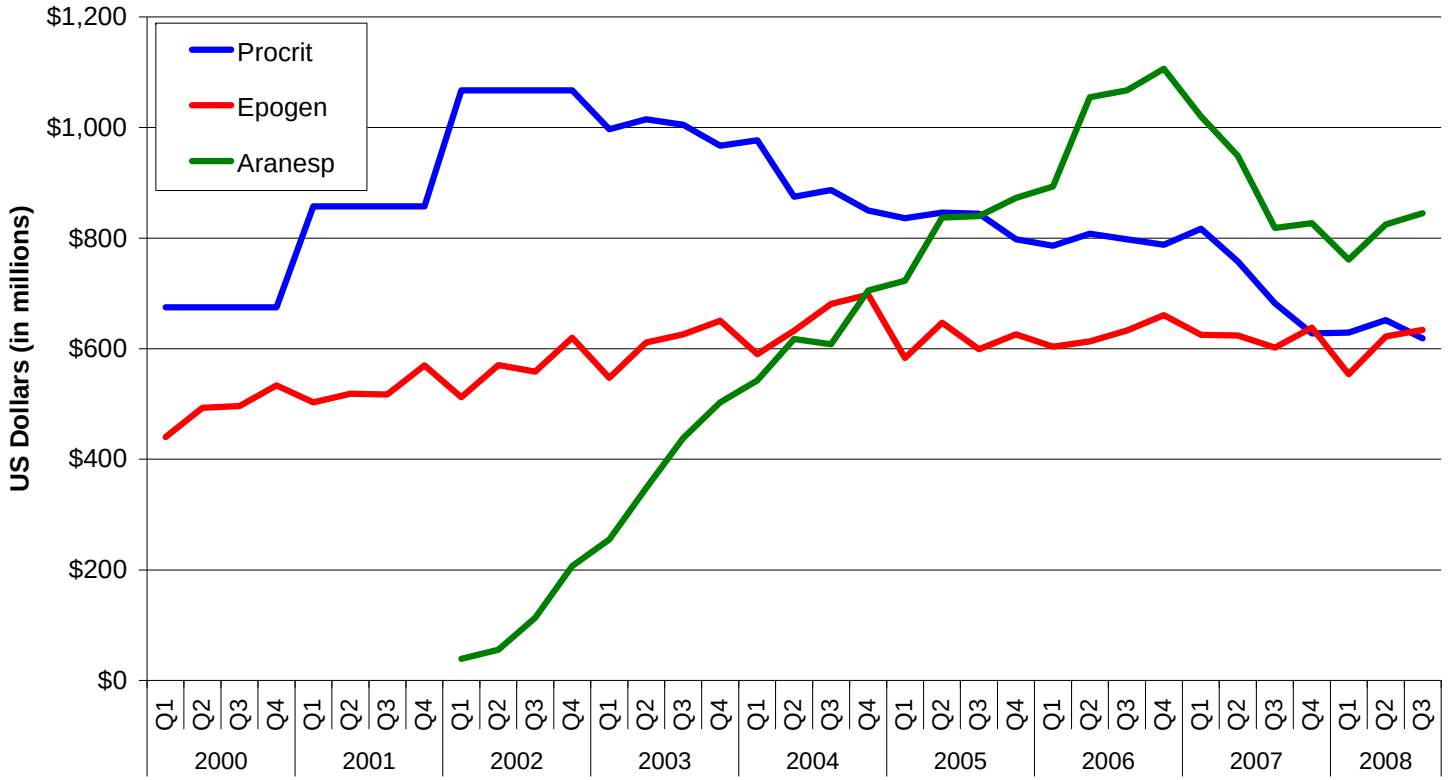
Sales of Products Originally Approved for Treatment of Colorectal Cancer



Sources: Genentech 10-K (2004-2007) and 10-Q (2004-2008), Bristol-Myers Squibb 10-K (2004-2007) and 10-Q (2004-2008), Amgen 10-K (2006-2007) and 10-Q (2007-2008).
Notes: Erbitux sales do not include sales by Merck KGaA.

Figure 2

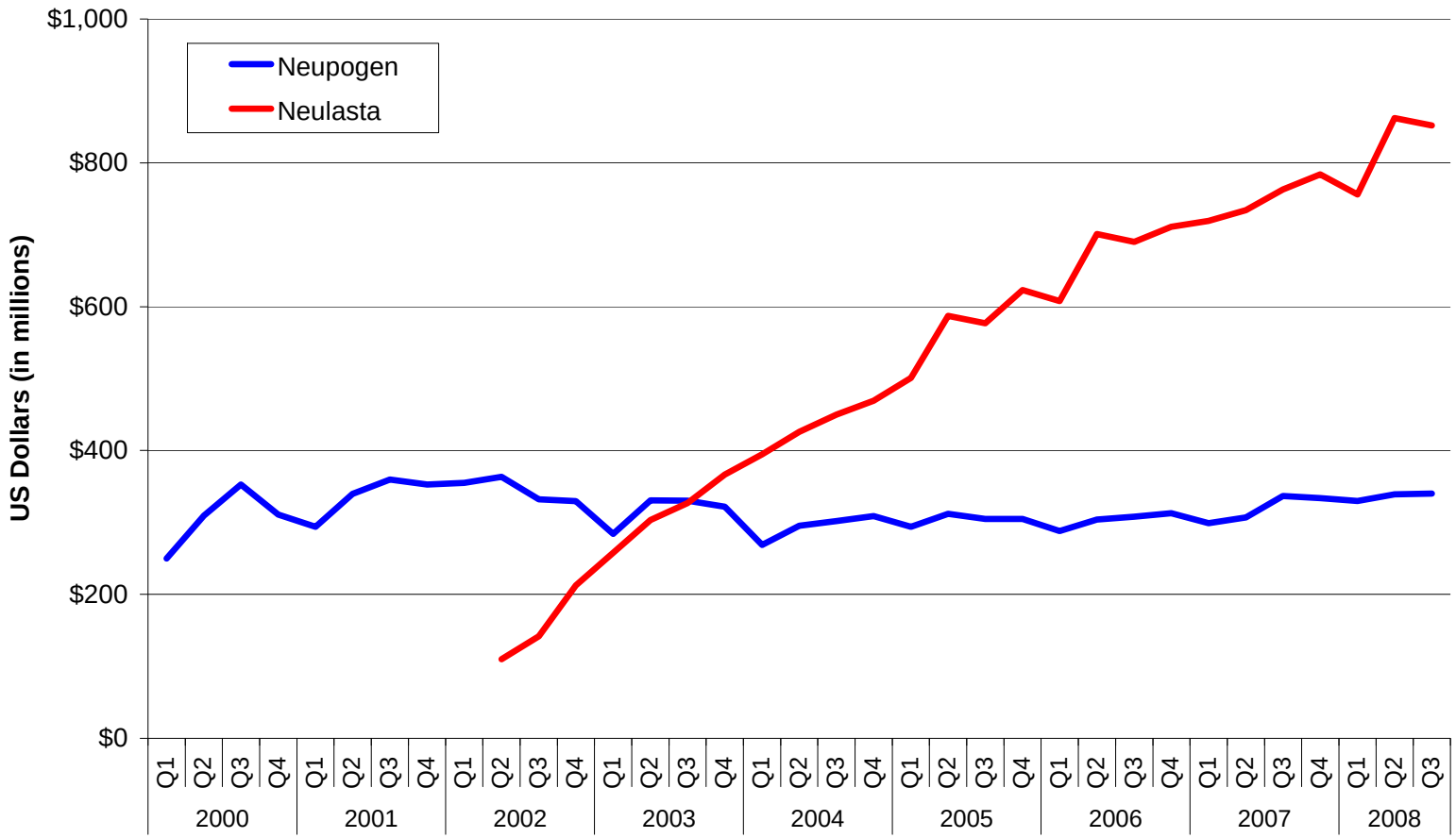
Sales of First Generation (Procrit/Epogen) and Next-Generation (Aranesp) ESA Products



Sources: Amgen 10-K (2000-2007), Amgen 10-Q (2000-2008), Johnson & Johnson 10-K (2001-2007), Johnson & Johnson 10-Q (2003-2008), and Tsao, A., "J&J's Rx for the Anxious Investor," *Business Week* , June 27, 2001.

Note: Quarterly sales were estimated for Procrit in 2000, 2001, and 2002 by dividing annual sales by 4 (quarterly sales were unavailable in these

Figure 3
Sales of First Generation (Neupogen) and Next-Generation (Neulasta) G-CSF Products



Sources: Amgen 10-K (2000-2007) and Amgen 10-Q (2000-2008).