Introduction

Current legislative proposals to establish a regulatory approval pathway for follow-on biologics (FOBs) raise questions regarding whether such policy will save the Federal government money, and if so, how much. By examining current biologics marketplace dynamics, reviewing the applicable literature, and assessing the experience with these products in other countries, Avalere Health has determined the likely parameters for each factor that will influence savings, and calculated the share of the impact on the Federal budget. The purpose of this work is to describe a budgetary scoring framework and to provide policymakers and stakeholders a realistic estimate of potential Federal budgetary savings over the ten year budget window (2008-2017).

In approaching this work, we identified the key factors integral to developing a scoring framework. In each of these areas, we describe the current biologics market dynamics, analyze the literature, evaluate the experience with biosimilars outside the United States, and then synthesize these insights to create scoring parameters. We show why we chose our final assumptions; as appropriate we compare and contrast our assumptions with other public FOB savings estimates. Once we have defined the baseline spending on biologics, we make key assumptions in our scoring framework to address:

1. Timing of FOB legislation and regulations;
2. Patent expiration and trade secrets;
3. Impact of market size on FOB entry;
4. Market share achieved by FOBs;
5. FOB pricing; and
6. Share of savings that will accrue to Federal health programs.

The elements of our Federal scoring model, as well as a discussion of where our assumptions might differ from other publicly-available estimates, are presented below, along with our modeling results.

Our approach does not attempt to parse savings to non-federal government entities, such as private payers and employers. In addition, our analysis is limited to the 2008-2017 budget window.

Finally, we create and rely upon a global framework—using readily-available data on aggregate spending, on the distribution of spending between classes of biologics, on the rates of adoption of new forms of biologics, and on historical trends and timelines related to legislative implementation, regulatory filings, and pricing behaviors. We have not developed a drug-by-drug estimate of on-patent/off-patent timing, nor have we estimated or modeled drug-specific utilization or pricing behaviors.

Baseline Spending on Biologics

Our scoring framework starts with an analysis of current spending on biologics. We used IMS data from 2005 which contains revenue data by product for all biologics on the market. We calculated total biologic spending in the United States at $32 billion in 2005.[1] Historical spending figures from IMS data show increases in spending over the last five years, with overall spending on biologics increasing by more than 20 percent annually on average since 2001. Introduction of new products, increased utilization, and price increases appear to be contributing factors driving this growth.

As researchers have noted, the biologics pipeline is large and growing.[2] New biologic products (with multiple years of patent protection left) are a factor driving the recent observed growth rates. Savings associated with the introduction of a regulatory pathway for FOBs depends in large measure on the movement of on-patent biologics to off-patent status. It is therefore important to understand the share of overall biologic spending growth that is related to the entry of new products so as not to overestimate the share of biologics spending subject to FOB competition in a given year. Accordingly we adjust our baseline to account for spending on off-patent products and spending on products likely to face FOB competition, and treat differently newly introduced products that we assume will not face FOB competition in the year they come to market.

We adjust our gross baseline calculation using data on the annual share of the *overall* biologics market that, historically, becomes subject to off-patent competition. These data consist of the aggregate spending on biologics, net of first-year spending of newly-available biologics. Thus, the adjusted baseline starting point is the overall market for biologics, net of first-year spending for newly-available biologics. To measure the spending attributable to new, patent-protected biologics, we calculate the portion of growth attributable solely to price inflation and increased utilization for older products, assuming the residual spending is from new products. To measure the share of growth for price and utilization we used National Health Expenditures (NHE) data, which are calculated by the Office of the Actuary (OACT) at the Centers for Medicare and Medicaid Services (CMS); NHE projects spending growth in the range of 8-10 percent annually over the next decade.[3] By removing from the baseline the first-year spending growth related to newly-available products, we calculate an adjusted baseline estimate for spending on current biologics comparable to our historic data of overall biologic spending potentially susceptible to FOB competition.

In addition to excluding first-year spending attributable to newly-available products, we also adjust the biologics baseline to account for spending on biologics for which there is currently an approval pathway for follow-on products. In the approval of Omnitrope in 2006, the Food and Drug Administration (FDA) expressed its view that an abbreviated approval pathway currently exists for follow-on versions of biologic products approved under the Food, Drug, and Cosmetic Act (such as insulins and human growth hormones).[4] However, for biologics approved under the Public Health Service Act, no such abbreviated approval pathway exists. Therefore, we model the effect of providing a new such pathway to this subset of current biologics, and we adjust the baseline to reflect this. Using 2005 IMS data, we estimate that 86% of total spending on biologics is for products for which there is not currently an abbreviated application pathway.

Both of these adjustments reduce the baseline modestly to more narrowly focus the model to calculate the effect of a FOB legislative proposal to the subset of biologics approved under the Public Health Service Act that we estimate may be subject to FOB competition.

Table 1: Projected Spending on Biologics from 2008-2017, With Downward Adjustments

In billions	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Baseline, unadjusted	$55.0	$66.2	$79.7	$95.9	$115.5	$139.1	$167.4	$201.6	$242.7	$272.2
Baseline, excluding first-year spend on new products	$48.1	$58.3	$70.3	$84.9	$102.5	$123.6	$149.0	$179.6	$216.7	$260.9
Baseline, net of FDCA biologics	$41.3	$50.0	$60.4	$72.9	$88.0	$106.2	$128.0	$154.3	$186.2	$224.1

The construction of this current law baseline is the starting point for our model. We then model the effect of the six additional factors (described below) that are likely to influence FOB budgetary savings. In this process, we develop an estimate of total spending on biologics when there are FOBs on the market. We then compare the first baseline estimate (pre-FOBs) with the estimate of spending with FOBs to generate an estimate of the national health care spending impact of FOBs on total biologics spending. We then attribute a portion of these costs and/or savings to Federal programs and spending to calculate an estimate of Federal budgetary savings in the 2008-2017 budget period. This methodology is typical of how Federal cost estimates for legislative proposals are produced. In this case, however, we are not scoring a specific proposal, so the model's inputs and outputs are based on a series of detailed assumptions and parameters consistent with a likely legislative approach to creating an FOB pathway scenario. These inputs and outputs are integral to conducting any cost estimate of specific FOB legislative proposals.

1. Legislative and Regulatory Timing for FOB Market Entry

A major lever affecting the potential savings from FOBs in the 10 year budget window (2008-2017) is the assumption about when FOBs are first able to enter the marketplace. Several public cost estimates predict FOB savings in the first year of enactment (see Table 2). Our own research suggests that this timing assumption is unrealistic. Two significant activities must occur between the passage of legislation and the subsequent market entry of FOBs: a) the promulgation of implementing regulations; and b) the submission and review of FOB applications under a newly created regulatory pathway.

Table 2: Cost Estimates of Savings to Payers from Approval of FOBs

Publisher	Year	Savings Accrued	Savings in First Year	Savings Over Ten Years
PCMA (Engel & Novitt LLP)[5]	2007	Medicare	$1.4 billion	$14 billion
Express Scripts, Inc.[b]	2007	Total US Spending	$13.7 billion	$71 billion

Promulgation of Regulations For the purposes of this analysis, we assume that FOB legislation is enacted in 2007 and has an effective date of October 1, 2007 (FY 2008). Once FOB legislation has been enacted, the FDA and other affected agencies must write implementing regulations to govern the application and review criteria for FOBs seeking to enter the market. Based on an analysis of prior lags between passage of legislation and promulgation of regulations by Federal agencies (see Table 3), we adopt a mid-line assumption that it will take the FDA three years to promulgate regulations to implement the new law. This assumption is supported by the observation that it took four years to generate the first of many regulations for a generic drug pathway under the Hatch-Waxman Act.[7] It is conceivable that the experience gained through that similar process will reduce the time it takes the FDA to promulgate FOB regulations, hence the three year assumption versus four.

We assume that FDA will communicate with the industry prior to promulgating the final regulations, and that FOB manufacturers will prepare to submit FOB applications (e.g. creating the FOB products, testing their safety and comparability to the reference product, and conducting other activities they anticipate will be required of them) during this time.

Table 3: Historical Experience of Time between Legislation and Promulgation of Final Regulations

Legislation	Final Passage	Final Regulations
Orphan Drug Act	January 1983	1998
Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman)	September 1984	1988 – 2003
Food and Drug Administration Modernization Act (FDAMA)	November 1997	1998 – 2005
Medicare Prescription Drug Improvement and Modernization Act (MMA)	December 2003	2005 (Medicare Prescription Drug Benefit)

As the FDA finalizes regulations, the steps necessary for FOB approval will be delineated. These steps could require clinical testing for some or all of the proposed FOB products. We anticipate that the FDA will require limited clinical tests in order for the agency to ascertain to what degree the FOB has achieved comparability to the reference product. Since the similarity of biologics is, in part, a function of the complexity of the underlying biologic protein, it is possible that the enacted legislation would require or authorize the FDA to create separate regulatory requirements for categories or classes of proteins based on their complexity. If this were to occur, we expect that the FDA would first tackle pathways for the less complex proteins, and over time, release regulatory guidance on more complicated proteins (as has occurred in the European Union's approach to regulating FOBs). Under this scenario, savings from FOBs targeting more complex biologics would occur later in the budget window because market entry would be delayed. For the purposes of developing our model, we took a simple approach with respect to timing and assumed a *single* pathway applicable to all biologics, that this pathway is created within three years, and either that FDA imposes minimal clinical testing requirements, or that manufacturers choose to conduct clinical testing contemporaneously with the FDA regulatory development process.

Review and Disposition of Applications In order to estimate the amount of time it would take for FDA to review FOB applications, we researched current application review times for

existing biologic products in both the United States and Europe. We found that application times vary by therapy area, geography, and time period, but that typical review times are around one year.[8] It is likely that, for the first set of FOB applications received by the FDA, the agency's review process will take longer than one year because of a lack of experience with the application process and the complexity of the products. Final disposition of FOB applications may also be delayed in the initial years because we expect that the FDA will have to process a number of FOB applications for already off-patent brand biologics. Therefore, the Avalere model assumes an average application review time of two years for the first applications FDA reviews after creating the FOB pathway.

The Avalere model predicts FOB applications will be submitted for many off-patent biologics as soon as the regulatory pathway is finalized. From a review of the trade press, we understand there are some companies interested in entering the market and producing FOBs. These companies will likely face several significant hurdles to entry, including: development of manufacturing facilities and/or contracting for manufacturing capacity; obtaining facility licenses from the FDA; procurement of necessary products for FOB manufacture; product testing; scaling production to supply the market; establishing distribution channels; and the creation of a sales force necessary to educate physicians and patients on the efficacy of these novel products.

Little has been written about how FOB manufacturers view these hurdles, and as a result it is unclear the progress FOB manufacturers may have made in overcoming them. For the purposes of this modeling exercise, we assume that FOB manufacturers will be able to overcome *all* of these hurdles, will be prepared to submit FOB applications *immediately* upon promulgation of final regulations, and will be prepared to introduce FOB products to the market *immediately* after FDA approval. If these assumptions are overly-optimistic, these supply-side delays would result in delays-to-market for some or many FOBs, and thus delay any savings to the Federal government resulting from FOB competition.

The table below describes the timeline we used to create our model.

Table 4: Model Timeline to FOB Entry

Effective Date of Legislation	Promulgation of Regulations	Submission of FOB Applications	FDA Review Time	FOB Entry
FY 2008	FY 2011	FY 2011	2 years	FY 2013

Given the model's 2008-2017 timeframe, our assumption set on the timing of implementing regulations and subsequent filing, and review and disposition of FOB applications is one of the major set of assumptions regarding the impact on Federal spending. The discussion above arrays our rationale for the five year delay between enactment of FOB legislation and the first availability of FOBs.

2. Patent Expiration Pace and Intellectual Property Considerations

A second set of assumptions critical to our model relates to the timing and pace of patent expiry of brand biologics. As stated in the section describing development of our baseline, Avalere analysis of patent information indicates that about 10 percent of the 25 highest revenue biologics are currently off-patent. Each year, additional, currently-available biologics

are expected to lose patent protection, even as new biologics enter the marketplace. Over time, patent expiry would, at first blush, increase the proportion of currently-available biologics that are off-patent. However, many current biologics have patents that extend through the 2008-2017 budget window, and when coupled with the introduction of new biologics with patent lives extending beyond the budget window, the overall proportion of off-patent biologics is estimated to remain at the 10 percent level identified by our analysis.

Our review of patent information indicates that currently marketed biologics are protected by a range of product and process patents; in addition, much of the information required to replicate the biotechnology process is protected as proprietary trade secret. Experience in small molecule markets clearly indicates that branded companies will aggressively seek to defend their patents and protect their intellectual property.

We conclude that it is not possible to predict with certainty when any given product will be available for follow-on competition. Because we chose an aggregate spending approach, we do not need to model the effect of individual biologics going off patent; rather we assume that, on average, 10 percent of baseline biologics spending will lose patent protection each year.[9] This rate of patent expiry roughly coincides with Avalere's analyses of patent expirations for individual biologic products.[10] This rate of patent expiry translates into approximately 25 products being open to FOB competition in the first year of entry (2013, see timing analysis above), and expanding to 35 products by the end of the budget window (2017).[11]

A complicating factor when assessing the timing of FOB entry is the importance of the manufacturing process to the characteristics of the final biologic product and the existence of patents covering the manufacturing process. These process patents are in addition to the patent on the biologic *protein*. Given the importance that the process plays in the quality, safety and efficacy of the biologic medicine, it may be challenging for FOB manufacturers to circumvent a process patent (whose expiry may differ from the protein's patent) even when the protein patent has expired.

Some manufacturing process information is held as trade secrets and therefore not publicly disclosed in the patents. Trade secret information may be important to product manufacture and thus be a hurdle for FOB manufacturers. We did not attempt to estimate the role of process patents, patent information release requirements, data exclusivity provisions, or unreleased trade secrets on FOB market entry timing as a factor in the model. As a result, to the extent such challenges delay further the introduction of FOBs, our model may over-estimate the potential Federal savings over the 2008-2017 period.

3. Impact of Market Size Dynamics on FOB Entry

To assess the extent to which FOB manufacturers will enter the market, we analyzed the current market dynamics for biologics and for generic drugs. Brand biologics command varying shares of the market within their class and in the total biologics market overall. A few biologics generate very significant annual revenues, a number generate mid-level revenues, and the majority of biologics report small revenues.

Capital markets are more likely to support entry into high-revenue categories, as the risks inherent in drug development can be offset in part by the potential for capture of larger markets. Further, because production of FOBs will require assumption of significant fixed costs of production and manufacture, we expect more FOB entry in classes where

manufacturers can expect to recoup the significant FOB development costs within a reasonable span of time. Similar to experience in the small molecule generics market, we assume that high revenue biologics would be more likely to generate FOB competition compared to mid-level and low revenue biologics (see Table 5). We also assume that the cost of producing FOBs would likely inhibit their entry into very small markets.[12]

Table 5: FOB Entrants by Biologic Market Size

Class	Annual Revenue Parameters	FOB Entrants Per Product
Large Revenue	> $1 billion	3
Medium Revenue	$250 million - $1 billion	1
Small Revenue	< $250 million	None

IMS data on market share provide a basis for these class distinctions. We chose to assume no FOB competition below the $250 million revenue level because this threshold approximates the annual revenues for Genotropin™, which has attracted only a single FOB competitor.

Other competitive forces could affect FOB potential market share but were not included in this model. We note that a common occurrence in pharmaceutical markets is incremental innovation, where the original innovator company will seek to improve their product by reformulating it with a superior side effects profile, more convenient dosing, or other features. These improved products often preserve or enhance the market share of the original branded product. In addition, manufacturers may introduce a biologic with one indication but may complete clinical testing to seek approval for other indications, thus affecting market share for products in those classes. While we expect this type of activity to occur in the biologics space, particularly for the more profitable biologics, we have not attempted to integrate the effect of such market activity into the present analysis. As such, to the extent such activity limits the marketability of FOBs in the face of incremental improvements to original biologics, our model may over-estimate the potential Federal savings over the 2008-2017 period.

4. Assessing FOB Market Penetration

Our model next considers the ability of the successful FOB manufacturer to sell its product(s) in the marketplace.

For the purposes of predicting what percent of the market FOBs will take from their brand counterpart, Avalere used research on market share gains by the small molecule generics as the point of reference. We did not use market share data from Europe for biosimilar products because the marketplace dynamics are still in the relatively early stages. In our model, we assume, at maturity, a 60 percent penetration rate for FOBs, with lower penetration in the first and second years because of adoption delays (patient transitioning) and adoption concentrated among new patient starts.[13] This market penetration rate is similar to overall generic utilization rates observed in the small molecule drug market across payers and patient populations.

This market share likely represents the upper-bound estimate over the ten-year window, given the newness of these products to both consumers and physicians and our assumption (discussed below, in detail) that FOB prices will not be priced dramatically lower than their

reference products. In addition, pharmacies are a significant driver of generic substitution of small molecule drugs, as a result of strong financial incentives, a supportive legal and regulatory climate, and favorable clinical and patient attitudes. By contrast, FOBs that are not deemed interchangeable may not be substitutable at or by the pharmacy – either by virtue of their label or the way in which state law treats pharmacy authority to substitute products. These factors would reduce market penetration – perhaps well below the estimated 60 percent rate.

On the other hand, payers and pharmacy benefits managers (PBMs) have clearly indicated their intention to move quickly and aggressively to encourage the utilization of FOBs as they have done with small molecule generics.[14] Because such a large percentage of biologics are provided in the physician office, payers and PBMs may elect to redesign benefits and to employ new utilization management tools for FOB products in order to try to achieve a level of substitution similar to that seen in the small molecule drug context.

Because of the two sets of countervailing marketplace pressures on potential market share gain for FOBs, we used a market share estimate consistent with current generic drug penetration rates, and consistent with predicted estimates of FOB penetration (see Table 6), -- with the understanding that actual penetration rates may be lower.

Table 6: Market Penetration Assumptions as a Share of Drugs Dispensed

Publisher	Year	Penetration Rate	Market Assumption
Henry Grabowski[15]	2003	64%	Generic drugs
Medicare Part D Compliance News[16]	2007	50-60%	Generic utilization in Part D
Express Scripts, Inc.[17]	2007	49%	Therapeutic alternatives
Pictet Funds[16]	2004	50-75%	Follow-on biologics
IMS Health market data	2005	33%	Share for three anemia biologics
Avalere Health	2007	60%	Follow-on biologics

5. Calculating Follow-On Biologic Pricing and Brand Biologic Pricing Response

While new FOB market entrants have a clear incentive to price lower than branded products, FOB manufacturers will also need to recoup the costs of development, manufacturing, and marketing of their products. Further, given the fewer number of expected entrants as described above, there will be an incentive for entrants to “shadow price” to the prices of brand products. In shadow pricing, firms choose to price their products just below the cost of the competitor product.

The Avalere model assumes FOBs will be discounted at 10 to 30 percent of the brand product prices, given the estimated higher production costs and the low number of market entrants in the near term (see Table 7).

Table 7: Estimates of FOB Pricing as a Discount off Brand Biologics

Publisher	Year	Estimate of Discount off Brand
Pictet Funds[19]	2004	10-20%
Generic Pharmaceutical Association (GPhA)[20]	2006	10-25%
PCMA (Engel & Novitt LLP)[21]	2007	5-30%
Express Scripts, Inc.[22]	2007	25%
Henry Grabowski[23]	2007	10-25%
Avalere Health	2007	10-30%

Analysts and stakeholders following the FOB policy debate have noted that the production, testing, and distribution costs for biologics are expected to be higher than the costs of bringing small molecule generics to market, and therefore predict that FOB discounts will be less than those experienced in the small molecule generic market.[24] For example, generic companies estimate that manufacturers' development costs will range between $10-40 million for FOBs[25] as compared to research by the Tufts Center for the Study of Drug Development citing $1-2 million for small molecule generics.[26] We assume that higher production costs for FOBs will translate into lower discounts than are typical for generic drugs. [27]

Researchers have also noted that generic pricing in the small molecule market is related to the number of generic market entrants – that is, as the number of entrants increases, the prices of both the generics and the brand decrease until the generics are "price takers." Our model adopts this pricing scenario. We expect FOB manufacturers to price relative to the reference product's price and to each other. With limited competition from other FOBs in some markets, we believe discounts will be small. Further, if payers and PBMs choose – or are forced – to treat FOBs as therapeutic alternatives to the reference biologic (rather than interchangeable), then the market may not respond the same way it has to pharmacy benefit structures that shift patients to generics.

We expect that FOBs will shadow price relative to the brand, and that in classes with more FOBs, prices will drop more than in markets with fewer FOBs (See Table 8). As is common in the small molecule drug market, we expect brand biologics manufacturers will increase the price of their product in the first year FOB competitors enter the market.[28] We then estimate a gradual lowering by 30 percent in pricing of the brand biologic. The table below provides details on our assumption for the pricing relationship between FOB entrants and the brand biologic. All price changes are relative to the brand biologic's price in the year prior to FOB entry.

Table 8: FOB and Brand Biologic Pricing in Years after FOB Market Entry, Expressed as Percent of Brand Biologic Price

	Year 1	Year 2	Year 3
Large Revenue Markets			
Brand Price	105%	85%	70%
FOB Price (3 FOBs)	80%	60%	49%
Medium Revenue Markets			
Brand Price	105%	90%	90%
FOB Price (1 FOB)	90%	81%	81%

6. Estimating Federal Budgetary Savings

Our model is designed to model budgetary savings to the Federal government over the 2008-2017 budget period that are attributable to legislation establishing a regulatory pathway for the introduction of FOBs. We have not modeled savings to entities other than the Federal government that may benefit from FOB legislation (private insurers, employers, consumers), and we have not modeled savings that may accrue in the post-2017 timeframe.

Our model starts with developing an aggregate baseline estimate of overall (Federal and non-Federal) biologics spending over the ten-year budget window. We then estimate how long it will take for legislation, regulation, and industry activity to produce a regulatory and product development pathway for the review and disposition of FOB applications. The model predicts the share of brand biologic savings going off patent in any given year and then estimates the number of market entrants, attaches pricing assumptions to those competitors, and develops an estimate of the resulting FOB market share. Avalere's model estimates that if FOBs come to market in 2013 (see Section 1, above), there will be an initial modest cost to the health care system as the brand biologics respond to the prospect of impending FOB competition by raising their prices while still maintaining large market shares. As FOBs begin to enter the market, our model predicts that these initial costs to the health care system will be offset by savings attendant to the assumed lower prices of FOBs and their gradually rising market share.

Policymakers in the Administration and Congress typically rely on budgetary estimates to assess the impact on the Federal budget. Avalere's estimate focuses on the Federal share of savings from FOBs; which is approximately 40 percent of the total savings, using estimates of the Federal share of pharmaceutical spending.[29] Due to the time we estimate it will take to create the pathway, we do not expect savings to occur during the five year budget window. Over the 2008-2017 budget window we estimate savings to the Federal government to be $3.6 billion (see Table 9). This savings figure would likely be smaller if less conservative assumptions were used with respect to market penetration that was based on actual FOB experience, or if other factors were incorporated into the model such as competition from additional innovative biotechnology entrants.

Below we provide our estimate of savings to the Federal government from FOB market entry:

Table 9: Projected Share of Savings Accrued to Federal Health Programs from 2008 to 2017

In billions	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2008-2017
Federal Effect	$0	$0	$0	$0	$0	$0.1	$(0.4)	$(1.0)	$(1.1)	$(1.2)	$(3.6)

Summary

Our work seeks to incorporate published literature, current pharmaceutical marketplace dynamics, and relevant experience in Europe with biosimilars to create a model that provides a reasonable estimate of the potential savings from FOBs over the next decade. We do show Federal budgetary savings, albeit in the latter portion of the scoring window. The assumptions that affect our estimate most are those pertaining to FOB entry timing after promulgation of regulations, FDA review times, and estimated market penetration rates.

The purpose of this study is not to assert a single scoring estimate, but to lay out an approach to assessing the potential savings from FOBs for public comment and review. We stress that many of our assumptions are subjective, although in most cases they are anchored back to existing literature. Further, our analysis is not based on a single legislative proposal, and as additional legislative concepts are layered into bills it is likely that further analysis will be required to accurately assess their effects on Federal spending.

[1] Avalere estimate using IMS data from March 2006 for calendar year 2005.
[2] Pharmaceutical Researchers and Manufacturers. "Medicines in Development." *Biotechnology*, July 2006. http://www.phrma.org/files/Biotech%202006.pdf, Accessed April 2007. Dolan, Kerry A. "Biology Rising." *Forbes.com*, May 12, 2006. http://www.forbes.com/2006/05/12/merck-pfizer-amgen-cz_kd_0512biologics_print.html. Accessed April 2007.
[3] National Health Expenditures Projections 2006-2016, http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2006.pdf. Accessed March 2007.
[4] Food and Drug Administration, "Omnitrope Questions and Answers" (2006), http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm. Accessed March 2007. Food and Drug Administration, "FDA Response to Citizens Petitions Related to Omnitrope" (2006), http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf. Accessed March 2007.
[5] Engel & Novitt, LLP. "Potential Savings That Might Be Realized By the Medicare Program From Enactment of Legislation Such As The *Access to Life-Saving Medicine Act* (H.R. 6257/S. 4016) That Establishes a New cBLA Pathway For Follow-on Biologics," *Pharmaceutical Care Management Associates* (January 2007).
[6] Miller, Steve and Jonah Houts. "Potential Savings of Biogenerics in the United States," *Express Scripts* (February 2007). Model estimates savings accrued from four therapeutic categories: interferons for multiple sclerosis, erythropoietin for anemia, growth hormone for growth failure, and insulin for diabetes.
[7] The FDA and other agencies have released a series of regulations relating to Hatch-Waxman amendments since passage of the law in 1984. We expect that in implementing a FOB pathway, FDA may also release multiple regulations, but do not attempt to model each release; instead we assume the FOB pathway regulations will be released
[8] Tufts Center for the Study of Drug Development. "EMEA Meets Performance Goals, But Lags U.S. FDA In Drug Approvals." *Impact Report*, January/February 2007.
[9] Congressional Budget Office, How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry (1998). The CBO study says that brands typically have 9-12 years of patent exclusivity on the market before generic entry.
[10] Based on preliminary Avalere analysis of patent expiry for biologic products in the top 25 for overall revenues, two-thirds of those products have patents that would not allow for follow-on biologic competition until after 2011.
[11] "Biogenerics: Long Rainbow, Small Pot of Gold; Limited Risk for Biotechs." *Bernstein Research*. October 27, 2006.

Bernstein assumes that five product markets may have FOBs by 2011, and an additional 50 products could be targeted.

[12] Grabowski, Henry, Iain Cockburn and Genia Long. "The Market for Follow-On Biologics: How Will It Evolve?" *Health Affairs* (September/October 2006).

[13] Grabowski, Henry G. "Patents and New Product Development in the Pharmaceutical And Biotechnology Industries", *Proceedings* (September, 2003). "Medicare Part D Generic Dispensing Rates for PDPs," *Medicare Part D Compliance News* (March 2007).

[14] See, for example: Houts, Jonah. Testimony Before the Committee on Oversight and Government Reform, U.S. House of Representatives. *Express Scripts, Inc.* March 2007. http://oversight.house.gov/documents/20070326173059-55945.pdf. Accessed April 2007.

[15] Grabowski, Henry G. "Patents and New Product Development in the Pharmaceutical And Biotechnology Industries", *Proceedings* (September, 2003). Penetration rate for generics after one full year on the market.

[16] Medicare Part D Compliance News. Medicare Part D Generic Dispensing Rates for Stand-Alone PDPs. March 2007.

[17] Miller, Steve and Jonah Houts. "Potential Savings of Biogenerics in the United States," *Express Scripts* (February 2007).

[18] "A Perspective on the Biogeneric Opportunity," *The Pictet Funds Biotech Newsletter* (April 2004).

[19] "A Perspective on the Biogeneric Opportunity," *The Pictet Funds Biotech Newsletter* (April 2004).

[20] "Biogenerics." *Generic Pharmaceutical Association.* http://www.gphaonline.org/AM/Template.cfm?Section=Federal_Affairs&CONTENTID=1948&TEMPLATE=/CM/HTMLDisplay.cfm. Accessed April 2007.

[21] Engel & Novitt, LLP.

[22] Miller, Steve and Jonah Houts. "Potential Savings of Biogenerics in the United States," *Express Scripts* (February 2007).

[23] Grabowski, Henry. Testimony to House Oversight and Government Reform Committee. March 26, 2007.

[24] See for example: "Follow-On Protein Meeting Sheds More Light on Topic," *BioWorld Today* (March 2, 2005); "Panelists Revisit Economics," NORD Conference: Exploring the Pathway to Generic Biologics (March 2003). SG Cowen Securities Corporation, Industry Report: Biotechnology – What's In Front of the FDA (October 1, 2004).

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[29] National Health Expenditures Projections 2006-2016, http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2006.pdf. Accessed March 2007.

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