Milliman Client Report

Prepared by:

Frank Kopenski Jr., MAAA
Principal and Consulting Actuary

Commissioned by Amgen Inc.

December 2011

Milliman

Understanding biosimilars and projecting the cost savings to employers

Milliman is among the world's largest providers of actuarial and related products and services. The firm has consulting practices in healthcare, property & casualty insurance, life insurance and financial services, and employee benefits. Founded in 1947, Milliman is an independent firm with offices in major cities around the globe. For further information, visit milliman.com.

TABLE OF CONTENTS

FOREWORD

One of the highest-trending components of healthcare expenditures today is specialty drug products. Depending upon the source, the average cost per prescription is trending at 8% to 12% and the utilization is trending at 8% to 10%. Whether provided under the medical benefit or drug benefit, these drugs associated with increasingly more common high-cost healthcare conditions such as cancer, rheumatoid arthritis, multiple sclerosis, etc., have become a bigger concern for employers.

The largest component of specialty drugs are *biologics*. In simplest terms, these are drugs that are manufactured in a laboratory using living organisms such as human protein. Currently, biologic drugs are assumed to be high-cost drugs of perhaps greater than $1,000 per prescription or $100 per dose. However, insulin analogs and some other drugs such as vaccines are of much lower cost and some may consider these drugs to be biologics based on the manufacturing process. Appendix A shows the list of drugs we considered to be biologics for this study after an extensive and subjective review of all specialty-type drugs. We did not include insulin analogs or all vaccines in our employer savings analysis.

The prescription drug market has and continues to undergo dramatic change as most of the longtime blockbuster drug products have seen or will see their patent(s) expire and cheaper priced generic products take their place. The patented drugs that are left will be predominantly specialty drugs because over the past 10 years, drug manufacturers have focused on biologic science for the treatment of certain diseases, cancer, and chronic conditions. There is no better evidence of this than the 2010 U.S. Food and Drug Administration (FDA) drug approval list, which consists of about 75% specialty drug products.

In the last 18 months, Congress, through the Patient Protection and Affordable Care Act (PPACA) and more specifically the Biologics Price Competition and Innovation Act of 2009 (BPCIA), has determined that chronically ill patients should have access to lower-cost drug alternatives, which has brought biologics and biosimilar drugs into the spotlight. Biosimilars, or follow-on biologics as they are often referred to, are approved drugs that attempt to replicate the original biologic drug manufacturer's development processes. Since the uninsured population has bigger concerns about healthcare than merely the prescription drugs they use, this paper focuses on biosimilars as they relate to the employer market and fully insured or self-insured members (employees and dependents). As Medicare is the primary insurance for retirees through benefit coordination, this paper further pertains to only active employees and their dependents.

I. INTRODUCTION AND OTHER FINDINGS

The following study covering the period 2010-2016 is a result of Milliman research and cost modeling analysis, using primarily 2010 commercial group actual prescription drug experience. The purpose of this study is to quantify the impact of biosimilar savings to employers and take a closer look at the potential drivers of cost savings and their variability.

The assumptions for this work were consistent with information that was available at the time the work was performed over the course of 2011. Given the time to publication, some of this information may have changed or new information may have become available, which would lead to modified assumptions and perhaps different results. We expect to update this analysis in 2012.

This study focuses on:

- Identifying biologic drugs and the percentage of overall healthcare costs they represent
- Consideration for the FDA approval pathway for brand-name drugs and generic drugs and reviewing the current status for biosimilars
- Creating an estimated savings timeline that projects employer savings based on sound actuarial assumptions using empirical data
- Evaluating the importance and impact of physician/patient behavior, market penetration, biosimilar pricing, and benefit design on employer savings

Employers can use the study to help understand the implications of such changes on future healthcare expenditures and determine the timing and to what extent human resources need to be devoted to this area of their healthcare cost management.

The results of the study might be different if the focus were on the senior population or state exchanges brought about by the PPACA.

Judith A. Johnson, a specialist in biomedical policy with the federal government agency Congressional Research Services (CRS),[1] recently wrote:

> The cost of specialty drug products, such as biologics, is often prohibitively high. For example, the costs per year (in 2009) of some commonly used biologic drugs: Enbrel for rheumatoid arthritis, $26,000; Herceptin for breast cancer, $37,000; Rebif for multiple sclerosis, $40,000; Humira for Crohn's disease, $51,000; and Cerezyme for Gaucher's disease, $200,000. A pathway enabling the FDA approval of follow-on biologics (i.e., biosimilars) will allow for market competition and reduction in prices, though perhaps not to the same extent as that which occurred with generic chemical drugs under Hatch-Waxman (P.L. 98-417).
>
> In contrast to chemical drugs, which are small molecules and for which the equivalence of chemical composition between the generic drug and innovator drug is relatively easy to determine, a biologic, such as a protein, is much larger in size and much more complex in structure. Therefore, comparing a follow-on protein with the brand-name product is more scientifically challenging than comparing chemical drugs. In many cases, current technology will not allow complete characterization of biological products. Additional clinical trials may be necessary before the FDA would approve a follow-on biologic.

It is important to note that Ms. Johnson, who works for the federal government, acknowledges the following:

- The cost for many biologics is prohibitively high for some patients.
- The biosimilar pricing may not be as deeply discounted as some might expect from historical generic pricing.
- The complexity of the manufacturing process makes it improbable to replicate a biologic drug precisely.
- As opposed to the current FDA generic drug approval pathway, biosimilars may require some degree of clinical trials.

Dr. Pablo Fernandez, senior vice president, medical affairs,[2] PharmaNet, wrote late last year:

> In light of the uncertain global regulatory environment and as the worldwide market for biosimilars continues to grow, mounting pressure will be placed on biopharmaceutical manufacturers as they jockey for position within the newly competitive marketplace. In spite of the uncertainties, one certainty remains: the need for significant R&D investment to get a biosimilar to market.
>
> The manufacture of biosimilar drugs requires specialized capabilities, meticulous planning, highly skilled staff and significant financial investment. This investment could, however, place strain upon a company, draining its resources and diluting its overall success.

Thus, deeply discounted biosimilars will be a challenge, particularly if extensive clinical trials are required.

A somewhat opposing viewpoint of Mark McCamish and Gillian Woollet[3] states:

> Biosimilars can have a major impact on the affordability and availability of important biologic medicines in all markets. Approval of biosimilars will facilitate patient access, and lower costs, thus making healthcare dollars available for the next generations of originator medicines.
>
> The quality of the biosimilars and the originator biologics to which they refer will be the same if the FDA applies consistent science-based and data-driven standards equally to all products. The U.S. is already the leading market for biotechnology-based products. Having led the world with the development of comparability in 1996 through guidance alone, we believe that the FDA has the expertise and experience needed, and is ideally suited, to review and approve biosimilar applications now. The FDA can encourage biosimilar applications today by expressing confidence in the science, as well as in their own reviewers experience and expertise.

Articles and testimonials on biosimilars generally discuss two important terms, biosimilarity and interchangeability. Biosimilarity is the determination that a new drug meets enough criteria to be effective in treating a particular condition without creating unreasonable safety concerns. Biosimilarity allows a new drug to compete against an existing biologic using a similar manufacturing process. Interchangeability goes one step further by saying the biosimilar drug can be substituted for the biologic drug without a material outcome difference. This would also imply that a patient could switch back and forth between two or more similar drugs without issue. Thus biosimilarity does not in and of itself imply interchangeability. From a cost savings and market penetration perspective, interchangeability is significant. Without interchangeability, a pharmacist, pharmacy benefit manager (PBM), and benefit design will have little impact on biosimilar market penetration. Biosimilar market penetration would be almost entirely dependent upon the physician, patient, and price. Interchangeability would not be an issue for new patients who have had no prior history of using either the biologic or biosimilar.

II. THE BIG PICTURE

Biologic drugs represent about 4% to 5% of the total healthcare spend for a commercial population. Less than 1% of employees and their dependents utilize biologic drugs, but the average biologic drug cost is roughly 40 times the average cost of a non-biologic drug, making it a much more significant topic from a cost perspective than a utilization perspective. A 30% savings due to biosimilars would represent a 1.2% to 1.5% reduction in the employer cost to provide healthcare benefits. For comparison, a $1.00 increase in the generic copayment translates into a 0.8% reduction in the employer cost to provide healthcare benefits.

Table 1 provides a breakdown of 2010 biologic cost experience for the nationwide average commercial population based on Milliman research. This data forms the basis for the savings projections provided later in this paper.

TABLE 1: 2010 COMMERCIAL POPULATION, BIOLOGIC ESTIMATED COST PMPM

BIOLOGIC DRUG	MEDICAL BENEFIT	DRUG BENEFIT	TOTAL
ENBREL	$0.01	$1.70	$1.71
REMICADE	1.36	.08	1.44
HUMIRA	.01	1.30	1.31
COPAXONE	.01	.94	.95
AVASTIN	.84	.00	.84
NEULASTA	.73	.09	.82
AVONEX	.00	.70	.70
RITUXAN	.54	.01	.55
ALL OTHER	2.99	3.32	6.31
TOTAL	$6.49	$8.14	$14.63

Source: Milliman 2010 proprietary data for a large, multi-payer commercial population. See Appendix A for a full list of biologic drugs represented in this study.

The $14.63 per member per month (PMPM) represents the historical gross cost before member cost sharing of biologic drugs provided in a hospital outpatient setting, physician's office, retail pharmacy, mail pharmacy, or specialty drug pharmacy. If drugs provided under the medical benefit are improperly coded (i.e., misuse of appropriate Level II HCPCS codes such as J, S, and Q) or are part of a bundled payment, then the medical PMPM of $6.49 PMPM may be understated. The use of the distinct National Drug Code (NDC) for retail, mail, and specialty pharmacy claims under the drug benefit makes material cost understatement highly unlikely.

Table 1 provides some evidence for the fact that each drug product, based on dispensing requirements or administrative complexity, is conducive to delivery under either the medical benefit or the prescription drug benefit but not equally across both benefits. An important consideration for employers is where these drugs belong from a benefit design, cost management, and price perspective. Dosing under the medical benefit is per treatment, whereas dosing under the drug benefit is typically based on a monthly fill, which, for drugs that are this expensive, is a significant concern from an unused and thus wasted medication perspective. However, there may be more clinical pharmacist intervention and thus drug management under the drug benefit.

At this time, the BPCIA provides a 12-year exclusivity period from date of first licensure for the biologic drug, so over the next five years, regardless of the FDA biosimilar approval pathway, biosimilar penetration in the market will be incremental. Using the earliest date for exclusivity expiration with no further marketing delay, it will take until 2016 before nearly all of the current biologic drug cost would be eligible for biosimilar savings. New biologic drugs entering the market in 2011 and later would not be impacted until beyond 2016 and conceivably as late as 2023. New therapies could render older therapies unmarketable, delaying further the impact of biosimilars. Table 2 shows the 2010 biologic cost of $14.63 PMPM incrementally as exclusivity expires. Newly approved biosimilar type drugs in 2010 had little market share.

TABLE 2: 12-YEAR EXCLUSIVITY EXPIRATION FOR 2010 HISTORICAL BIOLOGIC DRUG COST OF $14.63 PMPM

	2011	2012	2013	2014	2015	2016
PMPM	$8.79	$0.15	$1.06	$2.37	$0.36	$1.50
PERCENTAGE	60.1%	1.0%	7.2%	16.3%	2.4%	10.2%
CUMULATIVE %	60.1%	61.1%	68.3%	84.6%	87.0%	97.2%

Source: Milliman 2010 proprietary data for a commercial population. See Appendix A for a full list of biologic drugs represented in this study.

More than 50% of the cost for biologics is represented by drugs whose 12-year exclusivity is coming to an end. Thus the exclusivity time period established by the BPICA is not a great barrier to biosimilars unless, through litigation, the biologic drug manufacturer is able to extend the exclusivity period for additional years (e.g., evergreening).

III. THE DEBATE: BIOSIMILAR = GENERIC VERSUS BIOSIMILAR = BRAND

On November 2 and 3, 2010, the FDA held a hearing to gather testimonials from patient advocacy groups, providers, researchers, PBMs, and drug manufacturers on what approach should be taken with respect to the biosimilar approval process. Over the two days, more than 40 presenters provided opinions and answered questions from the FDA panel. The 784-page transcript[4,5] from the two-day hearing can be condensed into two mostly conflicting viewpoints or positions. Those two positions can be summarized as follows:

POSITION 1

- Patient safety and drug effectiveness are most important.
- It is not necessary to have unique nonproprietary names for biosimilars in the same drug class using similar manufacturing processes (similar to current generic naming convention).
- A pharmacist should be permitted to substitute biosimilars for biologics similar to generic substitution.
- The BPICA 12-year data exclusivity is too long and evergreening (i.e., obtaining multiple patents for separate attributes of the same product) should not be permitted.
- Biosimilar manufacturers should be able to use biologic clinical trial data and follow-up data in the approval process with possible payment for some of the original biologic manufacturer R&D cost.
- The FDA should abide by the Declaration of Helsinki Article 20 (a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association [WMA]) in order to minimize unnecessary human trials.
- The biosimilar price is dependent upon how rigid the interchangeable definition is and the extent to which clinical trials are required in the abbreviated approval pathway.
- Evidence used in gaining biosimilar approval in Europe through the European Medicines Agency (EMA) should be allowed as evidence for U.S. approval.
- Biosimilarity for one indication should be used for other indications.

POSITION 2

- Patient safety and drug effectiveness are most important.
- It is necessary to have unique names for biosimilars since no two will be alike and patients need to be able to identify the name of the drug they are taking, not the NDC or HCPCs code.
- A pharmacist should not be permitted to substitute biosimilars for biologics.
- The BPICA 12-year data exclusivity is appropriate given the research and development costs.
- The biosimilar should be required to go through appropriate pre-clinical and clinical trials to satisfy safety and effectiveness requirements.
- Biosimilar price is dependent upon how rigid the interchangeable definition is and the extent to which clinical trials are required in the abbreviated approval pathway.
- Evidence used in gaining biosimilar approval in Europe should not be allowed as evidence for U.S. approval.

- Biosimilarity must be shown for each drug indication and drug packaging should clearly state if the biosimilar product has not been approved for other indications that the biologic was approved for.

It is important to note that current manufacturers of biologic drug products will also be manufacturing biosimilar drugs primarily for biologic drugs they currently do not manufacture but perhaps even for drugs they do manufacture. Because of this business strategy, current biologic drug manufacturers do not all take Position 2 in the debate.

It was apparent that the FDA panel though rigorous questioning was trying to find some common ground that would bring the two positions closer together and perhaps make any preliminary biosimilar approval pathway somewhat of a compromise between the two positions. Based on the line of FDA questioning and the strength of the testimonials, one might conclude that the abbreviated approval pathway process for biosimilars will incorporate:

- Primary attention to patient safety and drug effectiveness.
- Some FDA incorporation of the EMA approval pathway and allowance for information used to approve the same biosimilar in Europe to be transferred to the U.S.
- Some degree of pre-clinical and/or clinical trials but not to the same extent as the biologic.
- A distinct proprietary name for each drug.
- Separate biosimilarity evidence for each drug indication.
- The pharmacist may be able to switch products but not for all biosimilars (i.e., interchangeability may be assigned on a case-by-case basis depending on the evidence provided during the biosimilar drug approval process).

The FDA heard extensive testimony on November 2 and 3, 2010, and also received written comment up until December 31, 2010, that it needed to wade through. It is not surprising that as of this writing, the FDA has not provided even a preliminary pathway for biosimilars that would be open to comment. We believe that the biggest issue the FDA faces is not the process, but determining first how to measure biosimilarity and second what additional criteria may be required to establish interchangeability.

One might look at the process as establishing an acceptable range of outcomes or variance from a single point or biologic outcome. However, over time the biologic drug experiences what is known as *drift*, or changes in the product due to new batches or manufacturing changes. Thus, an acceptable expectation for the biosimilar might be a range of outcomes around two distinct biologic outcome end points. The drift for any biologic product would not be represented by a single constant value. As an analogy, the approval process would hinge on the biosimilar falling between two goal posts where the distance between the goal posts is determined on a biologic drug case-by-case basis and represents an acceptable range of patient outcomes. The FDA would also need to consider at what point the difference between the goal posts becomes so wide as to constitute a new product.

Another significant issue that the FDA faces in determining interchangeability is *switching*. Switching involves a comparison of patient outcomes when a drug is used, then changed, and then changed back to the original drug again. In order to perform clinical trials on switching, a sample population may need to be observed for two to three years to allow ample time to measure the switching outcomes. Requiring a switching test would delay the approval process and certainly add to the cost of the biosimilar drug.

IV. DRIVERS OF BIOSIMILAR COST SAVINGS

The estimated savings impact of biosimilar drugs on employer healthcare costs will depend upon many factors. Some of these factors will have a more significant impact than others, and there may be some factors that emerge over time that are currently unknown. Future biosimilar drug cost savings may be dependent upon the following key cost drivers:

- The FDA approval pathway for biosimilar drugs and the length of data exclusivity protection (i.e., 12 years at this time) for the innovator biologic. Savings begin to be measured from the point of biosimilar introduction to the market, which will be different by drug therapy class and drug product.
- Assumed list of biologic drugs currently on the market, since new biologic product patents would preclude analysis of biosimilar counterparts until well beyond the study period (2011 to 2016) of this paper.
- The degree to which physicians accept and choose to dispense the biosimilar product in lieu of the original biologic (i.e., physician behavior).
- The degree to which newly diagnosed patients, differentiated from currently treated patients, accept the physician-recommended biosimilar product (i.e., patient behavior).
- Future trends in specialty and biosimilar drug utilization and cost per prescription including the continuing decline in the cost of protein synthesis.
- The price differential between biosimilar and biologic at point of market entry and over ensuing years.
- Shift in biologic/biosimilar drug dispensing from the medical benefit to the pharmacy benefit or vice versa.
- Potential increased/decreased drug and medical utilization due to increased/decreased side effects of biosimilars above and beyond the known side effects of the original biologic counterpart.
- Employer benefit changes (e.g., copay differential) to incentivize the use of biosimilars.
- The ultimate market penetration rate for biosimilars, which is dependent upon other cost savings drivers.
- The percentage of new patients using biologics for the first time to treat existing or newly diagnosed healthcare conditions.

Future drug savings will be sensitive to each of these cost drivers to a different extent, with patient/physician behavior, biosimilar penetration rate and price differential playing the most significant part in the savings outcome.

The remainder of this section provides an in-depth discussion of each assumption or cost driver.

FDA APPROVAL PROCESS AND DATA EXCLUSIVITY PERIOD

The FDA has yet to determine the abbreviated pathway for biosimilar drugs. There are drug manufacturers that are already making copies of biologic drug products whose exclusivity has expired in anticipation of entering the FDA queue as soon as the approval process is released. Regardless of the FDA timeline, based on the provisions of the BPICA, the innovator biologic has minimum exclusivity protection of 12 years. The 12-year period is currently being challenged by President Obama, who has recommended a shorter seven-year period.

Our analysis considered biosimilar introduction based on either the FDA patent expiration date or the data exclusivity date. According to Henry Grabowski of the American Enterprise Institute, “One of the most contentious issues is the data exclusivity period for a new biologic (also called the data protection

period). This is the period after a new product's approval before an imitative product can rely on the innovative firm's safety and efficacy data to enter the market with an abbreviated filing. This is relevant when there is little patent life after FDA approval, which can happen for a variety of reasons. For small molecular drugs, the Hatch-Waxman Act provides for five years of base data exclusivity and a stay on generic entry of up to 30 months in cases when the product is still subject to patent challenge. Patent challenges by generic firms have become rampant in recent years, and almost all commercially successful drugs are subject to patent challenges early in their product life cycles. The costly litigation process is problematic and needs to be resolved, as it leaves manufacturers uncertain about the length of time new drugs will have patent protection. Given that patents in biologics are often narrower in scope and subject to more uncertainty than those for small molecular drugs, the length of the data exclusivity period has become a particularly important issue in the deliberations over an abbreviated pathway for biosimilars."[6]

In most cases, the data exclusivity date would delay the biosimilar introduction until sometime after the patent expiration date.

We utilized various sources, including the FDA's Drug Approval Information webpage,[7] to estimate the point at which a biosimilar might enter the market for each biologic product in our study.

BIOLOGIC DRUG LIST

Appendix A shows the list of drugs we considered to be biologics for this study after an extensive and subjective review of all specialty-type drugs. We did not include insulin analogs or all vaccines in our employer savings analysis. Expansion or contraction of this drug list would change the resulting cost savings in this report but not necessarily the conclusions.

PATIENT / PHYSICIAN BEHAVIOR

There are differing opinions over how patients and prescribing physicians will react to lower-cost biosimilar drug products. One position is that patients will be very receptive to alternatives that provide some cost relief and some physicians believe that a number of the biologic drugs are not as complex as advertised and biosimilar drugs will closely replicate or possibly improve treatment effectiveness with minimal additional risk to the patient.

Another position is that patients who recognize the life sustaining or lifesaving significance of their current treatment will be unwilling to risk using cheaper medications that may (even if there is no clinical basis for that reasoning) be less effective and/or may introduce adverse healthcare outcomes. Concurring with these patients are some physicians who may not wish to risk currently successful treatment by changing the medication.

We believe that newly diagnosed patients for high-cost healthcare conditions such as multiple sclerosis (MS) will be more accepting of biosimilar drugs, having no prior treatment success for comparison. Patients currently being treated with innovator biologics will be less apt to take the risk of potential biosimilar unintended side effects unless affordability is an issue.

We assumed the following ranges for behavior:

New patients (i.e., first time biologic user) – 5% to 10% of total biologic users

New patient acceptance of biosimilars – 50% to 75%

Existing patient acceptance of biosimilars – 25% to 50%

Note: An assumption of 30% biosimilar penetration yields only 30% in total utilization shift if all biologics have lost patent protection and 100% of patients accept the biosimilar alternative. Thus, a larger new patient percentage and/or stronger patient behavior assumptions might lead to higher biosimilar market penetration as provided in Tables 5 and 6. It is apparent that there is a higher percentage of new biologic drug patients for most cancer-related conditions, but this may be somewhat offset by relatively low new patient rates for other conditions.

DRUG TRENDS

Milliman performs extensive research (e.g., Milliman Health Cost Guidelines) each year to quantify the cost for prescription drugs in various markets and the key drivers of cost. During our research, we perform drug price analysis from quarter to quarter, analyze changes in drug mix, and project drug cost for developing insurance premiums for future periods. As part of our research we also seek out publically available drug trend reports from various PBMs and determine the extent to which this information is reliable. An important part of the biosimilar cost modeling process is the projection of historical per capita costs for biologic drugs to future years. Table 3 shows the quarterly AWP price changes for 15 of the top biologic drugs in our study.

TABLE 3: BIOLOGIC DRUG PRICE TRENDS - TOP 15 BIOLOGICS BY DOLLARS SPENT

BIOLOGIC PRODUCT	AWP COST 4Q 2009[1]	AWP COST 4Q 2010[1]	ANNUAL PRICE TREND
ENBREL	$475.42	$498.71	4.9%
REMICADE	752.57	789.44	4.9%
HUMIRA	914.38	959.19	4.9%
COPAXONE	3,005.51	3,630.05	20.8%
AVASTIN	171.88	171.24	(0.4%)
NEULASTA	6,270.00	6,640.00	5.9%
AVONEX	690.60	817.20	18.3%
RITUXAN	66.43	69.96	5.3%
HERCEPTIN	3,359.47	3,546.77	5.6%
REBIF	467.52	520.35	11.3%
LOVENOX[2]	693.12	727.20	4.9%
PEGASYS	86.01	90.31	5.0%
TYSABRI	2,356.46	2,583.89	9.7%
EPOGEN	191.96	246.08	28.2%
BETASERON	210.82	245.90	16.6%
OTHER	N/A	N/A	N/A
TOTAL			8.3%

1 AWP for the most prevalent NDC for the product listed based on MediSpan.
2 Lovenox is considered to be a borderline biologic, having characteristics that only marginally fit the classification.

As part of our research we looked to publically available drug trend studies performed by leaders in the industry. The 2009 and 2010 Express Scripts Drug Trend Reports,[8] and in particular the section of the reports addressing specialty cost trends, is one of the best available sources for projecting specialty trends over the next few years because of the drug detail. Specialty trends are projected to be in the 20% to 25% range through 2013. Our trend assumptions vary by drug therapy class and composite to about 21% per year through 2016. Projecting trends for more than two years is very subjective given the constant change in the availability of drug products and market conditions.

Since predicting drug trends beyond a time horizon of 12 to 18 months is speculative, we chose to keep our analysis simple and used uniform trends by drug therapy class over the entire five-year projection period. We adjusted the trends for some drug classes whose projected utilization over the next 12 months was expected to be negative. We did not want to assume negative trends for five years for drug classes that represented a material amount of biologic market share.

BIOSIMILAR / ORIGINATOR PRICING DIFFERENCE

The price differences between generic and brand versions of small molecular drugs has been well documented from historical data. The first generic manufacturer typically has a six-month marketing exclusivity period and thus the price differential to the brand tends to be lower during this period, typically 10% to 20%. After the six-month exclusivity period and depending upon the generic competition, the price differential to the brand typically drops to 50% and over time may approach a 90% differential.

There has been limited evidence of such pricing in looking broadly at U.S. (full FDA approval process) and international biosimilars.

We assumed a range of 10% to 30% price savings for biosimilars.

Pricing at a 30% discount might be considered somewhat aggressive currently, particularly in light of an FDA approval pathway that may require some form of clinical trials. Given that the FDA has not provided any biosimilar guidance yet in 2011, the price differential assumption of 10% to 30% is largely based on what can be discerned from the global market to date.

One important driver of price that we believe is being overlooked in the biosimilar discussion is the Medicare Part D Coverage Gap Discount Program (CGDP). In 2011, brand drug manufacturers who want their drugs included under Medicare Part D coverage, must participate in the 50% discount program for drugs in the Part D benefit coverage gap (i.e., annual costs between $2,840 and $6,447.50). If CMS requires the biosimilar manufacturer to comply with the 50% discount in the coverage gap, pricing may be less aggressive. If CMS does not require the biosimilar manufacturer to comply with the 50% discount, since it applies only to brand-name drugs, then the biologic price will be more competitive with the biosimilar for the Medicare-eligible population in the coverage gap. Thus, the senior population and Medicare Part D may indirectly impact the biosimilar pricing in the commercial sector.

COST SHIFTING BETWEEN EMPLOYER BENEFITS

There are important differences between providing prescription drugs through the medical benefit versus the drug benefit that need to be recognized when reviewing employer benefits for active employees/ dependents (commercial market).

The cost to the employer for specialty drugs will typically be higher under the medical benefit than the pharmacy benefit for like medications if provider contracting is not well defined for drugs and supplies.

If the provider contracting for specialty drugs is reimbursed at Medicare allowed levels (i.e., average sales price (ASP) + 6%) then it will be cheaper for the employer to dispense specialty drugs through the medical benefit because pricing based on ASP is lower than pricing based on average wholesale price (AWP). It had been a common practice for specialists such as oncologists to charge more than AWP for specialty drug products until Medicare instituted the ASP pricing requirement on January 1, 2005. However, ASP pricing has not gained acceptance in the commercial provider marketplace at this time. Beyond the price paid for drugs, there may be some cost management opportunities and manufacturer rebates under the drug benefit.

The cost to the member will typically be lower under the medical benefit due to the out-of-pocket limit that applies to all medical services.

Without appropriate drug cost management under the medical benefit, there is little incentive to substitute generic drugs for multi-source brand drugs. In most cases, the patient is unaware of or concerned about administered medication choices, which is not the case when a patient visits the retail pharmacy.

Since this assumption would impact the biologic and biosimilar in a positively correlated manner, we have not modeled the potential benefit cost shift impact on cost savings in this paper.

BIOSIMILAR SIDE EFFECTS

Because of the subjective and clinical nature of this assumption, we have not modeled the potential impact on cost savings in this paper.

EMPLOYER BENEFIT CHANGES

Prescription drugs may be dispensed and/or administered in many different healthcare settings. If prescription drugs are dispensed from a pharmacy, then these drugs are typically covered under the terms of the employer's prescription drug benefit. Prescription drugs dispensed from an institutional or physician's office setting are covered under the employer's medical benefit. This analysis of biosimilar

savings excludes drugs provided from a hospital inpatient or nursing home stay because reimbursement is generally bundled with all other hospital ancillary charges or a nursing home daily rate.

When drugs are provided through the employer's medical benefit, the member cost sharing is commonly subject to one or more of the following: deductible, coinsurance (e.g., 20%), and out-of-pocket limit (e.g., $2,500). Based on a review of actual medical benefit claim data used in this analysis, patients covered under an employer-sponsored insurance plan typically pay 0% to 15% of the cost for specialty drugs when they are covered under the medical benefit.

When drugs are provided through the employer's drug benefit, the member cost sharing is commonly subject to a brand or specialty brand copayment or coinsurance, and in rare cases subject to some type of out-of-pocket limit.

According to the 2010-2011 Drug Benefit Cost and Plan Design employer survey performed by the Pharmacy Benefit Management Institute (PBMI),[9] the following information reflects the average employer's position on specialty drug benefits administered under the drug benefit:

- Only 18.5% of employers surveyed charged a separate drug tier copayment/coinsurance for specialty drugs. Most employers applied the same brand copayment to specialty drug products.
- The average copayment charged for specialty drugs at retail pharmacies was $88.75 and $113.93 at mail order pharmacies.
- The average coinsurance charged for specialty drugs at retail pharmacies was 18.8% and 21.7% at mail order pharmacies.
- It is uncommon for the prescription drug benefit to have an out-of-pocket limit; however, out-of-pocket limits similar to the medical benefit do become an employer consideration when the drug benefit cost sharing is based on coinsurance (e.g., 20%) rather than a fixed dollar copayment.

To simplify our analysis, we assumed that when specialty drugs are singled out in employer benefit design, the average member cost sharing might be about $100 per prescription. However, it is more prevalent for the copayment to be $30 to $50 like other brand medications depending upon retail or mail order dispensing.

BIOSIMILAR MARKET PENETRATION

At this time, it is difficult to determine the degree to which biosimilar drugs will take market share from the corresponding biologic or biologics within the same drug therapy class. Most discussions that we have researched indicate that the market share change will be more like the relationship between two brand drugs used to treat the same condition rather than a small molecular brand to generic comparison. With market results available for only a few drugs in the United States, we also looked internationally at the results in Europe and Canada to determine the potential penetration rate for biosimilars. The overall success of biosimilars currently available in the U.S. or internationally has been mixed, with some products experiencing as much as 30% market penetration (Binocrit in Germany) and others as little as 1% (Omnitrope in the U.S.).

Based on publically available information, we believe market penetration of 30% across all biologics with a biosimilar counterpart should be considered reasonable if not currently aggressive. This is not a market where generic penetration rates of 80% or even higher should be expected over the short term. Biosimilar drugs will not approach the pricing differences that current small molecular generic drugs have over the innovator brand drug and thus penetration will be dampened. This price difference plays a large part in the penetration rate for generic products. In addition, biosimilars are not considered bioequivalent, so some patients will not accept and pharmacists may not be allowed to automatically substitute a biosimilar for the biologic counterpart. This gets back to the issue of interchangeability.

PERCENTAGE OF NEW PATIENTS

Patient and physician behavior are not consistent for newly diagnosed and treated patients versus previously diagnosed and currently treated patients. Newly diagnosed and treated patients make drug choices without first-hand experience with biologics and rely heavily on the physician for guidance. This group of patients is more likely to view biosimilars as a viable treatment option. Previously diagnosed patients currently being treated with a biologic will be less receptive to switching to a biosimilar if their outcomes to date have been successful.

That bias exists because the current treatment is working and the biosimilar is not bioequivalent. The only factor that would overcome that bias is lower patient out-of-pocket cost. If the patient out-of-pocket cost difference is immaterial, it is more unlikely that a patient would switch to a biosimilar. For purposes of this study, we assumed 90% to 95% of biologic drug use is for previously treated patients and only 5% to 10% is for new patients. This assumption only impacts the resulting savings when the behavior towards biosimilars differs between new and existing patients.

V. PROJECTED SAVINGS BASED ON EMPIRICAL DATA

Each year since 1954, Milliman has performed research to estimate the loosely managed nationwide average healthcare cost for a commercially active population (*Health Cost Guidelines*).

In 2010, the commercial population (employees and their dependents covered under an employer-sponsored health benefits plan) spent about $14.63 PMPM, before member cost sharing, on biologic drugs. So for an employer insuring 10,000 lives (roughly 5,000 employees plus dependents), this translates to $1.76 million in annual covered expenditures for biologics before member cost sharing, which represents 3.2% of total covered healthcare costs (assuming $450 PMPM).

If a biosimilar was introduced for every chronic healthcare condition immediately and all patients used a biosimilar product that was 30% cheaper, the total covered healthcare costs would decrease by 1.0% (3.2% x .30) in 2011. This would obviously represent close to a best-case scenario, i.e., immediate and complete biosimilar alternatives across the entire biologic spectrum, all current biologic drug users switching to biosimilars with an average price savings of 30%. A more realistic savings would be lower than 1.0%, especially if we consider 2011 to be year one and the fact that the average employer does not contribute 100% to the cost of member healthcare coverage. Thus, some of the savings would be reflected in the employee share of the employer healthcare premium.

PROJECTED EMPLOYER SAVINGS SCENARIOS

Actual employer savings will depend upon many factors, but certain groups of assumptions or scenarios help to quantify the biosimilar impact to employers. Although a seemingly infinite combination of scenarios can be modeled, we created four benchmark scenarios and projected the biosimilar savings from 2011 to 2016. The four benchmark scenarios are:

- Scenario 1: Aggressive biosimilar market penetration using estimated data exclusivity expiration date with 100% acceptance from both physician and patient at a 30% price discount and $50 copay differential.
- Scenario 2: Moderate biosimilar market penetration using estimated data exclusivity expiration date with about 75% acceptance from both physician and patient at a 25% price discount and $50 copay differential.
- Scenario 3: Moderate biosimilar market penetration using estimated patent expiration date with about 50% acceptance from both physician and patient at a 25% price discount and no copay differential.
- Scenario 4: Lower biosimilar market penetration using estimated patent expiration date with about 25% acceptance from both physician and patient at a 20% price discount and no copay differential.

The key differences in the assumptions for the four benchmark scenarios are provided in Table 4.

TABLE 4: SUMMARY OF BENCHMARK SCENARIO 1-4 ASSUMPTIONS

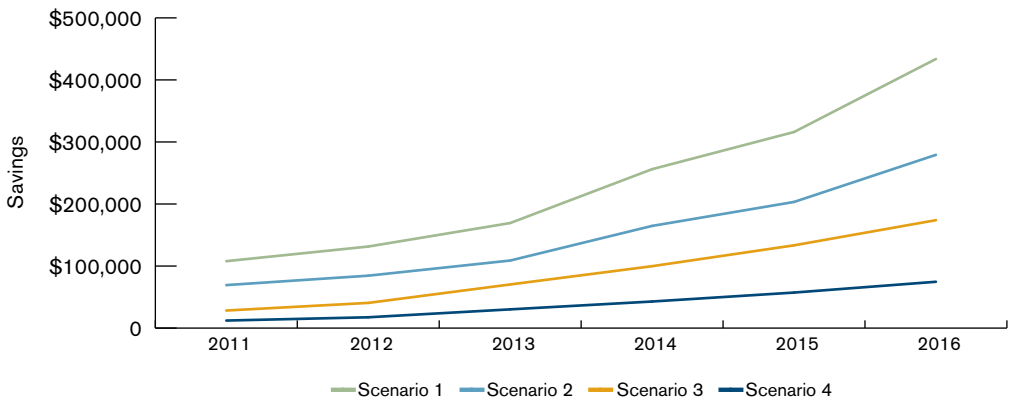
ASSUMPTION	SCENARIO 1	SCENARIO 2	SCENARIO 3	SCENARIO 4
BIOSIMILAR MARKET PENETRATION UPPER BOUND	30%	30%	30%	30%
NEW PATIENT %	10%	10%	5%	5%
NEW PATIENT ACCEPTANCE	100%	100%	75%	75%
EXISTING PATIENT ACCEPTANCE	100%	75%	50%	25%
MEDICATION COMPLIANCE	100%	100%	100%	100%
PRICE DIFFERENCE	30%	25%	25%	20%
BIOSIMILAR COPAY	$50	$50	$100	$100
BIOLOGIC COPAY	$100	$100	$100	$100
12-YEAR EXCLUSIVITY BASIS[1]	DE	DE	PE	PE

1 Data Exclusivity Date (DE), Patent Expiration Date (PE)

Each of these assumptions is described in greater detail in Section IV of the report.

Scenario 1 is representative of those who are optimistic of biosimilar drug introduction with an expedited exclusivity defined by data exclusivity expiration date. Scenario 4 represents a pessimistic view, and Scenarios 2 and 3 fall in between. The following graphic depicts the biosimilar savings for each scenario.

CHART 1: EMPLOYER PROJECTED SAVINGS FROM BIOSIMILARS ASSUMING 10,000 COMMERCIAL MEMBERS



The savings under the various scenarios range from 1.4% ($0.62 PMPM) to 8.0% ($3.61 PMPM) of 2016 total drug spend and 0.1% to 0.6% of 2016 total healthcare spend.

Although there are a number of variables that will contribute to the magnitude of the savings for employers, it eventually comes down to just two: price and market penetration. The other variables impact these two variables. Table 5 shows the range of savings based on the impact of these two variables in 2011 dollar terms and for some values in parentheses, as a percentage of total healthcare spend.

TABLE 5: 2012 BIOSIMILAR EMPLOYER PROJECTED SAVINGS MATRIX BASED ON 10,000 LIVES

BIOSIMILAR MARKET PENETRATION[1]	PRICE DIFFERENCE 10%		20%		30%		40%		50%	
10%	$11,342	(.023%)	$23,649		$35,957	(.074%)	$48,264		$60,571	(.125%)
20%	$22,684		$47,299		$71,914		$96,528		$121,142	
30%	$34,027	(.070%)	$70,948		$107,870	(.223%)	$144,792		$181,714	(.375%)
40%	$45,369		$94,598		$143,827		$193,056		$242,285	
50%	$56,711	(.117%)	$118,247	(.244%)	$179,784	(.371%)	$241,320	(.498%)	$302,856	(.625%)

1 The actual utilization shift to biosimilars will be less than stated due to patent protection on some biologics and physician/patient behavior.

The $107,870 (30%, 30%) is reflective of Scenario 1, year 2011 in the graph on page 16.

Table 6 shows the range of savings in 2016 dollar terms where all costs have been trended and a larger percentage of biologic drugs have lost exclusivity protection.

TABLE 6: 2012 BIOSIMILAR EMPLOYER PROJECTED SAVINGS MATRIX BASED ON 10,000 LIVES

BIOSIMILAR MARKET PENETRATION[1]	PRICE DIFFERENCE 10%		20%		30%		40%		50%	
10%	$46,655	(.066%)	$95,618		$144,581	(.203%)	$193,544		$242,506	(.341%)
20%	$93,311	(.131%)	$191,236		$289,162		$387,087		$485,012	
30%	$139,966	(.197%)	$286,854		$433,743	(.609%)	$580,631		$727,519	(1.022%)
40%	$186,622		$382,472		$578,323		$774,174		$970,026	
50%	$233,277	(.328%)	$478,090	(.672%)	$722,904	(1.015%)	$967,718	(1.359%)	$1,212,532	(1.703%)

1 The actual utilization shift to biosimilars will be less than stated due to patent protection on some biologics and physician/patient behavior.

The $433,743 (30%, 30%) is reflective of Scenario 1, year 2016 in the graph on page 16.

Over time, as more information becomes available, the matrix provided in Tables 5 and 6 may become more focused on a specific price differential and market penetration rate. Based on the current FDA status of the biosimar approval pathway, the study range is more narrowly defined within the shaded region of the two tables. The U.S. trails Europe by three to five years when it comes to biosimilars, and the market penetration for biosimilars outside the U.S. has not been dramatic to date.

VI. WHAT IMPACT WILL BENEFIT DESIGN PLAY?

Current employer drug benefit design does little to incentivize members to utilize any available generic drugs under the medical benefit. The concept of drug tiers, however, has played a pivotal role in maximizing the generic dispensing rate under the drug benefit.

Typically, the greater the copay difference between a generic and corresponding multi-source brand drug, the greater the incentive for the member to seek the generic alternative. The demand for generics is purely based on out-of-pocket cost with little concern about drug effectiveness. With biologic drugs, the drug effectiveness may be the driving force behind the physicians' and indirectly the members' decision making, and copay differential is secondary. If lowering the copayment for biosimilars does not increase the biosimilar market penetration, then the employer bears the cost for the lower copayment charged.

The savings analysis in this paper did look at a $50 copay differential for biosimilars but did not change the utilization to reflect greater demand for lower-priced biosimilars. It was assumed that the patient demand is more inelastic than in a non-biologic drug environment.

Another consideration when discussing drug tiers that may be relevant is rebates. If formulary management associated with drug tiering were to induce current biologic manufacturers to begin to pay a rebate, then there would be savings even if the biosimilar was not used. In addition, the biosimilar manufacturer could pay a rebate. This expectation of rebate savings was beyond the scope of our analysis and is not included in the savings projections.

VI. CONCLUSIONS

Based on my review of published articles on biosimilars and my cost modeling analysis of current biologic drug costs, I see biosimilars having an incremental and increasing impact on overall biologic drug costs over the next five years. I expect biosimilar drugs will not become prevalent in the market until sometime after 2016, trailing the biosimilar penetration curve in Europe by about five years. Even if the FDA approval pathway is shortened, more recently approved biologic drugs will have data exclusivity that extends well beyond 2016.

Since per capita specialty drug costs have exhibited such high trends, it may be difficult to notice the impact of biosimilars. By 2016, I expect the per capita spending on specialty drugs including biologics may be almost three times the level of 2010. If the FDA approval process is implemented in early 2012 expediting biosimilar market penetration, it still will take several years before there are enough products in the market to generate material savings. Even at peak availability, it may be difficult to get acceptance from currently treated biologic patients who can afford the medications based on income level or due to ample insurance coverage.

The overall savings as a percentage of total healthcare costs resulting from biosimilars is likely to be small (i.e., less than 1%) given the relatively small frequency of members with high-cost conditions. At this level of savings potential, it is unlikely that employers will change benefit provisions to incent the use of biosimilars over biologics. The drug decision process will be more involved than simply selecting a generic drug vs. a brand drug. As a result, it may be difficult to penalize the patient for making an appropriate decision based on his or her individual circumstances.

ACKNOWLEDGEMENTS

This research was supported by Amgen, Inc. The author is solely responsible for the manuscript's content. Although Amgen had the right to exert editorial control over the content of this manuscript, it did not, at any time, exercise that right. Instead, Amgen made a limited number of suggestions to the author which the author was free to incorporate at its discretion. At no time did Amgen require the author, implicitly or explicitly, to change the content of the manuscript. The author remained independent at all times and had total editorial control over the design and content of this study; the collection, analysis, preparation, and interpretation of the data; and final preparation of the manuscript.

Milliman is an independent firm of actuaries and healthcare consultants. The editing and content of this study are based on Milliman proprietary data and national healthcare consulting experience.

REFERENCES

(1) Johnson, Judith (March 2009). FDA Regulation on Follow-On Biologics. Retrieved May 2, 2011 from http://opencrs.com/document/RL34045/2009-02-24/

(2) Dr. Pablo Fernandez (August 2010). The Changing Landscape for Biosimilars. http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=680740&sk=&date=&%0A%09%09%09&pageID=2

(3) Mark McCamish and Gillian Woollet. (March/April 2011). Worldwide experience with biosimilar development. http://www.landesbioscience.com/journals/mabs/article/15005/

(4) FDA Public Hearing Day 1 (November 2, 2010). http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm

(5) FDA Public Hearing Day 2 (November 3, 2010). http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm

(6) Grabowski, Henry (2009). Data Exclusivity for Biologics: What Is the Appropriate Period of Protection? Retrieved September 2009 from http://www.aei.org/outlook/100068

(7) FDA Drug Approval Information. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

(8) Express Scripts 2009 and 2010 Drug Trend Reports http://www.express-scripts.com/research/research/dtr/

(9) PBMI Employer Drug Benefit Survey http://www.benefitdesignreport.com/

APPENDIX A

BIOLOGIC DRUGS REPRESENTED IN THIS STUDY

ASSUMED LIST OF BIOLOGIC DRUG PRODUCTS		
ACTHAR HP	HELIXATE FS	PEG-INTRON REDIPEN PAK 4
ACTIMMUNE	HERCEPTIN	PROCRIT
ACTIVASE	HUMATROPE	PROLASTIN
ALDURAZYME	HUMATROPE COMBO PACK	PROLEUKIN
AMEVIVE	HUMIRA	PULMOZYME
ARANESP	HUMIRA PEN	REBIF
ARANESP ALBUMIN FREE	HUMIRA PEN-CROHNS DISEASESTARTER	REBIF TITRATION PACK
ARANESP ALBUMIN FREE SURECLICK	HUMIRA PEN-PSORIASIS STARTER	RECLAST
ARCALYST	INCRELEX	REMICADE
AVASTIN	INFERGEN	REMODULIN
AVONEX	INTEGRILIN	REOPRO
BETASERON	INTRON-A	REPRONEX
BOTOX	INTRON-A W/DILUENT	RETAVASE HALF KIT
BOTOX COSMETIC	KEPIVANCE/PALIFERMIN	RITUXAN
BRAVELLE	KINERET	SAIZEN
CAMPATH	LEUKINE	SAIZEN CLICK.EASY
CATHFLO ACTIVASE	LOVENOX	SANDOSTATIN
CEREZYME	LUCENTIS	SANDOSTATIN LAR DEPOT
CIMZIA	MYOBLOC	SEROSTIM
COPAXONE	MYOZYME	SIMPONI
COPEGUS	NEULASTA	SOLIRIS
ELAPRASE	NEUMEGA	SOMATULINE DEPOT
ELIGARD	NEUPOGEN	SOMAVERT
ELITEK	NORDITROPIN CARTRIDGE	SUPPRELIN LA
ELSPAR	NORDITROPIN NORDIFLEX PEN	SYNAGIS
ENBREL	NPLATE	TEV-TROPIN
ENBREL SURECLICK	NUTROPIN	THYROGEN
EPOGEN	NUTROPIN AQ	TNKASE
ERBITUX	NUTROPIN AQ PEN	TYSABRI
FABRAZYME	ONCASPAR	VECTIBIX
FOLLISTIM AQ	ONTAK	XOLAIR
FORTEO	ORENCIA	
GENOTROPIN	ORTHOCLONE OKT3	
GENOTROPIN MINIQUICK	OVIDREL	
GONAL-F	PEGASYS	
GONAL-F RFF	PEG-INTRON	
GONAL-F RFF PEN	PEG-INTRON REDIPEN	

15800 W. Bluemound Rd.
Suite 100
Brookfield, WI 53005-6043
USA
+1 262 784-2250 tel

milliman.com