BIOSIMILARS
2015 TRENDS IN
REPORT
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WHAT ARE BIOLOGICS AND BIOSIMILARS?
A biologic medicine is a large molecule derived from living cells that is used to treat or prevent disease, such as a therapeutic protein, DNA vaccine, monoclonal antibody (i.e., MAB) or fusion protein. These medicines are far more complex than small molecule drugs and are highly sensitive, making them more difficult to characterize and produce. As more is learned about the biological mechanisms of diseases, new biologic medicines can be developed that target the causes of disease, potentially altering the course of disease rather than treating symptoms.

Biosimilars are biological medicines that are considered highly similar to the originator (the “reference” product). To be considered a biosimilar, there must be no clinically meaningful differences between the biosimilar and the approved biological product in terms of safety, purity and potency.

BIOSIMILARS ARE NOT GENERICS
Due to the highly intricate processes associated with translating biologics from living cells to mass production molecules, biosimilars can only be highly similar to their reference product. Each step in the manufacturing process, many of which are proprietary to the manufacturer, requires specific expertise to protect the protein while producing a therapeutically valid treatment. Since the processes differ by company and are not disclosed publicly, biologics cannot be reproduced identically by another manufacturer.
DEAR COLLEAGUES,

The global healthcare landscape is experiencing seismic shifts driven by the aging of the population, growing prevalence of non-communicable disease in developing countries as well as dramatic growth in access to pharmaceuticals. At the same time, our industry is setting a path to realize the next phase of the innovation lifecycle in biologic medicine: the introduction and expanding commercialization of biosimilars. Companies like Amgen, who have pioneered the field of study surrounding biologic medicine, now are applying those learnings and principles as we prepare alongside stakeholders for the patent expiry of some of the world’s leading biologic medicines and for the launch of the first biosimilars in the U.S. healthcare market.

We understand that the payers will face many challenges in preparing for the first biosimilars including, but not limited to, coverage policies, Pharmacy and Therapeutics (P&T) evaluation processes, formulary structure, and provider network prescribing guidelines and education. Working alongside an Editorial Council comprised of leading medical and pharmacy directors from across the nation’s leading health plans and PBMs, we are proud to share the second edition of the Trends in Biosimilars Report. This report is intended to give payers a guide to the latest topics, trends and issues pertinent to biosimilar introduction and adoption in the U.S.

We hope the 2015 Trends in Biosimilars Report is a resource for you and your colleagues as you prepare for the ongoing introduction, adoption and management of biosimilars. We look forward to working along with you in this important step in biologic medicine.

Mike Ryan, PharmD
Vice President & General Manager,
U.S. Value, Access and Reimbursement, Amgen

Most U.S. payers expect to treat biosimilars as lower-cost branded options.
DEAR COLLEAGUES,

Payers are focused on designing benefit structures that will improve reimbursement, access and quality. Shared risk models with providers and innovative process design are some approaches intended to enhance the quality of care delivered, appropriately align incentives and optimize the costs associated with care. As members of the U.S. reimbursement community, we are committed to the transition from the fee-for-service model to an outcomes/value-based model which aligns stakeholders to focus on high quality patient care.

Prescription drugs and biologicals are critical components of that mix. With the rapidly approaching commercial introduction of biosimilars in the U.S., payer organizations are actively planning for how biosimilars will be evaluated and managed through medical and pharmacy benefit design as well as coverage structures.

We are proud to contribute to the 2015 Trends in Biosimilars Report, which brings structure and perspective to some of the most pressing issues that payers are grappling with relative to coverage of biosimilars. This report addresses current data perceptions and assumptions about the market dynamics, preparedness strategies and considerations currently underway, as well as the dynamics of pricing and access as drivers of value for this new category of prescription pharmaceutical drugs.

Our intent for the 2015 Trends in Biosimilars Report is to address these priority areas to encourage education and dialogue. Furthermore, we believe this is a valuable resource and are proud to bring this report to our peers in the reimbursement community who are making informed decisions regarding the placement of biosimilars within their benefit designs and coverage structures, to ensure the appropriate role of biosimilars in provision of world-class U.S. healthcare services.

MESSAGE FROM EDITORIAL COUNCIL

This report offers insights and input from our Editorial Council, comprised of highly experienced medical and pharmacy directors representing the broad mix of managed care organizations throughout the U.S., as well as employer and benefit design consultants.

Sherry Andes, PharmD, BCPS, BCPP, BCACP, CGP, PAHM
Manager, Pipeline & Trend Surveillance
Drug Intelligence, Catamaran

Michael Boskello
Clinical Strategy, Aetna Pharmacy Management, Aetna

Cheryl Larson
Vice President, Midwest Business Group on Health

Elan Rubinstein, PharmD, MPH
Principal Consultant, EB Rubinstein Associates

Kenneth L. Schaecher, MD
Medical Director, SelectHealth

Scott Taylor
Executive Director, Industry Relations, Geisinger Health System

Editorial Council members are participating independently and their views may not reflect the interests of their respective companies.
THE 2015 TRENDS IN BIOSIMILARS REPORT

The 2015 Trends in Biosimilars Report is the second annual report focused on the introduction of biosimilars in the U.S. market. This report is designed as a guide for healthcare decision makers who are evaluating the key issues and topics relevant to biosimilar adoption in the U.S. healthcare system.

The report features the results of a survey of the U.S. reimbursement community, including representatives of national and regional managed care organizations, pharmacy benefit managers and integrated delivery networks, Veterans Affairs, accountable care organizations, and benefit consultants who advise employers on access to healthcare.

In addition, these data are supplemented by analyses of IMS MIDAS data plus a comprehensive literature review, featuring recent prominent peer-reviewed journal articles, research reports and white papers, which feature discussions and debates on the entry of biosimilars and their expected impact on the U.S. biologics market.

The icons above are placed throughout the report to identify the key data sources for the material.
Survey of Key Decision Makers from a Range of Organizations

Survey of 40 payers conducted to understand perceptions of biosimilars, incorporation of biosimilars into payer coverage policies, and how manufacturers of biologics, including biosimilars, are perceived as sources of reputable information on the subject of biosimilars.

<table>
<thead>
<tr>
<th>Organization Type</th>
<th>GEOGRAPHIC DISTRIBUTION</th>
<th>PLANS</th>
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<td>10</td>
</tr>
<tr>
<td>Regional Managed Care Organizations (MCOs)</td>
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<td>Pharmacy Benefit Managers (PBMs)</td>
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<td>Accountable Care Organizations (ACOs)</td>
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<tr>
<td>Benefit Consultants (BCs)</td>
<td>3 circles</td>
<td>3</td>
</tr>
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</table>

GEOGRAPHIC DISTRIBUTION

- NORTHEAST
- SOUTHEAST
- MIDWEST
- WEST
- TOTAL 40
INTRODUCTION & EXECUTIVE SUMMARY
In recent years, the U.S. market has evolved from essentially no pathway for biosimilars to a nearly complete set of draft guidelines supporting the commercialization of biosimilars. Interest in cost savings within the healthcare system has been amplified following the conception of the Affordable Care Act (ACA) in 2008, with a particular focus on the potential for biosimilars to serve as a cost-savings strategy to manage the ballooning $138B biologics industry (based on 2010 estimate). Current estimates indicate that biosimilars will provide meaningful cost benefits, though the specific savings remain a matter of debate. 

Guidance by the U.S. Food and Drug Administration (FDA) has facilitated the submission of the first biosimilar candidate application. The guidelines are still considered draft, but the FDA is under no obligation to issue final guidance, and the agency may effectively operate under draft guidance. The first regulatory evaluations and approval will likely address many of the outstanding issues. It should be noted that some FDA guidances associated with the Hatch-Waxman Act, which outlined regulations for generics entrance into the small molecule market during the 1980s, have never been finalized by the FDA. Impending patent expiry of a number of market-leading biologics has accelerated the need for clarity surrounding the commercial entry of biosimilars in the U.S. market.

While almost all biological products are regulated under the Public Health Service Act (PHS Act), it’s relevant to note that some natural-source biological products, including insulin and human growth hormone, are regulated as chemical drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). As a result, new versions of these products would not be considered biosimilars.

**TODAY’S U.S. BIOSIMILAR OUTLOOK**

Preparation for biosimilars in the U.S. has included the 2014 FDA release of the FDA’s “Purple Book” – a list of licensed biological products and interchangeable biosimilars – which will serve as the guide on suitable drug substitutions, and will aim to provide clarity to the community on one of the most challenging issues in biosimilars: interchangeability.
U.S. MARKET PREPARES FOR BIOSIMILARS

As the FDA more formally addresses the regulatory considerations for biosimilars, more manufacturers – including some of the leading pharmaceutical and biologic manufacturers – are making significant investments in biosimilar pipeline development. This is particularly apparent in therapeutic categories with significant use of biologics, such as oncology and rheumatology, and in biologics with near-term patent expiries.19

Many of these companies have experience in European markets, which have the best established framework for biosimilars to date.8 This experience may not be a direct analog for the U.S. market, given fundamental differences across health systems.8 However, a relevant observation with the introduction of biosimilars is that European markets have observed a decline in the average sales price of these molecules.20

Research indicates that the U.S. biologic medicines market will reach $200B by 2015 and an estimated $253B by 2020.21 With this in mind, U.S. payers are actively preparing strategies to evaluate and determine coverage based on a number of factors, such as pricing, potential for interchangeability, and number and quality of competitors in the market.

Payer Lead Time Required to Prepare for the Launch of Biosimilars6

Market research indicates that, based on current U.S. payer activity and planning, most payers think 4-9 months will be required to prepare for biosimilars6

Source: Amgen Data on File
EXECUTIVE SUMMARY

Payer perception of biosimilars
➢ According to market research, payers anticipate biosimilars will be a strategy to reduce specialty
drug prices and many believe the category represents a compelling business opportunity.6
➢ Most do not expect biosimilars to emulate the generics market; instead, payers expect to
consider them as lower-cost branded options.6
➢ While there are analogs from the European commercial experience, at this time, few U.S.
payers are relying on Europe’s experience for U.S. forecasting.72

Payer readiness for biosimilars
➢ Based on market research, most payers are taking action to plan for biosimilars, including
evaluations of alternative payment models and restructuring of historical drug tiers.6,68
➢ Guided by the momentum related to the commercialization of biosimilars, market research
shows that many payers are meeting with external partners to discuss biosimilars.6
➢ According to market research, a primary consideration for coverage is managing the possible
allowance of switching and interchangeability, yet questions remain on how this may be
implemented and managed with patient safety in mind.6

Payer expectations for pricing/access as value drivers for biosimilars
➢ Projections continue to vary on the expected cost savings that may result from near-term
biosimilar launches; a 2008 Congressional Budget Office report suggested roughly $25B in
savings from 2009 through 2018.23
➢ Per market research, most payers expect greater pricing discounts within 2-3 years of launch
for both biosimilars and their originators. Research indicates that payers believe originators’
net discount may be >30% after 30 months and biosimilars are expected to follow originator
discounting strategies.6
➢ Successful entry may be dependent on the total value of biosimilars, including cost, but also
robustness of data and individual manufacturer reliability.55
PAYER PERCEPTIONS OF BIOSIMILARS

As the potential role for biosimilars in the U.S. healthcare landscape comes into focus, payers are looking at a wide variety of sources of information to help inform their expectations about how to cover and reimburse biosimilars after they are approved. Research indicates the U.S. path may share few characteristics with the global experience to date.

KEY CONSIDERATIONS FOR PAYERS

1. Payers are eager for biosimilars to reduce specialty drug prices, but Europe’s experience shows the level of savings may vary.
2. Most payers expect biosimilars to be lower-cost options of branded biologics.
3. EU market uptake is interdependent on pricing, physician perception and patient acceptance.
Payers’ Perspectives on Biosimilars

Payers largely agree that the opportunity presented with biosimilars is compelling and will be important to integrate into their modeling.6

Most do not expect to treat biosimilars like chemical generic medicines. Instead, research suggests these medicines will be managed as lower-cost branded products.6

| Perception of the Future of Biosimilars6 |
|------------------|------------------|------------------|
| **I BELIEVE MY PLAN WILL TREAT BIOSIMILARS LIKE A SMALL MOLECULE GENERIC** | **I DO NOT EXPECT ANY BIOSIMILARS TO LAUNCH IN THE U.S.** |
| **AT LAUNCH** | **AT LAUNCH** |
| **80%** | **3%** |
| **17%** | Data represented as reported by original source. |
PROGRESS AND MOMENTUM IN THE U.S.

As regulatory pathways become more defined for the introduction of biosimilars in the U.S. market, more companies are making strategic investments in their biosimilar pipelines. Some of the largest multi-national pharmaceutical and biotechnology companies recognize the market potential for biosimilars and are focusing on larger therapeutic categories where biologics are the current standard of care; where biologic patents are expiring.

2008

No guidelines on biosimilars in the U.S., debate on key issues

2010

Implementation of the Biologics Price Competition and Innovation Act

Pathway passed as part of the ACA

POPULAR ORIGINATOR BIOLOGICS WITH BIOSIMILARS UNDER DEVELOPMENT

**Avastin®** (bevacizumab)
- Roche
- **ORIGINATOR COMPANY**
- Colorectal Cancer, Cervical Cancer, Kidney Cancer, Glioblastoma, Ovarian Cancer, Non-small Cell Lung Cancer
- **THERAPEUTIC AREA**
- **$7.0B**
- 2013 SALES (GLOBAL)
- **15**
- ESTIMATED NUMBER OF BIOSIMILARS IN DEVELOPMENT (GLOBAL)

**Remicade®** (infliximab)
- Merck/Johnson & Johnson
- **ORIGINATOR COMPANY**
- Rheumatoid Arthritis, Psoriasis, Ulcerative Colitis, Crohn’s Disease, Ankylosing Spondylitis, Psoriatic Arthritis
- **THERAPEUTIC AREA**
- **$8.9B**
- 2013 SALES (GLOBAL)
- **13**
- ESTIMATED NUMBER OF BIOSIMILARS IN DEVELOPMENT (GLOBAL)

**Herceptin®** (trastuzumab)
- Roche
- **ORIGINATOR COMPANY**
- Breast Cancer, Stomach Cancer
- **THERAPEUTIC AREA**
- **$6.8B**
- 2013 SALES (GLOBAL)
- **21**
- ESTIMATED NUMBER OF BIOSIMILARS IN DEVELOPMENT (GLOBAL)
and opening access for commercial introduction of one or more biosimilars; and, in areas with significant patient need, including oncology and rheumatology. As the first biosimilars are under review in the U.S. in 2014 with additional filings expected in 2015, the biosimilars pipeline is likely to continue to swell in the near-term.\textsuperscript{19}

**2012**

*Draft guidance issued from U.S. FDA with clarity on biosimilar approval pathway\textsuperscript{18}*

**2014**

*Sandoz and Celltrion filed biosimilar candidate applications for regulatory approval\textsuperscript{10,26}*

*Purple Book published: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations\textsuperscript{14,15}*

**Humira\textsuperscript{®} (adalimumab)\textsuperscript{19,114}**

*AbbVie ORIGINATOR COMPANY*

*Rheumatoid Arthritis, Ulcerative Colitis, Crohn’s Disease, Ankylosing Spondylitis, Psoriasis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis THERAPEUTIC AREA*

*$10.7B 2013 SALES (GLOBAL)*

*13 ESTIMATED NUMBER OF BIOSIMILARS IN DEVELOPMENT (GLOBAL)*

**Rituxan\textsuperscript{®} (rituximab)\textsuperscript{19,115}**

*Roche ORIGINATOR COMPANY*

*Rheumatoid Arthritis, Non-Hodgkin’s Lymphoma, Leukemia, Polyangiitis THERAPEUTIC AREA*

*$8.6B 2013 SALES (GLOBAL)*

*35 ESTIMATED NUMBER OF BIOSIMILARS IN DEVELOPMENT (GLOBAL)*

*$42B TOTAL 2013 SALES (GLOBAL)*

*97 TOTAL ESTIMATED NUMBER OF BIOSIMILARS IN DEVELOPMENT (GLOBAL) FOR THESE BRANDS*

Adapted from GABI 2014 \textsuperscript{19}
LESSONS FROM EX-U.S. EXPERIENCE

The European Medicines Agency (EMA) pioneered the biosimilar approval pathway. While the market has developed considerably since the first biosimilar was approved in Europe in 2006, the experience may not necessarily offer comparable insights on the potential trajectory of the U.S. market.

However, the European Commission suggests there are key learnings from the European biosimilars experience:

“The overall experience to date suggests that the most important conditions for market uptake of biosimilar medicines are driven by factors such as (i) physician perception, (ii) patient acceptance, (iii) local pricing and reimbursement regulations and (iv) procurement policies and terms.”

EUROPEAN COMMISSION, PHARMACEUTICAL INDUSTRY: A STRATEGIC SECTOR FOR THE EUROPEAN ECONOMY, 2014

DIFFERENCES IN THE CURRENT BIOSIMILAR APPROVAL AND TRACKING PROCESSES BETWEEN THE EU AND U.S.

<table>
<thead>
<tr>
<th>Approval Process</th>
<th>EUROPEAN UNION</th>
<th>UNITED STATES</th>
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<tbody>
<tr>
<td>Evaluated by comparing the biosimilar with its reference product to show that there are no significant differences between them (fewer clinical data requirements compared with originator)</td>
<td>Evaluated based on information demonstrating the biological product is highly similar, with no meaningful differences in safety, purity, or potency to the reference product</td>
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<table>
<thead>
<tr>
<th>Naming</th>
<th>Determined by approving body in individual member states</th>
<th>Determined by manufacturer and FDA</th>
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<table>
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<tr>
<th>Labeling</th>
<th>Clearly identify all biological medicines with a black symbol and standardized explanatory sentence</th>
<th>Include clear statement that the product is a biosimilar for stated indication(s) and route(s) of administration, and if it is interchangeable with the reference product</th>
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<table>
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<th>Interchangeability</th>
<th>No interchangeability recommendations provided by EMA</th>
<th>Determined by the FDA based on additional data (optional evaluation)</th>
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<table>
<thead>
<tr>
<th>Automatic Substitution</th>
<th>Determined by individual member states</th>
<th>Determined by state laws</th>
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<tr>
<th>Pharmacovigilance (PV) Recommendations</th>
<th>All biologics should be identified with product name and batch number</th>
<th>FDA regulates and encourages product-specific post-marketing safety monitoring</th>
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Nine Examples of Authorized Biosimilars by the European Commission (EC) through August 2014

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<tr>
<th>TRADE NAME</th>
<th>INN*/COMMON NAME</th>
<th>COMPANY</th>
<th>DECISION DATE(S)</th>
<th>DECISION</th>
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<tr>
<td>Omnitrope®</td>
<td>Somatropin</td>
<td>Sandoz</td>
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<tr>
<td>Binocrit®</td>
<td>Epoetin alfa</td>
<td>Sandoz</td>
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<tr>
<td>Epoetin alfa Hexal®</td>
<td>Hexal</td>
<td>Hexal Medice</td>
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<tr>
<td>Abseamed®</td>
<td>Epoetin zeta</td>
<td>Hospira Stada</td>
<td>18-Dec-07</td>
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<tr>
<td>Retacrit®</td>
<td>Epoetin alfa</td>
<td>Hospira Stada</td>
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<td></td>
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<tr>
<td>Silapo®</td>
<td>Filgrastim</td>
<td>Teva Ratiopharm AbZ-Pharma GmbH</td>
<td>15-Sep-08</td>
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<td>Tevagristim®</td>
<td>Filgrastim</td>
<td>Teva Ratiopharm AbZ-Pharma GmbH</td>
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<td>Filgrastim</td>
<td>Hospira Apotex</td>
<td>18-Oct-13</td>
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<td>Zarzio®</td>
<td>Filgrastim</td>
<td>Hospira Sandoz</td>
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<tr>
<td>Filgrastim Hexal®</td>
<td>Filgrastim</td>
<td>Teva Celltrion</td>
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<td>Nivestic®</td>
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<td>Grastofil®</td>
<td>Filgrastim</td>
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<td>27-Sep-13</td>
<td>Approved</td>
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<td>Inflectra®</td>
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<td>Remsima®</td>
<td>Follitropin alfa</td>
<td>Teva</td>
<td>27-Sep-13</td>
<td>Approved</td>
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* International Non-proprietary Name

MOST U.S. PAYERS SURVEYED ARE NOT Basing THEIR PROJECTIONS OF BIOSIMILARS UPTAKE ON EUROPEAN MODELS

Despite similarities in the regulatory approval processes for biosimilars across Europe, research indicates U.S. payers may not base their forecasts and projections on the European model for biosimilars, as Europe has a highly dynamic commercial environment, with significant variation between country structures, pricing and reimbursement models, marketing patterns and other factors. For example, the EMA does not make determinations of interchangeability. Further, the European model for pricing is likely not relevant to U.S. pricing expectations due to the centralized price/access controls and hospital tendering in some countries.22

EXAMPLE:
Drug prices in Spain are considered to be lower than many other European countries. In 2003, new regulations set the price of the first generic medicine at least 30% below the price of the originator. Further, the price of a generic medicine must not exceed the established reference price.50
INCONSISTENT SAVINGS FROM BIOSIMILARS IN EUROPE

Biosimilars uptake may be related more to the political decisions allowing structural supports within a country than to biosimilar/originator price differences. That said, the cost savings seem compelling enough to cause EU governments to act.

EXAMPLE: France is implementing a restricted form of automatic substitution for biosimilars; the legislation signals an interest in supporting the uptake of biosimilars as a cost management strategy.

Not all EU countries support the practice. As of June 2013, no country has explicitly authorized the substitution of biologicals from different manufacturers and a number of EU Member States have gone as far as banning this practice.

“Health insurers have to ask, ‘Does this make sense for us?’ ‘Will we save money?’ Our feeling is that we don’t always save money with biosimilars.”

A. MARINI, GKV-SPITZENVERBAND, AS PRINTED IN APM NEWS. 2012

EU28 Biosimilar Market Share Against Innovator Biologic Medicine Over Time and Among ESA and G-CSF Classes

Data does not include long-acting products.

Source: Amgen Data on File
GRADUAL PRICE EROSION OF ORIGINATORS WITH ENTRANCE OF BIOSIMILARS IN EUROPE

U.S. payers may expect price erosion as biosimilars enter therapeutic areas or market segments. In Europe, biosimilars have not always been priced below reference products and the level of price erosion has been gradual.20

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**CSF PRODUCT CLASS, AVERAGE PUBLIC PRICE ACROSS EU28**

- **ORIGINATOR PRODUCTS**
  - RATIOGRASTIM® (filgrastim)
  - FILGRASTIM L.U.® (filgrastim)
  - GRANULOKINE® (filgrastim)
  - GRASALVA® (filgrastim)
  - FILGRASTIM NOVT® (filgrastim)
  - NIVESTIM® (filgrastim)

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**ESA PRODUCT CLASS, AVERAGE PUBLIC PRICE ACROSS EU28**

- **ORIGINATOR PRODUCTS**
  - NEORECORMON® (epoetin beta)
  - ERYPO® (epoetin alfa)
  - ABSEAMED® (epoetin alfa)
  - EPOETIN ALFA HEXAL® (epoetin alfa)
  - BINCRIPT® (epoetin alfa)
  - RETACRIT® (epoetin zeta)

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Source: Amgen Data on File; Based on IMS MIDAS data
With the first U.S. biosimilar candidates under regulatory review in 2014, payers are taking substantial action to plan for the introduction of biosimilars.

**KEY CONSIDERATIONS FOR PAYERS**

1. Payers are taking varying levels of action to plan for biosimilars, starting with meetings with external partners and in some instances, restructuring benefit design.

2. Patient switching and the potential interchangeability of biosimilars could complicate effective pharmacovigilance.

3. Payer product selection will need to balance the economics of switching with the readiness and reliability of the manufacturer.

4. Varying state regulations may impact substitution at the retail pharmacy level.
WITH INCREASING SPECIALTY MEDICINE COSTS, PAYERS ARE CONSIDERING ALTERNATIVE PAYMENT MODELS

In 2013, 70% of the 27 drugs approved by the FDA were specialty medications. The average cost of branded oncology treatments has doubled over the past decade, from $5,000 to $10,000 per month. Only 4% of patients use specialty drugs, including biologics, which together comprise 25% of total U.S. drug spending.60

Increasing use of expensive specialty drugs has caused some U.S. payers and integrated health systems to institute new pricing and benefit strategies to reduce both cost and year-over-year trend.60 Both government and commercial payers are considering alternative payment models to fee-for-service.61

The use of approaches, such as bundled payments, in which lump sum amounts are provided to cover a given episode of care, would provide incentives to choose less-costly agents and reward savings by providers. This may support greater uptake by providers or patients who otherwise may be hesitant to replace known therapies with new biosimilar alternatives.25

Examples of Leading U.S. Biologic Products with Anticipated Patent Expiries Through 202020,66

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>2013 U.S. SALES ($M)</th>
<th>ESTIMATED U.S. PATENT EXPIRY</th>
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<tbody>
<tr>
<td>COPAXONE® (glatiram acetate)</td>
<td>$3,711</td>
<td>05/2014</td>
</tr>
<tr>
<td>LANTUS®/LANTUS SOLOSTAR® (insulin glargine)</td>
<td>$5,623</td>
<td>02/2015</td>
</tr>
<tr>
<td>EPOGEN® (epoetin alfa)</td>
<td>$2,282</td>
<td>05/2015</td>
</tr>
<tr>
<td>NEULASTA® (pegfilgrastim)</td>
<td>$3,587</td>
<td>10/2015</td>
</tr>
<tr>
<td>RITUXAN® (rituximab)</td>
<td>$3,298</td>
<td>09/2016</td>
</tr>
<tr>
<td>HUMIRA® (adalimumab)</td>
<td>$5,566</td>
<td>12/2016</td>
</tr>
<tr>
<td>AVASTIN® (bevacizumab)</td>
<td>$2,697</td>
<td>02/2018</td>
</tr>
<tr>
<td>REMICADE® (infliximab)</td>
<td>$4,115</td>
<td>09/2018</td>
</tr>
<tr>
<td>HERCEPTIN® (trastuzumab)</td>
<td>$1,945</td>
<td>06/2019</td>
</tr>
<tr>
<td>LEVEMIR® (insulin detemir)</td>
<td>$1,570</td>
<td>06/2019</td>
</tr>
<tr>
<td>LUCENTIS® (ranibizumab)</td>
<td>$1,860</td>
<td>06/2020</td>
</tr>
</tbody>
</table>

Source: Amgen Data on File
PAYER CONSIDERING ALTERNATIVE MODELS

UHC Pilot Aims to Reduce Total Spend

In 2009, United Healthcare conducted a pilot study in which oncology groups received bundled payments for medical services and drugs administered. Each medical group selected a single chemotherapy regimen for each adjuvant therapy episode. Using the existing fee schedule for each group, United Healthcare calculated the drug margin for each adjuvant regimen by subtracting the average sales price from the contracted rate for the drugs.

The primary objective was to decrease the total medical cost by using aligned financial incentives supported by actionable use and quality information. This goal was met, as demonstrated by a 34% reduction of the predicted total medical cost. The secondary objective was to remove the linkage between drug selection and medical oncology income. Without this linkage, it was expected that chemotherapy drug cost (CDC) trends would decrease. Paradoxically, the pilot resulted in 179% ($13M) more CDC than predicted when compared with the controls. Despite the additional cost, the total medical costs were reduced by $33M.

UPCOMING ENTRIES OF BIOSIMILARS WILL TRIGGER COST MANAGEMENT DISCUSSIONS

With many market-leading originators approaching patent expiry in the U.S. in the coming years, these milestones inherently will create opportunities to expand the field of potential biosimilar entrants. For example, research indicates that payers expect 2-3 biosimilars of a TNFα inhibitor originator to launch within 30 months of patent expiry.

Rheumatoid Arthritis (RA) is a condition that has promise in terms of developing a new payment model. A potential model could be a time-defined bundle that would involve primary care and rheumatology and incentivize appropriate monitoring of symptoms, judicious use of testing, coordination of care with referral to rheumatologists at the appropriate time, and appropriate drug utilization.

Payer Expectations for Biosimilar Entrants Over Time

Data represented as reported by original source.

Source: Amgen Data on File
PAYERS ARE ACTIVELY PREPARING FOR BIOSIMILAR ENTRY

Rating of Biosimilars as a Priority for Payer Organizations

Most payer groups are making biosimilar planning a priority

Most benefit consultants currently are not prioritizing biosimilars

Source: Amgen Data on File
One influential factor on the expected uptake of biosimilars in the U.S. is expected to be the determination of how physicians and pharmacists could select an approved biosimilar instead of an originator product, and to what extent there is flexibility to switch between biosimilars in the same class.67

Interchangeability designations are likely to be a subsequent consideration in the approval process, and the clinical data currently required as part of the biosimilar review process limits the number and scope of biosimilars that may gain an interchangeability designation in the near future.11,71

**Interchangeability vs. Therapeutic Equivalence**

Small molecule therapies are often substituted for generic alternatives because they are considered to be identical and therapeutically equivalent and thus interchangeable, with few exceptions. Since biosimilars are not identical to the originator biologic product, the concept of interchangeability has been redefined.67

The 2010 law that allows the FDA to approve biosimilars established two distinct standards: biosimilarity and interchangeability. The FDA’s 2012 draft guidance further clarified the data sets required to demonstrate biosimilarity. Drug candidates require unique sets of analytical and nonclinical data as well as clinical pharmacology and immunogenicity studies to demonstrate biosimilarity, and may require additional clinical studies prior to approval if deemed necessary.4

Once a product has achieved a biosimilarity designation by the FDA, it may be considered for a determination of interchangeability with the reference product, which assumes the product produces the same clinical result in any given patient and poses no additional risks by switching between the biosimilar and the reference product.70

Biosimilars deemed interchangeable with reference products could potentially be substituted without consulting the prescriber, though individual state pharmacy acts will be responsible for establishing the required process for pharmacist substitution.71
IMPACT OF POTENTIAL LABELING DIFFERENCES

The FDA approval of a biosimilar may include some or all of the originator’s labeled indications, depending on the data set submitted with the application. P&T committees will need to carefully consider coverage policies for biosimilars whose FDA-approved indication do not match those of the reference product or one another.

The P&T committees also will need to address switching between reference products and their biosimilars, and between biosimilars of the same reference product.

Biosimilars may not automatically receive all of the indications of the reference medicine and indication extrapolation for non-studied indications requires scientific justification

European and Canadian regulators have reviewed the same biosimilar TNF-α and arrived at different conclusions about the range of its labeled indications

“Whereas conventional generic medicines are usually considered or classified as interchangeable, this is not necessarily the case for biosimilars: here interchangeability should be demonstrated by scientific data proving that two products can be safely substituted for one another and do not create adverse health outcomes, e.g., generating a pathologic immune response after repeated switching.”

G. KRESSE, ROCHE. EUR J PHARM BIOPHARM. 2009
I think a lot of the unknown comes back to the FDA and their review process and how much risk physicians are going to be willing to accept comes back to language on interchangeability… I think that will drive a lot of what we are able to do, and then how it filters down to the patient level.

MEMBER OF EDITORIAL COUNCIL
The potential impact of state laws on biosimilar substitution

States are poised to permit the substitution of FDA interchangeable biologics, include other provisions consistent with generic substitution, and vary in their approach to pharmacy-prescriber communication of dispensed biologics.

Prior to 2013, no state laws specifically addressed the substitution of biologics. As of January 2015, eight states have enacted biologics substitution laws which share common elements among each other and with their rules for generic drug substitution:

1. That only biological products determined as interchangeable by the FDA are permissible to be automatically substituted under state law, similar to how many states rely upon the FDA's determination of therapeutic equivalence for generic substitution.
2. That the prescriber could prevent substitution at his/her discretion.
3. That pharmacy records of dispensed medications must be retained for a length of time.
4. That the patient should be informed of the substitution. States have taken different approaches regarding whether and how dispensing information should be communicated to the prescriber after the fact.

As of January 2015, of the eight laws enacted, seven require some form of prescriber notification.

Example:
In Delaware, for example, Senate Bill 118, signed into law on May 28, 2014, established circumstances under which a pharmacist may substitute FDA-designated interchangeable biosimilar biological products for a prescribed biological reference product. The prescriber has the right to require that the specific product prescribed be dispensed, consistent with state law. The pharmacist must notify the patient of the substitution at the time of dispensing; record the information in an interoperable electronic health record system for prescriber access, or inform the prescriber after the fact; record specified information on the label and dispensation record; and maintain a three-year record, consistent with current law.
Substitution may complicate effective pharmacovigilance, as repetitive switching of agents may subvert the ability to attribute adverse events to the appropriate agent, and could force withdrawal of treatment.\footnote{T. DORNER, ET AL., ANN RHEUM DIS. 2013}

There are inadequacies of the current system for accurate pharmacovigilance. Adverse event (AE) reporting is required of manufacturers but not physicians or other groups.\footnote{74,78} More than 90% of AE reporting comes from manufacturer reports, as required.\footnote{74}

**Inadequacies of Current Systems for Accurate Pharmacovigilance\footnote{75}**

**EXAMPLE: ENOXAPARIN**

**Spontaneous Reporting System**
- Reports submitted to the FDA or manufacturers
- Used to detect new safety signals

**FINDINGS (SPONTANEOUS REPORTS):**
- PRODUCTS ID’D: Poorly
- OBSERVATIONS:
  - 26% ambiguous reports (generic name only)
  - Identification of reports to brand or generic manufacturers did not track to volume share

**Active Surveillance**
- Administrative claims databases
- Useful for answering specific questions

**PHARMACY BENEFIT: (33%)**
**FINDINGS (PHARMACY CLAIMS):**
- PRODUCTS ID’D: Yes (via NDC)

**MEDICAL BENEFIT: (67%)**
**FINDINGS (INSTITUTIONAL DATA AND MEDICAL CLAIMS):**
- PRODUCTS ID’D: No

**Source:** Grampp et al. ASHP. 2014

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**Volume Share**

- SANOFI: 50%
- SANDOZ: 6%
- WINTHROP: 5%
- OTHER: 40%

**Adverse Event Reports**

- IDENTIFIABLE TO SANOFI: 69%
- IDENTIFIABLE TO A SPECIFIC GENERIC: 26%
- NOT IDENTIFIABLE: 5%
SWITCHING RAISES PHARMACOVIGILANCE CONSIDERATIONS THAT MAY INFLUENCE PAYER DECISIONS

Switching and Pharmacovigilance

All biologic medicines carry risk related to an individual patient’s reaction to proteins in the medicine, which may affect the biologic’s efficacy or safety. Data on the impact on efficacy and safety should be collected to fully understand the clinical consequences of these immune responses.76

“Longitudinal tracking of the patient could be more critical in this instance than tracking the drug because where you originate (site of care) may predict your future track.”

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AE reporting is collected by manufacturers from a variety of sources based on currently accepted surveillance practices. This process relies on the voluntary participation of the healthcare community, which is not always consistent and often results in underreporting. Further, the quality of reports varies and the medication suspected of causing the AE is not always fully identified.77

Tracing AEs associated with biologics is challenging because the event may not manifest immediately. Reporting may occur weeks or months later, and most likely after the product packaging has been discarded. Under these circumstances, AE reporting depends on the reporter’s memory or the patient’s medical record.78

There are inconsistencies in the identification of biologics that limit accurate tracing of reported AEs. Effectively distinguishable products may help facilitate more accurate AE reporting and tracing.77

“Our finding of biosimilarity, just like our approval of a new drug, is going to be a prediction of performance. Sometimes there are unexpected findings in the postmarket period, both for a newly approved drug, and we expect perhaps for biosimilars, though we hope that doesn’t happen. If it does, we want to be able to detect it very rapidly, attribute it to the correct product, and take the appropriate action.”

J WOODCOCK, FDA, AS PRINTED IN BIOCENTURY. 201479
SWITCHING CONSIDERATIONS BY POPULATION

There may be variability in physician willingness to prescribe biosimilars to patients who have been treated with an originator biologic (existing patients) compared with those who have not been treated previously (treatment-naive patients). Further, certain sub-populations of patients may not necessarily be immediate candidates to switch to a biosimilar product if they are particularly susceptible to an unwanted immune response. Examples could include pediatric patients or immunocompromised patients. In this case, physicians may opt to maintain use of originator biologics for these types of patients.

Highlights of a Tufts Center for the Study of Drug Development 2014 survey of physicians and payers aware of biosimilars:

Physician perspectives (n=14):
- Most respondents (70%) are likely to prescribe biosimilars to a new patient as soon as they are FDA approved.
- The majority (69%) feel comfortable switching an existing patient from the originator biological to a biosimilar.

Payer perspectives (n=8):
- To maximize cost savings, payers will likely employ formulary management tools, such as higher-cost sharing for originators and lower-cost sharing for biosimilars.
- Most (75%) would recommend therapeutic switching of biosimilars.
- 75% of payer respondents expect biosimilars to have a 15–35% price discount.

Physician Likelihood of Switching an Existing Patient from an Originator to a Biosimilar

Physician Likelihood of Prescribing a Biosimilar to a Patient Who Has Not Previously Been Treated

Adapted from Cohen et al. GABI J. 2014

To me, the physician is the link, because we will be telling the physician to prescribe biosimilars first. The patients might learn that there’s a lower co-pay or access point, but they will be asking their doctors for counsel. It is the physician who has to be trained on what the health plan is asking and what the patient will get.

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DEBATE CONTINUES ON THE IMPLEMENTATION OF SWITCHING

The broader healthcare community has differing points of view with regard to switching, citing concerns over patient safety and ownership of the treatment decision between the prescribing physician and the patient.

“...The arguments currently being raised against biosimilar substitution are similar to arguments used against traditional generic drug substitution following the passage of the Hatch-Waxman Act in 1984. ...Generic prescription drugs are now broadly viewed as completely safe and an appropriate substitution for the brand-name version, and now represent 86 percent of U.S. prescriptions. The widespread availability and acceptance of generic drugs has also resulted in substantial savings to the healthcare system.”

L. Purvis, AARP Public Policy Institute. 2014

While generally in agreement with the intent of the AARP position, the American College of Rheumatology advocates a more cautious position on implementation, writing in a 2011 position statement, “...While cost savings are highly desirable, the approval process for biosimilars (generic biologics) needs to place safety and efficacy, supported by scientifically sound evidence, as the highest priorities.”

American College of Rheumatology Position Statement. 2011

“...You want to indicate the product is biosimilar, so you don’t want mistakes. You don’t want the product mixed up so there is inadvertent switching. You want to know what the patient actually got, so you can track it.”

J. Woodcock, FDA, as printed in BioCentury. 2014
**CODE SHARING MAY HAVE IMPORTANT IMPLICATIONS**

> From a managed care perspective, how will we monitor utilization of preferred products among biosimilars if we can’t tell them apart?

*MEMBERS OF EDITORIAL COUNCIL*

### Implications of Shared or Distinct HCPCS (Healthcare Common Procedure Coding Systems) Codes Between Biosimilars and Originators:

#### Products

- All hyaluronic acid (aka, hyaluronan) (as of December 2014)\(^62\)
  - Hyalgan®/Supartz®, J7321, Average Sales Price (ASP)=$90.81/dose
  - Orthovisc®, J7324, ASP=$186.89/dose
  - Synvisc®, J7325, ASP=$12.50/1mg
  - Euflexxa®, J7323, ASP=$161.12/dose

#### Differentiation

- None are designated as “biosimilar”
- United Healthcare coverage policy: “There is no evidence that use of one intra-articular hyaluronan product is superior to another”\(^83\)

#### Cost Considerations

- Hyalgan® and Supartz® share a HCPCS code, and their ASP is a blend of cost and market share\(^119\)
- Baxter, the maker of Glassia®, another brand of alpha 1 proteinase inhibitor, applied for and was granted a separate HCPCS code in 2011, J0257\(^93\)
- The ASP for these two HCPCS codes for alpha 1 proteinase inhibitor, effective December 2014 are (per 10 mg): $4.11 (J0256) and $3.98 (J0257), respectively\(^2\)
- Brands that code share J0256 have a single payment amount reflecting the weighted average of their net prices and sales volume, whereas the ASP for one brand that is J0257 reflects only that brand’s net price and sales\(^119\)

* CMS conducts reviews to ensure that separate payment is made for single source drugs and biologics.\(^84\)

> In contrast to drugs dispensed by pharmacies, which are billed for using NDCs [National Drug Codes], physician-administered drugs are typically billed for using Healthcare Common Procedure Coding System (HCPCS) codes. Unlike NDCs, HCPCS codes do not identify the manufacturer responsible for paying a rebate. To assist States in collecting rebates for physician-administered drugs, the DRA [Deficit Reduction Act] essentially required the States to provide for the gathering of data (including NDCs) necessary to collect rebates...

*DEPT. OF HEALTH & HUMAN SERVICES, MEDICAID DRUG REBATE DISPUTE RESOLUTION COULD BE IMPROVED. 2014*\(^85\)
PREPARATIONS INCLUDE SHIFTS IN BENEFIT DESIGN AND DRUG TIERS

Questions remain on how payers will assign biosimilars to formulary tiers. In addition, because some therapeutic areas have more “weight” than others when it comes to benefit design and contracting, it is likely that payers will focus on some categories before others. Another complexity is that payers may contract with a manufacturer across a therapeutic portfolio, so decisions made for one area could impact others. This could impact competition in some therapeutic areas as a result. Payer benefit designs, coverage policies and prescriber bundling will evolve, with impact to the commercial success of existing and newly approved biosimilars.72

Biosimilars will no doubt become more routinely used when increasing experience and adequate time on the market convince clinicians that these products are safe and effective. In the meantime, P&T committee members must play a leadership role in adopting and using biosimilars appropriately by applying formulary and practice management tools and principles.71

C. VENTOLA, ET AL., P&T, 2013

TIER ASSIGNMENTS FOR ORIGINATORS AND BIOSIMILARS WILL IMPACT THEIR UPTAKE AND RELATIVE MARKET SHARE

Tier assignment of an originator biologic and its biosimilars will impact uptake of the biosimilars, the relative market share of originator to all biosimilars and the market share of plan-favored biosimilars over excluded or disfavored biosimilars.

In its 2014 employer health benefits survey, the Kaiser Family Foundation reported that 20% of covered workers are enrolled in health plans using formularies with four or more tiers. Of covered workers facing four or more tiers, 49% pay a coinsurance for fourth-tier drugs. The average amount of the coinsurance for a fourth-tier drug is 29% of the drug’s allowed cost, which is subject to a maximum out-of-pocket dollar spend for 47% of these covered workers.86
EXAMPLE: In November 2013, the self-insured employer, North Carolina State Health Plan, made the decision to assign a favored biosimilar to Tier 4, and the originator to Tier 5. The Tier 4 listed biosimilar carries a lower beneficiary cost share than does the Tier 5 listed originator. If a patient finds the cost-share difference to be a heavy burden, he/she may ask the physician to prescribe a medication on a lower Tier, such as a biosimilar of the prescribed medication (or may ask the pharmacist to contact the physician to request such a change).

North Carolina State Health Plan 2013 Pharmacy Benefits Recommendations Including Biosimilars

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>TRADITIONAL 70/30 PLAN</th>
<th>ENHANCED 80/20 PLAN</th>
<th>CONSUMER-DIRECTED HEALTH PLAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1 Most cost-effective medications, which includes mostly generic drugs</td>
<td>$12 per 30-day supply</td>
<td>$12 per 30-day supply</td>
<td>15% coinsurance after deductible (in-network)</td>
</tr>
<tr>
<td>Tier 2 Preferred brand medications, including some high cost generic drugs and compound drugs</td>
<td>$40 per 30-day supply</td>
<td>$40 per 30-day supply</td>
<td>35% coinsurance after deductible (out-of-network)</td>
</tr>
<tr>
<td>Tier 3 All other non-preferred brand drugs for which alternatives are available in lower tiers</td>
<td>$64 per 30-day supply</td>
<td>$64 per 30-day supply</td>
<td></td>
</tr>
<tr>
<td>Tier 4 Preferred specialty medications which may include some Biosimilar specialty medications</td>
<td>25% coinsurance up to $100 per 30-day supply</td>
<td>25% coinsurance up to $100 per 30-day supply</td>
<td></td>
</tr>
<tr>
<td>Tier 5 Non-preferred specialty medications which may include some Biosimilar specialty medications</td>
<td>25% coinsurance up to $150 per 30-day supply</td>
<td>25% coinsurance up to $150 per 30-day supply</td>
<td></td>
</tr>
<tr>
<td>ACA Preventive Medications List of preventive medications required by the ACA to be covered at 100%</td>
<td>N/A</td>
<td>$0 (covered at 100%)</td>
<td>$0 (covered at 100%)</td>
</tr>
<tr>
<td>CDHP Preventive Medications List of preventive medications used to help prevent and manage certain chronic health conditions</td>
<td>N/A</td>
<td>N/A</td>
<td>15%, no deductible</td>
</tr>
</tbody>
</table>

For 80/20 and 70/30 Plans, brand name drugs with a generic equivalent – Member pays the Tier 1 copay plus the difference between the Plan’s cost of the brand name drug and the Plan’s cost of the generic drug, not to exceed $100 per 30-day supply of the brand medication. Source: NCSHP, 2014.
Medicare Part B In Traditional Medicare Program:
A proposal contained within the President’s 2015 Budget for the Department of Health and Human Services (HHS), modifies how Part B pays for treatment where generic biologics are available by allowing them to be classified in the same category as their biosimilar. Reimbursement would be made based on the weighted average sales price. This proposal would save money in Medicare and Medicaid. [$4 billion in Medicare savings over 10 years].
DEPT. OF HEALTH & HUMAN SERVICES, FY2015 BUDGET IN BRIEF. 2014

Medicare Part D:
Part D vendors may institute specialty tiers in their formularies. Biologics, including biosimilars, are most likely to be assigned to a specialty tier. There are certain CMS-imposed restrictions on what the Part D vendors may do with respect to the specialty tier.

For Medicare Beneficiaries Enrolled In Medicare Advantage Plans (Medicare Part C):
Under the MA (Medicare Advantage) program, Medicare buys insurance coverage for its beneficiaries from private plans with payments made monthly. The coverage must include all Medicare Part A and Part B benefits except hospice. All plans, except PFFS [Private Fee for Service] plans, must also offer an option that includes the Part D drug benefit.
MEDICARE ADVANTAGE PROGRAM PAYMENT SYSTEM. 2013

Coverage for Biosimilars Within Medicare
For Biosimilars Covered Under...
The expectation of cost savings associated with biosimilars is a major factor in support of this new market. Payers are designing projections to gain clarity on the expected pricing activity that originators may take around biosimilar entry to preserve market share. Pricing and access, among other critical factors, are central value drivers for the adoption of this new category.

1. Projections continue to vary on the expected cost savings that may result from near-term biosimilar launches; a 2008 Congressional Budget Office report suggested roughly $25B in savings from 2009 through 2018.
2. Most payers expect pricing discounts of a biosimilar at launch and originators to offer additional discounts over time.
3. Successful entry of a biosimilar is dependent on its overall value, including cost, but also quality and manufacturer reliability.
PRIMARY VALUE OF BIOSIMILARS IS COST SAVINGS BUT PROJECTIONS VARY ON HOW MUCH

Part of the promise of biosimilars is that this category of medicines could offer cost savings which would help to reduce some of the burden on the healthcare system. Currently available sources for cost savings projected with the introduction of biosimilars widely vary in their estimations.\textsuperscript{23,91} This variance likely reflects the uncertainty around how healthcare stakeholders will perceive and prescribe biosimilars once they are FDA approved.

Express Scripts projects savings associated with biosimilars approaching $250B, while in 2008 the Congressional Budget Office predicted a more conservative $25B in savings.\textsuperscript{23,91} Yet a 2014 Health Affairs article noted that even these savings may be too optimistic at this stage; as the market evolves, more accurate forecasts will emerge.\textsuperscript{9}

MANAGING AND SETTING EXPECTATIONS FOR BIOSIMILAR COST SAVINGS

Payers report that the primary drivers for coverage of biosimilars is cost containment.

<table>
<thead>
<tr>
<th>Primary Objective for Biosimilars\textsuperscript{6}</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAIN COST</td>
</tr>
<tr>
<td>73%</td>
</tr>
</tbody>
</table>

\textsuperscript{6}n=40 PERCENT OF RESPONSES

Data represented as reported by original source. Source: Amgen Data on File

Express Scripts (ESI) projects the U.S. would save $250B between 2014 and 2024 if only the 11 likeliest biosimilars would enter the market\textsuperscript{91}. In 2008 CBO projected $25B in savings between 2009 and 2018\textsuperscript{23}. CBO expects $25B reduced total expenditures on biologics over the 2009-2018 period. Over that 10-year period, such savings would equal roughly 0.5% of CBO projections\textsuperscript{23}.

Congressional Budget Office (CBO)
ORIGINATOR PRICING LIKELY TO EVOLVE AT LAUNCH AND OVER TIME, WITH EXPECTED OVERALL REDUCTIONS

Payers continue to debate the initial net discount of products attributed to biosimilars, but most believe it will be at least 30% within a few years.\(^6\)

**EXAMPLE:** At launch, many payers expect the manufacturer of a TNF\(\alpha\) inhibitor originator to maintain a net price premium, but to offer net price at or below biosimilar 30 months after launch.\(^6\)

### Expected Level of Discount for a Biosimilar to Offer off the WAC Price of a TNF\(\alpha\) Inhibitor\(^6\)

<table>
<thead>
<tr>
<th>WAC Discounts Due to Biosimilars Competition</th>
</tr>
</thead>
<tbody>
<tr>
<td>8%</td>
</tr>
<tr>
<td>35%</td>
</tr>
<tr>
<td>58%</td>
</tr>
</tbody>
</table>

\(n=40\)

### Expected Actions of TNF\(\alpha\) Inhibitor Innovator if Faced with Potential Loss of Coverage for Product Upon Biosimilar Launches\(^6\)

- **Offer Minimal Additional Rebates/Price Protection**
- **Offer Additional Rebates/Price Protection But Maintain a 10-15% Premium Over Biosimilar**
- **Offer Discounts/Price Protection Which Meet/Exceed the Net Price of the Biosimilar**
- **Offer Additional Rebates/Price Protection Only to Grandfathered Population, and Maintain a 10-15% Premium Over Biosimilar**
- **Offer Substantial Discounts/Price Protection Which Meet/Exceed the Net Price of the Biosimilar, But Only to Grandfathered Population**

\(n=40\)

Data represented as reported by original source. Source: Amgen Data on File.
There is consolidation happening now so timing is everything. By 2017, we will have narrowed our categories and we will no longer be playing with several TNFs, but will have one preferred, so where do we go then?  

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Ultimately, as a share of covered lives, a minority of existing patients will be incentivized or required to switch to a biosimilar in this TNF$\alpha$ inhibitor example:

**Expected Approach for New and Existing Patients Starts, Assuming Net 10% Savings from Each TNF$\alpha$ Inhibitor Patient and Assuming the Biosimilar Is Approved for All Indications as the Originator**

<table>
<thead>
<tr>
<th><strong>EXISTING PATIENTS</strong></th>
<th><strong>NEW PATIENT STARTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>WILL NOT ASK, INCENT, OR REQUIRE PATIENT TO SWITCH</td>
<td>COVER BIOSIMILAR AND REFERENCE PRODUCT EQUALLY AND DEFER TO THE PRESCRIBING PHYSICIAN</td>
</tr>
<tr>
<td>INCENT PATIENT TO SWITCH TO BIOSIMILAR THROUGH DIFFERENTIAL COST SHARING</td>
<td>COVER BIOSIMILAR AND REFERENCE PRODUCT ON PREFERRED TIER AND RELY ON PATIENT COPAY DIFFERENTIAL</td>
</tr>
<tr>
<td>INCENT PHYSICIAN TO SWITCH THROUGH PERFORMANCE TARGET BONUS (I.E. “PAY FOR PERFORMANCE” RELATED TO % OF BIOSIMILAR PRESCRIPTIONS)</td>
<td>COVER BIOSIMILAR ON PREFERRED TIER, MOVE REFERENCE PRODUCT TO NON-PREFERRED TIER, AND RELY ON PATIENT COPAY DIFFERENTIAL</td>
</tr>
<tr>
<td>REQUIRE SWITCHING TO BIOSIMILAR THROUGH NDC BLOCK ON REFERENCE PRODUCT</td>
<td>COVER ONLY BIOSIMILAR ON A PREFERRED TIER, AND REQUIRE A PA WITH A STEP PRIOR TO ACCESSING REFERENCE PRODUCT</td>
</tr>
<tr>
<td>NOT SURE</td>
<td>NOT SURE</td>
</tr>
</tbody>
</table>

Source: Amgen Data on File
CONSIDERING EMPLOYER SAVINGS POTENTIAL

Based on certain assumptions, large employers may see variability in savings from biosimilars. Actual savings will depend upon many factors, but certain assumptions help to quantify the biosimilar impact to employers, offering scenarios that project the anticipated potential savings. Ultimately, biosimilar savings as a percentage of total healthcare costs is likely to be small (less than 1%) given the relatively small frequency of members with high-cost conditions. With this estimate, research indicates that employers may be unlikely to change benefit provisions to incent the use of biosimilars over reference product. However, the drug selection process will be more involved than simply selecting a generic drug versus a brand drug."}

"Though unclear about the direct impact of biosimilars, employers are excited about their potential. Ultimately, they are waiting on input from their health plans and PBMs." —MEMBER OF EDITORIAL COUNCIL

Example of Employer Projected Savings from Biosimilars, Assuming 10,000 Commercial Members"}

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Biosimilar Prices</th>
<th>Patient Biosimilar Copays</th>
<th>Acceptance of Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30% Discount Off Reference Product Prices</td>
<td>$50 Less than Reference Product Copays</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>25% Discount Off Reference Product Prices</td>
<td>$50 Less than Reference Product Copays</td>
<td>75%</td>
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<tr>
<td>3</td>
<td>25% Discount Off Reference Product Prices</td>
<td>The Same as Reference Product Copays</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>20% Discount Off Reference Product Prices</td>
<td>The Same as Reference Product Copays</td>
<td>25%</td>
</tr>
</tbody>
</table>

Adapted from Kopenski, 2011
BEYOND COSTS: THE VALUE OF BIOSIMILARS

While it is expected that cost will remain a central factor in biosimilar uptake, the acceptance is also dependent on the total value offered by these biologic alternatives, including intangible costs, quality and manufacturer reliability, as new therapeutic options in the arsenal of physicians treating challenging diseases.9

*NEW ALTERNATIVES AND NEW OPPORTUNITIES TO OPTIMIZE RISK-SHARING*<sup>25, 94</sup>

*MORE THERAPEUTIC OPTIONS, LOWER OUT-OF-POCKET COST*<sup>121</sup>

*GREATER COMPETITION WITH THE GOAL OF REDUCING SPEND AND TREND PER COURSE OF TREATMENT*<sup>71</sup>

*POTENTIAL TO REDUCE OVERALL COSTS AND TRENDING IN EXPENSIVE POPULATIONS*<sup>92</sup>
CONSIDERING VALUE FROM ALL STAKEHOLDERS

FDA-approved biosimilars will compete with their reference products and other biosimilars as therapeutic alternatives, on the basis of quality, manufacturer reputation and price.9

Over time, the success of biosimilars will depend on gaining the confidence of patients, prescribers and payers, maintaining a strong safety profile, and reducing the cost of care – without impairing care quality or outcomes.9

At Its Heart, Value-Based Healthcare (VBH) Involves a Simple Equation: Value = Outcomes/Cost In Practice, It Involves Complexity on Several Levels.9

Value is measured by a product’s performance characteristics and attributes for which customers are willing to pay.97 Applied to healthcare, according to Michael Porter of Harvard Business School, value is equal to health outcomes that matter to patients, divided by the cost of delivering those outcomes; where “outcomes” are the full set of health results for a patient’s condition over the care cycle, and “costs” are the total costs of care for a patient’s condition over the care cycle.98

Defining parameters

- Which outcomes (survival, quality-adjusted life year [QALY], patient experience, economic benefits, societal benefits)?
- What is included in “cost” (price of treatment, total care, patients’ own costs)?
- Any exceptions (societal priorities, rare diseases, age groups, end-of-life care)?

Providing evidence

- Are data on outcomes robust enough?
- Are data on costs robust enough?
- Are we using the right comparators?
- Is different evidence needed in different markets?

Implementing decisions

- Will this involve a rethink of care pathways?
- How will providers/suppliers be paid?
- Will provider-supplier relationships change?

Perspectives and Potential Value End Points

Effect on innovation

- Is VBH a race to the bottom on pricing?
- How do we demonstrate value for ground-breaking treatments?
- Will it prevent new treatments being developed or marketed?

Sources:
- The Economist, 2014
- Yong et al. IOM. 201096

Adapted from Yong et al. IOM. 201096
VARYING PERSPECTIVES ON VALUE

STAKEHOLDER PERSPECTIVES OF BIOSIMILARS VALUE ARE EXPECTED TO BE CRITICAL FOR THE SPEED AND EXTENT OF THEIR SUCCESS IN THE U.S. MARKET AND REFLECT THEIR PRIMARY PRIORITIES.96,99,101,102

Payers:

“Based on our review of VBP (value based purchasing) programs in operation, VBP program sponsors tend to identify multiple high-level goals that focus on improving clinical quality (75% of the programs we reviewed) and cost/affordability (53% of the programs we reviewed). Less commonly reported were goals related to improving patient outcomes (34%) and patient experience (17%).”

RAND HEALTH, RESEARCH REPORT. 201499

Patients:

“We have heard that for patients, perceived value in healthcare is often described in terms of the quality of their relationship with their physicians. It has been highlighted that value improvement means helping them better meet their personal goals or living lives that are as normal as possible. It does not necessarily mean more services or more expensive services, since it was stated patients are more likely driven by sensitivity to the value of time and ensuring that out-of-pocket payments are targeted to their goals.”

INSTITUTE OF MEDICINE, VALUE IN HEALTH. 201096

Physicians:

“In practical terms, promoting high value care means supporting the use of tests and treatments that scientific evidence demonstrates are most likely to improve survival and quality of life. This means taking proactive steps as a profession to reduce the use of unnecessary procedures and ineffective treatments. Studies have demonstrated the role of evidence-based guidelines in reducing costs.”

AMERICAN SOCIETY OF CLINICAL ONCOLOGY, STATE OF CANCER CARE IN AMERICA REPORT. 2014101

But not all perspectives are likely to carry equal weight: “When asked who will have the greatest influence in how value will be defined within the next 3-5 years, payers are roundly believed to have the most influence. In the recent survey, 75% of U.S. payers, 66% of providers, and 59% of EU payers ranked them in their top two.”

QUINTILES, STAKEHOLDER SURVEY OF PERCEPTIONS ON VALUE IN HEALTHCARE, 2013102
CONSIDERING VALUE IN THE AGGREGATE

A successful biosimilar entry may require:

1. Understanding that biosimilars are similar but not identical to reference products, unlike small molecule generics, which are exact replicas.
2. Trusted manufacturing partner with proven track record of quality and reliability.
3. Compelling data on highly similar quality and no meaningful differences in safety and efficacy.
4. Relentless attention to pharmacovigilance, traceability and accountability.
5. Confidence and buy-in from all stakeholders to realize the full potential of savings.

Post-entry, successful maintenance and growth of biosimilar market share may require continued manufacturer support, including:

1. Expansion of product labeling to include most if not all originator approved indications.
2. Avoidance of product shortages, or if there are shortages, then effective market communications and rapid deployment of resources to resolve.
3. Efficient and reliable distribution, including responsive customer service.
4. Responsiveness to provider quality and efficacy related questions.
5. Patient support (e.g., copay assistance, transportation support, nurse educators, etc.) programs (which generics manufacturers never sponsor, but which biosimilars manufacturers likely will need to provide).
6. Effective reimbursement and formulary coverage.
QUALITY AND RELIABILITY ARE CRITICAL

Companies seeking to compete successfully in the biologics and biosimilars space must invest in process and facility design, quality control systems and management oversight, all of which can help the reliability and consistency of the manufacturing process.110

Complexities of Manufacturing

Biologics are manufactured with living cells that have been engineered to produce large quantities of therapeutic proteins. The complex manufacturing process requires careful design of controls, precise measurements and strict adherence to protocol, as any changes can potentially influence the quality of the final product, including the structure, function and purity of the active ingredient.103

The complexities of manufacturing biologic medicines also apply to biosimilars, which are approved on the basis of demonstrating similarity to originator biologic medicines.103 Since the biologic production processes are proprietary to each manufacturer, it is impossible for another manufacturer to precisely replicate the manufacturing process of the original biologic or the active ingredient of the protein product.5

IMPORTANCE OF QUALITY AND CONSISTENCY

It is possible that certain structural differences of biologics, such as protein folding, structural modifications (such as glycosylation), batch composition and even the product container, may have an unanticipated impact on the safety or efficacy of the final biologic product.103

Unexpected manufacturing events or quality control issues can have a meaningful impact on patient safety, and may lead to product recalls or drug shortages, any of which can have profound effects on the company, customers, providers and patients.103
The challenge is, how do we roll out a benefit design that addresses a third option vis-à-vis the biosimilar?

2015 will be a dynamic, informative year for biosimilars, with the first candidates potentially gaining approval. As payers continue to prepare for the entry of biosimilars, events in 2015 will generate not only increasing experience and interest in this category, but also an increasingly robust dialogue with more organizations weighing in on key topics that will shape market activity. Finally, additional regulatory clarity guiding the first introductions will inform a productive conversation with all stakeholders.

Many of the remaining unknowns about market projections and shifts may be resolved with these approvals and resulting manufacturer and provider activity.

We look forward to being a part of this discussion.

SINCERELY,

Mike Ryan, PharmD
Vice President & General Manager,
U.S. Value, Access and Reimbursement, Amgen
Examples of Leading U.S. Biologic Products with Anticipated Patent Expiries Through 2020

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>2013 U.S. SALES ($M)</th>
<th>ESTIMATED U.S. PATENT EXPIRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPAXONE® (glatiramer acetate)</td>
<td>$3,711</td>
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</tr>
<tr>
<td>LANTUS®/LANTUS SOLOSTAR® (insulin glargine)</td>
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</tr>
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<td>EPOGEN® (epoetin alfa)</td>
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<td>RITUXAN® (rituximab)</td>
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<tr>
<td>LEVEMIR® (insulin detemir)</td>
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</tr>
<tr>
<td>LUCENTIS® (ranibizumab)</td>
<td>$1,860</td>
<td>06/2020</td>
</tr>
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</table>

MANAGING AND SETTING EXPECTATIONS FOR BIOSIMILAR COST SAVINGS

ESI projects $250B potential of biosimilars91

In 2008 CBO projected $25B in savings between 2009 and 201823

CBO expects $25B reduced total expenditures on biologics over the 2009-2018 period. Over that 10-year period, such savings would equal roughly 0.5% of CBO projections23

Source: Amgen Data on File

Express Scripts (ESI)  Congressional Budget Office (CBO)
**Adverse Event** An unfavorable and unintended medical problem that happens during treatment with a drug or other therapy. It is also referred to as an adverse effect.¹

**ASP** Average Sales Price is the volume-weighted average of the average sales prices for all products included within the same “multiple source drug” billing and payment code.¹⁰⁴

**Biologic** A biological medicine is a medicine that contains one or more active substances made by or derived from a biological source (i.e., living organisms).¹

**Biosimilar** Biosimilars are biological medicines that are proven to be highly similar to the reference biologic (notwithstanding minor differences in clinically inactive components) and exhibits no clinically meaningful differences in terms of safety, purity, and potency.⁴

**CDC** The Centers for Disease Control and Prevention is a U.S. health protection agency that increases the health security of our nation and protects Americans from health threats.¹⁰⁵

**EMA** The European Medicines Agency is a decentralized agency of the EU responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU.¹⁰⁶

**FDA** The U.S. Food and Drug Administration is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the nation’s food supply, cosmetics, and products that emit radiation.¹⁰⁷

**Generic** Generics are bioequivalent copies of existing chemical medicines replicated and produced by other manufacturers after the patent expiry of the originator drug. Generic names usually refer to the chemical (non-proprietary) name of the drug.¹

**HCPCS** The Healthcare Common Procedure Coding System is a collection of standardized codes that represent medical procedures, supplies, products and services. The codes are used to facilitate the processing of health insurance claims.¹¹¹

**Indication** A medical condition, disorder, or disease for which a certain medication or procedure is used.¹
**MAB** A monoclonal antibody is a type of protein made in the laboratory that can bind to substances in the body, including cancer cells.\(^{31}\)

**P & T Committee** A Pharmacy and Therapeutics committee is an advisory committee responsible for developing and maintaining a formulary and establishing and implementing policies on the use of drug products.\(^{122}\)

**Pharmacovigilance** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.\(^{1}\)

**RA** Rheumatoid arthritis is a chronic inflammatory disorder that typically affects the small joints in the hands and feet.\(^{108}\)

**Reference Product** A reference product (aka, originator product) is a previously licensed product used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy.\(^{1,4}\)

**TNFα** Tumor necrosis factor-alpha (TNF) is a cytokine responsible for destructive inflammatory processes when present in elevated concentrations in the body.\(^{123}\)

**WHO** The World Health Organization is the directing and coordinating authority for health within the United Nations system.\(^{100}\)
REFERENCES


BIOSIMILARS KEY CONSIDERATIONS CHECKLIST

2015 will be a dynamic, informative year for biosimilars, with the first candidates potentially gaining approval. Many of the remaining unknowns about market projections and shifts may be resolved with these approvals and resulting manufacturer and provider activity.

Payer Perceptions of Biosimilars

1. Payers are eager for biosimilars to reduce specialty drug prices, but Europe’s experience shows the level of savings may vary.

2. Most payers expect biosimilars to be lower-cost options of branded biologics.

3. EU market uptake is interdependent on pricing, physician perception and patient acceptance.

Payer Readiness for Biosimilars

1. Payers are taking varying levels of action to plan for biosimilars, starting with meetings with external partners and in some instances, restructuring benefit design.

2. Patient switching and the potential interchangeability of biosimilars could complicate effective pharmacovigilance.

3. Payer product selection will need to balance the economics of switching with the readiness and reliability of the manufacturer.

4. Varying state regulations may impact substitution at the retail pharmacy level.

Payer Expectations of Price and Access as Central Value Drivers for Biosimilars

1. Projections continue to vary on the expected cost savings that may result from near-term biosimilar launches; a 2008 Congressional Budget Office report suggested roughly $25B in savings from 2009 through 2018.

2. Most payers expect pricing discounts of a biosimilar at launch and originators to offer additional discounts over time.

3. Successful entry of a biosimilar is dependent on its overall value, including cost, but also quality and manufacturer reliability.