Biosimilars
What you should know, now and in the future
To anyone keeping an eye on rising health care costs in the U.S., the development of biosimilar drug therapies has held the promise and potential to tamp down skyrocketing costs for specialty medications. However, the road to widespread adoption of biosimilars has proven to be a rougher ride than expected. What could biosimilars do for the specialty drug industry, and what are the obstacles? What does the future hold for biosimilar drug therapies?

What a biosimilar drug is, and what it isn’t

First, let’s establish what a biosimilar is.

Biological medical products, or biologics, are a class of specialty prescription medicines. Biologics are different from conventional drugs — more about that in a minute. A biosimilar, or biosim, is an approximation or an almost-identical copy of a similar biologic, manufactured by a different company.

While this is similar to a generic version of a conventional drug, there is a key difference. By law, a generic must be an exact copy of the original medication, or reference product. It must have identical active ingredients and the same chemical structure. Due to the nature of biological reference products, biosims can’t be exact copies. They must be very similar with no clinically meaningful difference, but cannot be identical.

Biologics vs. conventional drugs

Biologics are medicines made from living cells, manufactured in living systems like microorganisms or plant or animal cells.¹ The influenza vaccine is an example of a widely used biologic. Many biologics use recombinant DNA (rDNA) technology: inserting combined DNA from two different species into a host organism, to produce new genetic combinations. This requires a complex manufacturing process with extensive quality controls, because the living systems used to produce biologics can change ever so slightly over time. However, despite complex challenges, biologic drug manufacturing processes must maintain appropriate product consistency to meet Food and Drug Administration (FDA) approval standards.

By contrast, conventional drugs are much simpler to produce. Ingredients are combined in an ordered process, much like following a recipe. This leads to a product with a well-defined chemical structure. A conventional drug can be analyzed to determine all the ingredients or components, and it’s fairly easy to replicate, even if the manufacturing process is different.

Biosims vs. generics

So again, while generics are identical to their reference drugs, biosims are almost identical to their reference biologics. Because of the complexity of the medication and the specialized manufacturing process, it just isn’t possible to perfectly replicate biologics. But as illustrated in Figure A, a biosim is very close to its reference product.

Biosims that have met additional requirements are designated as interchangeable products.² Interchangeable products must demonstrate they can be expected to produce the same result as the reference product, and that there’s no risk associated with switching back and forth between interchangeable and reference products. To date, no biosims are considered interchangeable.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Generics</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Simple and well-defined</td>
<td>Complex with potential structural variations</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Predictable chemical process to make identical copy</td>
<td>Specialized biological process to make similar copy</td>
</tr>
<tr>
<td>Complexity</td>
<td>Easy to fully characterize</td>
<td>Difficult to characterize</td>
</tr>
<tr>
<td>Stability</td>
<td>Relatively stable</td>
<td>Sensitive to storage and handling conditions</td>
</tr>
<tr>
<td>Adverse immune reaction</td>
<td>Lower potential</td>
<td>Higher potential</td>
</tr>
<tr>
<td>Manufacturing quality tests</td>
<td>≤ 50</td>
<td>≥ 250</td>
</tr>
<tr>
<td>Approval requirements</td>
<td>Small clinical trials in healthy volunteers</td>
<td>Large clinical trials in patients</td>
</tr>
</tbody>
</table>

Biosims in the U.S.: current state

Only three biosims are commercially available in the U.S. as of Q1 2018. These include Zarxio®, which treats neutropenia, and Inflectra® and Renflexis®, which treat inflammatory diseases. Six additional products — treatments for various cancers, as well as additional treatments for inflammatory diseases — have been approved by the FDA but aren’t yet available. Roughly 11 more products are expected to be approved during 2018.

Challenges to adoption of biosims

Despite lower costs and proven effectiveness, biosims face an uphill climb toward being widely prescribed. Legal issues, uncertainty about pricing, and a general lack of knowledge about biosimilar products are some current roadblocks.

Battling the brands

Understandably, manufacturers of biosims’ brand-name reference products, or innovator products, are scrambling to maintain their market share. They fight this battle on two fronts: the courtroom and the marketplace.

Oftentimes, lawsuits for patent infringement are filed while a biosim is still in development, setting up a legal barrier to any product launch. For example, in 2016, the FDA approved Amjevita®, a biosimilar to Humira®, to treat inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis. Despite FDA approval, Amjevita won’t be commercially available until 2023 or later, due to complex patent litigation.

Manufacturers of innovator biologics also combat biosimilar market share encroachment through competitive pricing strategies. Rebates, exclusive contracting and multi-year deals to offer the brand name biologic as the preferred treatment can box out biosimilars before they have a chance to gain ground.

Communication/education

The other challenge biosims face is the problem of educating physicians and consumers about the benefits of what seems like a totally unfamiliar drug.

While biosims are generally expected to be less costly than their brand-name reference drugs, that’s far from certain due to the competitive pricing strategies previously mentioned. And providers often don’t have visibility into what a patient’s cost will be, at the time the prescription is being written. So, the touted cost savings of biosims has not proven to be a draw for consumers quite yet.

Educational marketing materials about biosims also must overcome physicians’ fear of the unknown. Many physicians aren’t familiar with the rigorous approval process for biosims, and they aren’t convinced that a biosim can match its innovator drug in terms of health benefit to the patient. Understandably, physicians are wary of switching a patient to a biosim for management of their chronic condition, particularly when the current drug is working.

What opportunities do biosims present for employers?

A more competitive specialty drug market could hold big savings for employers, as well as their employees. For example, two of the biosims currently on the market treat inflammatory diseases like rheumatoid arthritis and psoriasis. Medications for these conditions account for about 35% of spending among the top five specialty drug therapy classes.

Increased competition in a drug category that represents more than a third of specialty drug spending can only boost cost savings, for employers and consumers alike.
The future of biosimilars

As you can see in Figure B, the currently approved biosimilars treat inflammatory conditions, cancers, and neutropenia, which is often a complication of cancer treatment. Biosimilars are expected to play a major role in the fields of rheumatology and oncology, for the foreseeable future.

In rheumatology, the FDA-approved biosimilars treat:
- Rheumatoid arthritis
- Plaque psoriasis
- Psoriatic arthritis
- Ankylosing spondylitis
- Polyarticular juvenile idiopathic arthritis
- Crohn’s disease

In the field of oncology, conditions for which there are approved biosims include:
- Neutropenia
- HER2+ breast cancer
- Glioblastoma
- Metastatic colorectal cancer
- Metastatic renal-cell carcinoma
- Lung cancer
- Cervical cancer

A June 2017 U.S. Supreme Court decision paved the way for biosims in development, ruling that a biosimilar applicant is not required to share its application for FDA approval with the biologic innovator, and that they have some flexibility around timing of the “heads-up” that a biosim is coming. Several biologic drug patents expire in the next few years, so we can expect to watch this play out in the courts and in the marketplace, over the coming decade.

We will also see innovation evolve into differentiation among competing biosimilars, and between biosims and their reference products. By adding value in the form of anti-drug antibody, individualized monitoring, and subcutaneous formulations for greater convenience, Celltrion differentiated Inflectra® from the competition.

The innovation and technology to develop biologics will continue to evolve to meet the demand for treatments to prolong life and ease suffering. And where biologics are introduced, biosimilars are sure to follow.

### Figure B

<table>
<thead>
<tr>
<th>Biosimilar product</th>
<th>Reference product</th>
<th>Condition</th>
<th>FDA approval date</th>
<th>Date available in market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zarxio</td>
<td>Neupogen</td>
<td>Neutropenia</td>
<td>March 2015</td>
<td>September 2015</td>
</tr>
<tr>
<td>Erelzi</td>
<td>Enbrel</td>
<td>Inflammatory diseases</td>
<td>August 2016</td>
<td>Q4 2018 – Q2 2019</td>
</tr>
<tr>
<td>Emjevita</td>
<td>Humira</td>
<td>Inflammatory diseases</td>
<td>September 2016</td>
<td>2023</td>
</tr>
<tr>
<td>Inflectra</td>
<td>Remicade</td>
<td>Inflammatory diseases</td>
<td>April 2016</td>
<td>November 2016</td>
</tr>
<tr>
<td>Renflexis</td>
<td>Remicade</td>
<td>Inflammatory diseases</td>
<td>April 2017</td>
<td>July 2017</td>
</tr>
<tr>
<td>Cytezo</td>
<td>Humira</td>
<td>Inflammatory diseases</td>
<td>August 2017</td>
<td>2018 – 2022</td>
</tr>
<tr>
<td>Mvasi</td>
<td>Avastin</td>
<td>Lung, kidney, cervical, colorectal, brain cancers</td>
<td>September 2017</td>
<td>July 2019</td>
</tr>
<tr>
<td>Ogivri</td>
<td>Herceptin</td>
<td>Breast cancer</td>
<td>December 2017</td>
<td>December 2018 – Q2 2019</td>
</tr>
<tr>
<td>IXifi</td>
<td>Remicade</td>
<td>Inflammatory diseases</td>
<td>December 2017</td>
<td>2018</td>
</tr>
</tbody>
</table>

Source: fda.gov (March 2018).

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3 fda.gov (March 2018).
4 FDA, Developing Products for Rare Diseases & Conditions (February 26, 2018): fda.gov/industry/developingproductsforrarediseasesconditions/default.htm.