A BIOLOGIC is an active pharmaceutical ingredient prepared by the use of living systems, such as tissues or cells. Most biologics cannot reasonably be produced by chemical synthesis. Some examples of biologic drugs and chemical drugs:

<table>
<thead>
<tr>
<th>BIOLOGIC DRUG</th>
<th>CHEMICAL DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Growth factors (e.g., GCSF)</td>
<td>Tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Antibody-drug conjugates</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Insulin</td>
<td>mTOR inhibitors</td>
</tr>
</tbody>
</table>

Changes to any step of the manufacturing process can impact the final product on many levels. It is commonly said that “the process determines the product”.

While chemical drugs can be precisely copied into generics, the same is not true of biologics. Because the way a biologic is manufactured impacts the final product, a biologic cannot be copied. Instead, “copy” versions of biologics are called biosimilars.

As this name indicates, they are similar, but not identical, to the reference products.

According to the Biosimilar Medicinal Products Working Party at the European Medicines Agency, a biosimilar is a “copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.”

A copy version that has not undergone this rigorous comparability exercise cannot be called a biosimilar.
Because biosimilars are copies of already approved molecules, they are approved on the basis of an accelerated/reduced approval process. The guiding principle of biosimilar clinical trials is to demonstrate comparability to the originator process, not patient benefit.

Biosimilars are approved on the basis of a stepwise process. At each step of the process, the biosimilar must demonstrate comparability to the reference product (approved biologic) before testing can continue.

As a biosimilar progresses along the development path, the amount of required testing decreases. That is, a biosimilar must have very thorough quality and preclinical testing, but only a small phase III trial in a representative indication is required.

If the biosimilar is approved on the basis of this clinical trial process, it may be granted all indications of the reference product, including those in which it was not tested. This is known as extrapolation. Examples of extrapolation:

- Biosimilar GCSF tested in chemotherapy-induced neutropenia; approved in all indications of the originator, including mobilization of stem cells for transplant.
- Biosimilar infliximab tested in rheumatoid arthritis; approved for all indications of the originator, including Crohn's disease and colitis.

Extrapolation is determined by regulatory bodies on a case-by-case basis and only with strong scientific justification.
Biosimilar monoclonal antibodies differ from other biologics in many ways.

- Size: 30,000 daltons for erythropoietin versus 150,000 daltons for a mAb.
- Complex tertiary structure that includes multiple functional domains.
- Variability: mAbs have greater potential for glycosylation—the addition of sugar residues during manufacture—which impacts their function and increases variability. Because of this, changes to the manufacturing process have even greater impact on mAbs.
- Multiple poorly understood mechanisms of action.

Because of the complexity of mAbs, and because they are often used to treat fatal diseases like cancer, special guidelines are in place for the development of biosimilar mAbs.

According to the guidelines, biosimilar mAbs require the same level of testing as other biosimilars, but with two important distinctions:

- Clinical trial testing must be done in the most sensitive and homogenous patient population. This is the population in which differences between the biosimilar and reference product might be most easily detected. For example, in breast cancer this population would be neoadjuvant, because patients with more advanced breast cancer are not homogenous due to their prior lines of therapy and greater disease burden.
- The most sensitive endpoint should be used in clinical trials. This may not be the endpoint that demonstrates patient benefit. The guidelines suggest overall response rate as a sensitive endpoint.

The first biosimilar mAbs approved in Europe were Remsima™ and Inflectra™, two biosimilars of infliximab (Remicade®). Biosimilars of trastuzumab (Herceptin®) and rituximab (MabThera®), among others, are in development.
Prior to approval, all biosimilars manufacturers must submit a risk management plan for post-approval pharmacovigilance to ensure the long-term safety of their products. These plans are usually identical to the risk management plans for the reference biologics.

As of 2014, all biologics in Europe, including biosimilars, carry a black symbol on their label. This symbol indicates that the product is subject to additional monitoring and reporting requirements.

Currently a biosimilar is given the same international nonproprietary name (INN) as its reference biologic, unless a different name is requested by the manufacturer. The World Health Organization is currently debating this issue. It is recommended that biologics be prescribed by brand name in order to prevent confusion.

Further Information

For more information and complete references, please visit www.prIMEoncology.org/biosimilarslidekit