Demystifying CMC Regulatory Strategy for Biologics

Part 1: Biologics CMC Regulation Is Complex

By John Geigert, PhD, RAC

Note: Demystifying, according to Merriam-Webster’s dictionary, is “to remove the mystery or mystique; to make rationale or comprehensive.” This is the first part of a series on demystifying CMC regulatory strategy for biologics. Part 2 will explain why biologics are not regulated as chemical drugs. Part 3 will discuss the factors needed for an effective corporate CMC regulatory strategy for biologics.

Owing to the Biologics Price Competition and Innovation Act of 2009 that permits the US Food and Drug Administration (FDA) to pursue an abbreviated market approval pathway for biologics, along with industry projections that biologics may represent one in every four newly commercialized drugs in the future, much attention is focused on this class of pharmaceutical products.

But to many, a Chemistry, Manufacturing & Controls (CMC) regulatory strategy for biologics is a mystery, especially since CMC regulation for biologics seems so complex. Different regulations between regulatory authorities, two US laws and two FDA centers, and examples of apparent inconsistent application for biologics reinforce this perception.

What’s in a Name?

Understanding the terminology of any industry is paramount for effectively communicating with those in that field.

According to FDA, “Biological products often represent the cutting edge of medical science and research. Also known as biologics, these products replicate natural substances such as enzymes, antibodies, or hormones in our bodies. Biological products can be composed of sugars, proteins, or nucleic acids, or a combination of these substances. They may also be living entities, such as cells and tissues. Biologics are made from a variety of natural resources—human, animal, and microorganism—and may be produced by biotechnology methods.”

The European Medicines Agency (EMA) has a simpler general definition of a biologic: “A biological medicinal product is a medicinal product whose active substance is made by or derived from a living organism.”

Natural-sourced proteins, biotechnology-derived proteins, monoclonal antibodies, viruses, gene therapy vectors and cell-based medicines easily meet the general regulatory definition of a biologic. But the fact that a product is produced by a living organism is not sufficient to make it a biologic. Antibiotics, many of which are produced by fermentation of living microorganisms, are chemical drugs.

Interestingly, heparin, a sulfated glycosaminoglycan isolated from pig intestines and used to prevent coagulation during renal dialysis, is listed as a chemical drug with FDA, but as a biologic with EMA. Complexity of the manufacturing process and the product, along with derivation from a living source, are all important in the regulatory determination that a product is not a chemical drug, but a biologic.

Navigating the US Biologic Regulatory Maze

Biologics are impacted by two separate pharmaceutical laws and regulated through two main FDA review centers. Needless to say, this is confusing, especially since exceptions occur.

Not One, But Two Pharmaceutical Laws for Biologics

The Food, Drug, and Cosmetic Act (FD&C Act), originally passed by Congress in 1938 with many amendments since, defines “drugs” as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.” The regulatory pathway required under the FD&C Act is the New Drug Application (NDA), and is illustrated in Figure 1a. Although the act regulates all chemical drugs (both natural sourced and chemically synthesized), it also regulates biologic hormones and some biologic enzymes (see Table 1).

The Public Health Service (PHS) Act, originally passed by Congress in 1944 with many amendments since, legally defines “biological product” as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsenphenamine or derivative of arsenphenamine (or any other trivalent organic arsenic
compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.” The regulatory pathway required under the PHS Act is the Biologics License Application (BLA), and is illustrated in Figure 1b. In addition to the vaccines and plasma-derived proteins, the act regulates the following “analogous products:”

- biotechnology-derived proteins (except protein types previously mentioned under the FD&C Act)
- monoclonal antibodies
- gene therapy products (i.e., the administration of nucleic acids, viruses or genetically engineered microorganisms that mediate their effect by transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome)
- cellular products, including products composed of human, bacterial or animal cells

FDA further subdivides the following PHS Act biologic types into “specified biologics:”

- therapeutic DNA plasmid products
- therapeutic synthetic peptide products of 40 or fewer amino acids
- monoclonal antibody products for in vivo use
- therapeutic recombinant DNA-derived products

This subset of PHS Act biologics is an interesting collection. Not all recombinant DNA-derived proteins meet the definition of specified biologics. If the recombinant protein is used to treat a disease, it would be considered specified, but if it is used in a prophylactic manner (i.e., as a vaccine antigen), it would not be specified.

Table 1 displays a CMC regulatory mystery. Natural-sourced and recombinant DNA-derived enzyme proteins have been regulated under both the PHS Act and the FD&C Act. Although hormones are regulated under the FD&C Act, recombinant human erythropoietin hormone protein is regulated under the PHS Act. It is difficult for regulatory affairs to understand the rationale for these differences.

**Significant CMC Regulatory Differences Between the Two Laws**

Whether they are regulated under the PHS Act or the FD&C Act, biologics are treated by FDA in a similar fashion. For example, all biologics are inspected under the same current Good Manufacturing Practice (CGMP) regulations in Title 21 Section 211 of the US Code of Federal Regulations (CFR). All biologics use the same Form FDA 1571 for clinical development regulatory submissions, and all use the same Form FDA 356h for marketed product regulatory submissions.

This similar treatment can lead regulatory professionals to believe that the two laws treat biologics identically. However, that is far from the case as there are significant differences in

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**Table 1. Examples of US Approved Biologics**

<table>
<thead>
<tr>
<th>Enzyme proteins</th>
<th>Regulated Under FD&amp;C Act (NDAs)</th>
<th>Regulated Under PHS Act (BLAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural sourced</td>
<td>Elspar - asparaginase from E. coli</td>
<td>Natural sourced</td>
</tr>
<tr>
<td></td>
<td>Kinlytic - urokinase from human neonatal kidney cells</td>
<td>Xiaflex - collagenases from Clostridium histolyticum</td>
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<td></td>
<td>Hydase - hyaluronidase from bovine testicles</td>
<td>Biotechnology derived</td>
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<tr>
<td></td>
<td>Chymodiactin - chymopapain from papaya</td>
<td>Fabrazyme - human agalsidase beta</td>
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<tr>
<td></td>
<td>Zenpep - porcine-derived pancrelipase</td>
<td>Naglazyme - human galsulfase</td>
</tr>
<tr>
<td>Biotechnology derived</td>
<td>Cerezyme - human imiglucerase</td>
<td>Myozyme/Lumizyme - human aiglucosidase alfa</td>
</tr>
<tr>
<td></td>
<td>Ceredase - human algulceraese</td>
<td>Aldaurzyme - human laronidase</td>
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<tr>
<td></td>
<td>Hylenex - human hyaluronidase</td>
<td>Elaprase - human idursulfase</td>
</tr>
<tr>
<td></td>
<td>VPRIV - human velaglucerase alfa</td>
<td>Krystexxa - human pegloticase</td>
</tr>
<tr>
<td>Hormone proteins and peptides</td>
<td>Natural sourced</td>
<td>Epogen - human erythropoietin</td>
</tr>
<tr>
<td>Natural sourced</td>
<td>bovine- and porcine-derived insulins</td>
<td></td>
</tr>
<tr>
<td>Biotechnology derived</td>
<td>Humalog - human insulin lispero</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nutropin - human growth hormone</td>
<td></td>
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<tr>
<td></td>
<td>Fortical - salmon calcitonin peptide</td>
<td></td>
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<tr>
<td></td>
<td>Natrecor - human B-type natriuretic peptide</td>
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<tr>
<td></td>
<td>Victoza - human glycogen-like peptide-1</td>
<td></td>
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</tbody>
</table>

* Information obtained from CDER website (Drugs@FDA) and CBER website (Licensed Biological Products with Supporting Documents)
the CMC regulatory requirements for biologics under the PHS Act compared to biologics under the FD&C Act as shown in Table 2.

Not One, But Two FDA Centers for Biologics

FDA has two centers responsible for the review and oversight of biologics—the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). CDER is responsible for all of the biologics regulated under the FD&C Act (the NDA pathway). One would intuitively think CBER, because of the word “biologics” in its name, would be the center responsible for all biologics regulated under the PHS Act (the BLA pathway). However, FDA has transferred oversight of the following PHS Act therapeutic biologics from CBER to CDER:

- monoclonal antibodies for in vivo use
- proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics) and other novel proteins, except for those specifically assigned to CBER (e.g., vaccines and blood products), including therapeutic proteins derived from plants, animals or microorganisms, and recombinant versions of these products
- immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response)
- growth factors, cytokines and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo

Although these biologics have been transferred to the responsibility of CDER, it is most important for regulatory professionals to note that they are still regulated under the full requirements of the PHS Act.

A Simpler Biologics Regulation in EU

The EU pharmaceutical regulatory system for biologics is illustrated in Figure 1c. Investigational medicinal products are regulated by the individual national Competent Authorities (CAs) of the 27 Member States. As part of the Clinical Trial Authorization (CTA) that a company must file in order to initiate a clinical study, an Investigational Medicinal Product Dossier (IMPD) is required to be filed with each Member State where the clinical study is to be conducted. To obtain market approval, a
Market Authorization Application (MAA) dossier is required to be filed.

In the EU, the MAA can be approved by either a national authorization procedure or the Centralized Procedure. Some naturally-sourced biologics are approved by the Mutual Recognition Procedure (for example, naturally-sourced clostridium botulinim neurotoxin); but for the majority of biologics, the Centralized Procedure is mandatory.

Compulsory MAA centralized EMA review is required for the following biologics:

- biologics developed by means of one of the following biotechnological processes: (1) recombinant DNA technology, (2) controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or (3) hybridoma and monoclonal antibody methods
- advanced therapy medicinal products such as gene therapy and cellular therapy
- biologics for human use containing a new active substance for which the therapeutic indication is the treatment of any of the following diseases: (1) acquired immune deficiency syndrome, (2) cancer, (3) neurodegenerative disorder, (4) diabetes, (5) auto-immune diseases and other immune dysfunctions or (6) viral diseases
- biologics that are designated as orphan medicinal products

In addition, optional centralized EMA review of the MAA for a biologic can occur if one of the following requirements is met:

- biologic contains a new active substance that has not been previously authorized in the European Community
- applicant shows that the biologic constitutes a significant therapeutic, scientific or technical innovation or that authorization is in the interests of patients’ health at the Community level.

**Embrace the Complexity of Biologics Regulation**

Abandon the urge to simplify everything, and embrace the complexity of biologic regulation. Regulatory professionals play a pivotal role in educating company staff members about the CMC regulatory differences between the various pharmaceutical laws and the regulatory authorities that execute them. Both FDA6 and EMA7 provide additional guidance on their respective websites to better understand the CMC regulatory process for biologics.

In Part 2, why biologics are not regulated as chemical drugs will be explained.
Table 2. Significant CMC Differences in Biologic Regulation Between US Pharmaceutical Laws

<table>
<thead>
<tr>
<th>PHS Act Regulation</th>
<th>CMC Regulatory Difference From FD&amp;C Act</th>
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| 21 CFR 610.12 Sterility | • The PHS Act requires the bulk material, in addition to the final biologic product, to be tested for sterility. The bulk material for a PHS Act biologic is the material immediately after the sterilization process step (typically the 0.2 micron sterile filtration step) and before it enters the filling step. (Note, FDA has recently proposed eliminating the bulk material requirement in the sterility test.)  
• For sterile biologics, the FD&C Act requires only that the final drug product be tested for sterility. |
| 21 CFR 610.11 General Safety | • The PHS Act requires a general safety test involving mice and guinea pigs for the detection of extraneous toxic contaminants for biologics; an automatic waiver from this test has been granted for specified biologics and for cell-based products.  
• The FD&C Act does not require this test for biologics. |
| 21 CFR 610.14 Identity Test | • Both the FD&C Act and the PHS Act require visual inspection after labeling to ensure that the correct label has been applied.  
• However, only the PHS Act requires the contents of a final container of each filling of each lot to be tested for identity after all labeling operations have been completed. |
| 21 CFR 610.2 FDA Batch Pre-Release | • Under the PHS Act, FDA can require a pre-release protocol for any lot of a marketed biologic. This is typically done for plasma-derived proteins and vaccines, where both samples and protocols are required to be submitted to FDA for each batch; the company cannot release the batch into distribution until approval is granted by FDA. This has typically not been required for specified biologics or for cell-based products.  
• The FD&C Act does not require this protocol for biologics. |
| 21 CFR 600.14 Biological Product Deviation | • Under the PHS Act, it is required that quality/safety concerns discovered after a lot has been released into the marketplace must be reported to FDA using Form FDA 3486 within 45 days.  
• Under the FD&C Act, it is required to report these issues to FDA using Form FDA 3331 within three days. |
| 21 CFR 601.2 License Suspension | • The PHS Act provides authority to FDA to immediately suspend licenses in situations where a danger to public health exists.  
• No such provision is provided for biologics under the FD&C Act; FDA must seek the support of the Department of Justice to issue an injunction or seek product. |
| Abbreviated Regulatory Approval Pathway | • Biologics Price Competition and Innovation Act of 2009 amended the PHS Act to permit ‘biosimilars’ to be approved by an abbreviated pathway (but FDA is still deciding how to implement it).  
• FD&C Act permits ‘follow-on biologics’ to be approved by the 505(b)(2) NDA pathway.  
Note, to date, these biologics have not been approved by the generic ANDA pathway. |

References