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Orphan Drug Sameness for Monoclonal Antibodies

An approved Orphan Drug[1] product benefits from seven years of market exclusivity which prevents the Food and Drug Administration (FDA) from approving another product that is considered the same drug for the same indication, unless the subsequent product is shown by the sponsor to be clinically superior. Determining whether a new product is the "same drug" has been relatively straightforward for small molecule drugs. However, this determination has been a challenge for macromolecules, such as proteins, nucleic acids, carbohydrates and closely related, complex, partly definable drugs, including vaccines and surfactants. Moreover, the determination of "sameness" for Orphan Drug exclusivity requires an even more specialized approach to address the unique characteristics of antibodies and related products.

FDA's Draft Guidance: FDA's current thinking on the determination of Orphan Drug sameness for monoclonal antibody products was issued in a draft Guidance for Industry in 1999.[2] According to the draft guidance, only the principal molecular structure of the antibody -- namely, the complementarity determining regions (CDRs) of the heavy and light chains which form the antigen binding site of the molecule -- will be considered in determining sameness for Orphan Drug purposes. For example, as descried by the draft guidance, two monoclonal antibody drugs would be considered the same if the amino acid sequences of the CDRs were the same or if there were only minor amino acid differences between them. FDA would make the determination of what amino acid differences would be considered "minor" on a case-by-case basis. According to the draft guidance, other potentially important amino acid differences, glycosylation patterns, and post translational modifications in the framework regions and the constant region would not cause the products to be considered different, unless the subsequent product was shown to be clinically superior.

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[1] A drug for a rare disease or condition may be designated as an Orphan drug: (1) if the product is intended to treat a disease or condition that has a prevalence in the United States of less than 200,000 persons; or (2) if the sponsor can show that there is no reasonable expectation that the costs of developing and marketing the drug will be recovered from sales in the United States.

[2] Guidance for Industry, Interpreting Sameness for Monoclonal Antibody Products under the Orphan Drug Regulations (Draft Guidance), July 1999, http://www.fda.gov/cber/gdlns/orphan.pdf. Although this document has not been issued as final guidance, it continues to represent FDA's current thinking on the interpretation of sameness for monoclonal antibody products (as confirmed in a communication with FDA in December 2008).

The draft guidance applies to whole antibodies, fragments, conjugates, fusion proteins, bispecific antibodies, and soluble T cell receptor products. According to the draft guidance, the determination of sameness for monoclonal antibodies which have had relevant functional elements added will be based on a determination of sameness for the monoclonal antibody element and a determination of sameness for the added functional element. Similarly, the draft guidance provides that two bispecific antibodies will be considered the same if both sets of CDRs are the same.

Implications of FDA's Interpretation: As a result of this interpretation, monoclonal antibody products which might have been altered structurally to have different safety and efficacy characteristics will be assumed to be the same, unless the subsequent sponsor can demonstrate clinical superiority. For example, monoclonal antibodies and related products with substantial structural differences -- such as framework and constant region changes that humanize a non-human derived monoclonal antibody, modify antigen contact, stabilize the binding site, alter receptor binding, or change the species from which certain structural elements are derived – could have the same antigenic specificity and, accordingly, would be considered the same for Orphan Drug purposes. As a consequence, a single product could preclude market competition from a wide range of products which have significantly different characteristics unless and until subsequent sponsors could show clinical superiority. The cost and time associated with demonstrating clinical superiority to overcome a presumption of sameness might preclude structurally different and potentially superior products from being marketed during the original product's seven-year Orphan Drug exclusivity.

Summary: Understanding FDA's approach for determining sameness for monoclonal antibody products will permit sponsors to take advantage of strategic opportunities and avoid pitfalls associated with Orphan Drug exclusivity for these products. For assistance in evaluating and addressing the strategic implications of sameness for monoclonal antibody products, please contact Gregory J. Glover, MD, JD, Gregory.Glover@PharmaLawGrp.com, 202 589 1781.

For more information on regulatory market exclusivity issues for pharmaceutical and biotechnology products in the United States, please visit www.pharmalawgrp.com.