

Guidance for Industry

Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY¹

Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations

I. INTRODUCTION

The regulations implementing the Orphan Drug Act are codified in 21 CFR Part 316. FDA published the Proposed Rule for these regulations on January 29, 1991 (56 FR 3338) (Ref. 1) and the Final Rule on December 29, 1992 (57 FR 62076) (Ref. 2). One of the incentives for orphan drug development is the exclusive approval of a product for a period of seven years. During this seven year period, no approval will be given to a subsequent sponsor's marketing application for the same drug product for the same indication unless the subsequent product is shown by the sponsor to be clinically superior, as defined in 21 CFR 316.3 (b)(3). In determining whether or not two products would be considered the same, FDA recognized that different criteria were necessary for macromolecules versus small molecules [21 CFR 316.3(b)(13)]. Macromolecules include a variety of structures including proteins, nucleic acids, carbohydrates and closely related, complex, partly definable drugs such as vaccines or surfactants. The current definition of sameness for protein drugs [21 CFR 316.3(b)(13)(ii)(A)] however, does not adequately consider the unique nature of antibodies. The purpose of the present document is to describe FDA's current thinking on the criteria by which two monoclonal antibody products would be considered the same under the Orphan Drug Act and its implementing regulations.

II. BACKGROUND

21 CFR Part 316.3(b)(13)(ii) defines sameness for a macromolecule as "...a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug..." Two protein drugs would be considered the same "...if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence ..." [21 CFR Part 316.3(b)(13)(ii)(A)]. For monoclonal antibody products, these definitions lay the groundwork for the determination of sameness but, because of the unique series of processes involved in creating an antibody molecule, additional guidance as to what would be considered the same under the Orphan Drug regulations is needed.

¹This guidance document represents the Agency's current thinking on the interpretation of the Orphan Drug regulations as they pertain to monoclonal antibodies. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of applicable statutes, regulations, or both.

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An antibody molecule is composed of four polypeptide chains, two identical heavy (H) chains and two identical light (L) chains. Both heavy and light chains are divided into variable (V) and constant (C) regions. The V_H - V_L pairs confer specificity for antigen while the constant region of the heavy chain is responsible for effector functions such as, but not limited to, complement fixation and antibody dependent cellular cytotoxicity. The variable and constant regions were so named because amino acid sequence data showed that the amino terminal regions of heavy and light chains from different antibodies had different sequences while the carboxy terminal region amino acid sequences were the same within a given isotype (class or subclass). Subsequent analysis of variable region amino acid sequences defined three hypervariable regions (also known as complementarity determining regions or CDRs) each in the V_H and V_L regions which form the antigen binding site of the molecule (Ref. 3).

Antibody diversity is created by the use of multiple germline genes encoding variable regions and a variety of somatic events. The somatic events include recombination of variable gene segments with diversity (D) and joining (J) gene segments to make a complete V_H region and the recombination of variable and joining gene segments to make a complete V_L region. The recombination process itself is imprecise, resulting in the loss or addition of amino acids at the V(D)J junctions. These mechanisms of diversity occur in the developing B cell prior to antigen exposure. After antigenic stimulation, the expressed antibody genes in B cells undergo somatic mutation. Based on the estimated number of germline gene segments, the random recombination of these segments, and random V_H - V_L pairing, up to 1.6×10^7 different antibodies could be produced (Ref. 4). When other processes which contribute to antibody diversity (such as somatic mutation) are taken into account, it is thought that upwards of 1×10^{10} different antibodies could be generated (Ref. 5). Because of the many processes involved in generating antibody diversity, it is unlikely that independently derived monoclonal antibodies with the same antigen specificity will have identical amino acid sequences.

III. SCOPE

For the purpose of this document, a monoclonal antibody is a clonal product defined as any intact antibody, antibody fragment, conjugate, fusion protein, or bispecific antibody that contains a V_H - V_L pair where the CDRs form the antigen binding site. Antibody fragments or fusion proteins containing only constant region domains are not within the purview of this document.

The mechanisms generating antibody diversity are the same for all antibodies whether they are immortalized as monoclonal antibodies or purified from serum as polyclonal antibodies. The policy described in this document, however, will apply only to monoclonal antibody products.

Diversity of the T cell receptor is also generated by multiple T cell receptor specific germline genes and somatic events similar to those described for antibodies. The T cell receptor is membrane bound in its native functional form. The FDA anticipates the development of soluble T cell receptor products for therapeutic use. The interpretation of sameness for monoclonal antibody products in the present document will apply to soluble T cell receptor products.

IV. INTERPRETATION OF SAMENESS FOR MONOCLONAL ANTIBODY PRODUCTS

A. Structural Features of Antibodies

As described in section II above, antibodies have two functional regions, the variable region, which is responsible for antigen-specific binding, and the constant region which carries out effector functions. The variable region is divided into complementarity determining regions (CDR1, CDR2 and CDR3) and framework regions (FR1, FR2, and FR3). CDRs 1, 2, and 3 are delineated by amino acid positions 31-35, 50-65, and 95-102 for heavy chains and amino acid positions 24-34, 50-56, and 89-97 for light chains. While these amino acid positions define the boundaries of each CDR, the lengths of the CDRs can vary (Ref. 6). The CDRs create the antigen binding pocket of the molecule through the interaction between heavy and light chain variable regions while the framework regions provide the scaffolding on which the antigen binding pocket sits. The constant region is responsible for antibody effector functions but, has little influence on antibody specificity or affinity.

B. Sameness for Naked Monoclonal Antibody Products

The definition of sameness for a macromolecule is based on its principal molecular structure. For the purpose of determining sameness of naked monoclonal antibodies under the Orphan Drug Act and its implementing regulations, the complementarity determining regions of the heavy and light chain variable regions will be viewed by the FDA as the principal molecular structural feature of a monoclonal antibody product. The residues comprising the CDRs will be those stated in Section A. above as defined by Kabat et al. (Ref. 6).

The proposed interpretation of sameness for two monoclonal antibodies is that two monoclonal antibody drugs would be considered the same if the amino acid sequences of the complementarity determining regions were the same or if there were only minor amino acid differences between them. Other potentially important amino acid differences outside the complementarity determining regions, or differences due to glycosylation patterns or post translational modifications would not per se cause the products to be considered different unless the subsequent drug was shown to be clinically superior.

In the Orphan Drug Regulations Final Rule (57 FR 62076), Section II.B. (Summary of and Response to Comments; Sameness Versus Difference), comment 31 refers to a suggestion that a guidance document be developed to describe the differences in amino acid sequence of a protein which would be considered “minor”. Now, as then, the FDA declines to provide examples for hypothetical situations. This determination would be made on a case-by-case basis. The types of information that would be useful in making such a determination include (but are not limited to) the sequence of the heavy and light chain variable regions of the product, any modifications made during the development process, and whether any particular residues have been established to be important for antigen binding.

C. Sameness for Antibody Conjugates, Fusion Proteins, and Bispecific Antibodies

Monoclonal antibody products can be conjugated by chemical methods with radionuclides, drugs, macromolecules, or other agents or can be made as fusion proteins. A monoclonal antibody fusion protein contains a V_H - V_L pair where one of these chains (usually V_H) and another protein are synthesized as a single polypeptide chain. These types of products differ from naked monoclonal antibodies in that they generally have an important additional functional element; the active moiety of a small molecule or the principal molecular structural feature of the conjugated or fused macromolecule.

The determination of sameness of monoclonal antibodies which have had relevant functional elements added will be based on a determination of sameness for the monoclonal antibody element and on a determination of sameness for the added relevant functional element (see, for example, 21 CFR 316.3(b)(13)(i) regarding small molecules and 21 CFR 316.3(b)(13)(ii) regarding macromolecules. A difference in any one of these elements may result in a determination that the molecules are different. Conversely, two monoclonal antibody conjugates or fusion proteins would be determined to be the same if both the CDR sequences of the antibody and the functional element of the conjugated molecule were the same.

Bispecific antibodies are generated by combining a heavy-light chain pair from a monoclonal antibody of one specificity with a heavy-light chain pair from a monoclonal antibody of a different specificity and therefore, have two different sets of CDRs. Two bispecific antibodies will be considered the same if both sets of CDRs are the same.

V. CHANGES IN ANTIBODY STRUCTURE THAT DO NOT CONSTITUTE DIFFERENCES BETWEEN TWO MONOCLONAL ANTIBODY PRODUCTS WITH THE SAME COMPLEMENTARITY DETERMINING REGIONS

Listed below are potential changes in areas outside the CDRs in monoclonal antibody products. For the purpose determining sameness of monoclonal antibodies under the Orphan Drug Act and its implementing regulations, such changes do not constitute differences between two monoclonal antibody products with the same CDRs unless the subsequent product is shown to be clinically superior.

A. Framework Regions

Framework region changes include, but are not limited to, humanizing a non-human derived monoclonal antibody or engineering certain framework residues that are important for antigen contact or for stabilizing the binding site.

B. Constant Region

Constant region differences include, but are not limited to, changing the class or subclass of the constant region, changing specific amino acid residues which might alter an effector function such as Fc receptor binding, or changing the species from which the constant region is derived.

C. Antibody Fragments

Intact monoclonal antibodies and antibody fragments with the same CDR sequences will not be considered different. This is consistent with FDA's policy regarding peptides and whole proteins as explained in Orphan Drug Regulations Final Rule (57 FR 62076), Section II. Summary of and Response to Comments, B. Sameness Versus Difference, comment 21 where it is stated that "...in order for a peptide that resembles a portion of a protein product to be considered a different drug, FDA will require a clear demonstration that the peptide is clinically superior to the entire protein."

VI. REFERENCES

1. Federal Register, 56 FR 3338 1/29/91, Orphan Drug Act: Proposed Rule, [Docket No. 85N-0483].
2. Federal Register, 57 FR 62076 12/29/92, Orphan Drug Act: Final Rule.
3. Kabat, E. A., "The Structural Basis of Antibody Complementarity". *Advances in Protein Chemistry*. Vol.32; pp. 1-75. 1978.
4. Max, E. E. *Immunoglobulins: Molecular Genetics*. In *Fundamental Immunology*. Third Edition (Ed. W. E. Paul) pp. 315-382, Raven Press, New York, New York, USA. 1993.
5. Burrows, P.D., Schroeder, H.W., and M. D. Cooper. *B-Cell Differentiation in Humans*. In *Immunoglobulin Genes*. Second Edition. (Ed. Honjo, T. and F. W. Alt) pp. 3-32, Academic Press, San Diego, California, USA. 1995.
6. *Sequences of Proteins of Immunological Interest*. Kabat, E. A., T. T. Wu, H. M. Perry, K. S. Gottesman and C. Foeller (Eds.) U. S. Department of Health and Human Services, National Institute of Health, Bethesda, MD. 1991.