
Guidance for Industry

Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Orphan Products Development (OOPD)**

**April 2014
CMC**

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*Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov*

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*orphan@fda.hhs.gov
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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to describe the Agency'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.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The regulations implementing the Orphan Drug Act are codified in 21 CFR Part 316. The Agency published the Proposed Rule for these regulations on January 29, 1991,² and the Final Rule on December 29, 1992.³ More recently, the Agency finalized certain amendments to Part 316 in order to clarify regulatory provisions and make minor improvements to address issues that have arisen since 1992.⁴

One of the incentives for orphan drug development is the exclusive approval of a product for a period of 7 years. During this 7-year period, no approval will be given to a subsequent sponsor's marketing application for the same drug for the same indication unless the sponsor demonstrates that the subsequent product is clinically superior and therefore does not contain the same drug.⁵

¹ This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) and FDA's Office of Orphan Product Development (OOPD).

² FDA, Orphan Drug Regulations Proposed Rule, 56 FR 3338 (Jan. 29, 1991).

³ FDA, Orphan Drug Regulations Final Rule, 57 FR 62076 (Dec. 12, 1992).

⁴ FDA, Orphan Drug Regulations Final Rule, 78 FR 35117 (June 12, 2013).

⁵ See 21 CFR 316.3 (b)(3) & (b)(12).

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In determining whether or not two drugs would be considered to be the same under the orphan drug regulations, we recognized that different criteria were necessary for macromolecules versus small molecules.⁶ Macromolecules include a variety of molecules, such as proteins, nucleic acids, carbohydrates, as well as closely related, complex, partly definable drugs such as live viral vaccines.

A drug containing macromolecules is the same as another, previously approved drug if it “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”⁷ Two protein drugs would be considered the same “if the only differences in structure between them were due to posttranslational events or infidelity of translation or transcription or were minor differences in amino acid sequence”⁸ For monoclonal antibody drugs, these definitions lay the groundwork for the determination of sameness, but, because of the unique considerations applicable to antibody molecules, additional guidance as to how two monoclonal antibody drugs would be considered to be the same drug under the Orphan Drug regulations is needed.

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 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 (the variable region), while the carboxy terminal region amino acid sequences were the same within a given isotype (class or subclass) (the constant region). Subsequent analysis of variable region amino acid sequences defined three hypervariable regions (also known as complementarity determining regions (CDRs)) each in the V_H and V_L regions, which form the antigen binding site of the molecule.⁹

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.¹⁰ When other processes that contribute to antibody diversity (such as somatic mutation) are taken into account, it is thought that upwards of 1×10^{10} different antibodies could

⁶ See 21 CFR 316.3(b)(14).

⁷ 21 CFR Part 316.3(b)(14)(ii).

⁸ 21 CFR Part 316.3(b)(14)(ii)(A).

⁹ Kabat, E.A., 1978, “The Structural Basis of Antibody Complementarity,” *Advances in Protein Chemistry*, 3, pp. 1-75.

¹⁰ Max, E.E., 1993, “Immunoglobulins: Molecular Genetics,” In *Fundamental Immunology*, Third Edition (Ed. W.E. Paul), pp. 315-382.

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be generated.¹¹ 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 guidance, a monoclonal antibody is a clonal product defined as any intact antibody, antibody fragment, conjugate, fusion protein, bispecific, or multi-specific antibody that contains a V_H-V_L pair, single V domain, or combinations of single V domains 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 guidance.

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 recommendations described in this guidance, however, apply only to monoclonal antibody products.

Diversity of the T-cell receptor also is 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. We anticipate the development of soluble T-cell-receptor-products for therapeutic use. The considerations underlying the interpretation of sameness of monoclonal antibody products in this guidance should apply to soluble T-cell-receptor-products.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amended the Public Health Service (PHS) Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product.¹² The interpretation of sameness of monoclonal antibody products in this guidance is intended only for the purposes of determining sameness under the Orphan Drug Act, and the Agency does not intend to apply the considerations discussed in this guidance to determinations under the BPCI Act.

IV. INTERPRETING SAMENESS OF MONOCLONAL ANTIBODY PRODUCTS

A. Structural Features of Antibodies

As described in Section II, 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, FR3, and FR4). Using the Kabat system, CDRs 1, 2, and 3 are delineated by amino acid positions 31-35, 50-65, and 95-102, respectively, for heavy chains and amino acid positions 24-34, 50-56, and 89-97, respectively, for light

¹¹ Burrows, P.D., Schroeder, H.W., and Cooper, M.D., 1995, "B-Cell Differentiation in Humans," *Immunoglobulin Genes*, Second Edition (Ed. T. Honjo and F.W. Alt), pp. 3-32.

¹² See sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Public Law 111-148).

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chains.¹³ Alternatively, the International Immunogenetics (IMGT) information system defines the positions of both heavy and light chain CDRs 1, 2, and 3 as amino acid positions 27 – 38, 56 – 65, and 105 – 117, respectively.¹⁴ While these amino acid positions define each CDR's boundaries, the CDR lengths can vary.¹⁵ 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 of Unmodified Monoclonal Antibody Products

The sameness of a macromolecule for purposes of the Orphan Drug Act and its implementing regulations is based on its principal molecular structures.¹⁶ For the purpose of determining sameness of unmodified monoclonal antibodies under the Orphan Drug Act and its implementing regulations, the Agency will consider the CDRs of the heavy and light chain variable regions to be the principal molecular structural features of a monoclonal antibody product. The residues comprising the CDRs will be those defined by either the Kabat or IMGT systems as stated in Section IV.A. above.¹⁷

FDA intends to interpret the applicable regulatory provisions such that two monoclonal antibody drugs would be considered to be the same drug if the CDRs' amino acid sequences were the same or if there were only minor amino acid differences between them. Other potentially important amino acid differences outside the CDRs, or differences due to glycosylation patterns or posttranslational modifications, would not necessarily cause the products to be considered to be different.

FDA intends to make determinations of this nature on a case-by-case basis. The types of information that would be useful in making such a determination include the sequence of the heavy and light chain variable regions of the product, any modifications in antibody sequence, and whether any particular residues have been established to be important for antigen binding.

C. Sameness of Antibody Conjugates, Fusion Proteins, and Bispecific and Multispecific 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 or C_H) and another protein are synthesized as a single amino-acid chain. These types of products differ from unmodified monoclonal antibodies in that they generally have an important additional functional

¹³ National Institutes of Health, U.S. Department of Health and Human Services, 1991, "Sequences of Proteins of Immunological Interest," Kabat, E.A., Wu, T.T., Perry, H.M., Gottesman, K.S., and Foeller, C. (Eds.).

¹⁴ Lefranc, M.P., Pommie, C., Ruiz, M., Giudicelli, V., Foulquier, E., Truong, L., Thouvenin-Cntet, V., and Lefranc, G. 2003. IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains. *Developmental and Comparative Immunology*, 27, pp 55-77.

¹⁵ See footnotes 13 and 14.¹⁶ 21 CFR 316.3(b)(14).

¹⁶ 21 CFR 316.3(b)(14).

¹⁷ See footnotes 13 and 14.

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element: the active moiety of a small molecule or the principal molecular structural feature(s) of the conjugated or fused macromolecule.

FDA intends to interpret the applicable regulatory provisions such that the determination of sameness of such monoclonal antibodies will be based on a determination of sameness of the monoclonal antibody element and sameness of the functional element of the conjugated molecule.¹⁸ A difference in any one of these elements can result in a determination that the molecules are different. Conversely, two monoclonal antibody conjugates or fusion proteins would be determined to be the same drug if both the CDR sequences of the antibody and the functional element of the conjugated molecule were the same.

Many different platforms produce bispecific antibodies. In general, 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. In some cases, a bispecific antibody can be composed of two single V domain antibodies with different specificities. A multispecific antibody generally contains multiple single V domain antibodies or V_H-V_L pairs, each with unique specificities. Two bispecific or multispecific antibodies will be considered to be the same drug if all sets of CDRs are the same or had only minor amino acid differences between them.

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

Listed below are certain potential changes that sponsors may make in areas outside the CDRs in monoclonal antibody products. FDA intends to consider such changes as not necessarily causing two monoclonal antibody products with the same CDRs to be different drugs for the purpose of determining sameness of monoclonal antibodies under the Orphan Drug Act and its implementing regulations.

A. Framework Region

Framework region changes include, humanizing a nonhuman-derived monoclonal antibody or engineering certain framework residues that are important for antigen contact or stabilizing the binding site.

B. Constant Region

Constant region differences include changing the class or subclass of the constant region, changing specific amino acid residues that might alter an effector function such as Fc receptor binding, or changing the species from which the constant region is derived.

¹⁸ See 21 CFR 316.3(b)(13)(i) regarding small molecules and 21 CFR 316.3(b)(13)(ii) regarding macromolecules.

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C. Antibody Fragments

Intact monoclonal antibodies and antibody fragments with the same CDR sequences or with only minor amino acid differences between them, will not be considered to be different drugs. This is consistent with the Agency's policy regarding peptides and whole proteins as explained in the Orphan Drug Regulations Final Rule, which states 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."¹⁹

¹⁹ Final Rule, *supra* note 3, at 62078.