Bispecific Antibody Development Programs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2019
Pharmaceutical Quality/CMC

Bispecific Antibody Development Programs

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2019
Pharmaceutical Quality/CMC

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

A. Monoclonal and Bispecific Antibody Development 2

B. General Considerations 2

C. Regulatory Considerations 3

III. SCIENTIFIC CONSIDERATIONS 3

A. CMC Quality Considerations 4

B. Nonclinical Considerations 4

C. Clinical Considerations 5

1. Clinical Pharmacology Studies 5

2. Clinical Studies 6

REFERENCES 7

Bispecific Antibody Development Programs Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to assist industry and other parties involved in the development of bispecific antibodies. Discussion includes general considerations and recommendations for bispecific antibody development programs, as well as regulatory, quality, nonclinical, and clinical considerations in the context of bispecific antibody development programs. This guidance does not discuss development considerations for other multitarget therapies that are combinations of monoclonal antibodies or are antibody cocktails or polyclonal antibodies.[2] Although this guidance is specific to bispecific antibodies, the principles discussed in this guidance may also be applicable to the development of other types of bispecific protein products.

This guidance focuses on general regulatory and scientific considerations for bispecific antibodies, not on development of a particular bispecific antibody. Industry and other stakeholders are encouraged to engage FDA to discuss their individual bispecific antibody development program.

In general, FDA's guidance documents 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.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] In a polyclonal antibody, a mixture of antibodies recognizing either specific or diverse targets is obtained by purification of pooled plasma or serum. In an antibody cocktail, different antibodies are mixed together during manufacturing. In a combination of monoclonal antibodies, separate antibodies are used together. Each of the products can follow its own dosing regimen or can be combined at the time of administration.

II. BACKGROUND

A. Monoclonal and Bispecific Antibody Development

Since the first therapeutic monoclonal antibody was commercialized in 1986, monoclonal antibodies have become a vital component of therapy for various diseases and conditions including, but not limited to, cancer, autoimmune and infectious diseases, and inflammatory conditions (Ecker et al. 2015). The regulatory pathway for evaluation of monoclonal antibodies is well established, but additional guidance is needed regarding antibody-based products that target more than one antigen. Advances in technology and an interest in novel therapies that combine targets have led to the development of bispecific antibodies, which are genetically-engineered, recombinant antibodies that consist of two distinct binding domains capable of binding two different antigens or two different epitopes of the same antigen (Brinkmann and Kontermann 2017; Kontermann 2012).[3]

There is often a strong scientific rationale for engaging two targets in the therapeutic strategy for a specific disease. Bispecific antibodies can target multiple disease-modifying molecules with one drug, with possible advantages over combination therapy or the use of antibody mixtures. The possibility of immune cell retargeting through the delivery of an effector or effector cell to a specific target or the possibility of synergistic efficacy through engagement of multiple targets gives bispecific antibodies the potential to advance the development of antibody-based therapies (Suresh et al. 2014; Kontermann 2012). There are a number of challenges in developing bispecific antibodies, one of which may be significant immunogenicity caused by novel epitopes. This guidance addresses these considerations and provides recommendations regarding the type of data necessary to support the approval of bispecific antibodies.

B. General Considerations

FDA anticipates there will be a spectrum of bispecific antibodies developed for the prevention, treatment, or diagnosis of diseases, each with unique considerations for the specific product and targeted indication. Within this spectrum there are two broad categories of bispecific antibodies:

(1) Bispecific antibodies that function to bridge two target cells (e.g., a bispecific antibody that is designed to bring immune effector cells into close contact with particular tumor-associated antigens to facilitate cell killing).

(2) Bispecific antibodies that do not bridge two target cells (e.g., a bispecific antibody that targets two soluble cytokines or binds different epitopes of the same tumor or viral antigen). In this category, the bispecific antibody may not be required to bind both targets at the same time for efficacy.

[3] Although this guidance focuses on bispecific antibodies, it may also apply to other novel constructs that may have three or more antigen-binding domains.

Within each category there are particular considerations for the bispecific antibody development program, including determining whether both targets need to be engaged simultaneously, determining the affinity and on- and off-rates of each arm for its target, and determining potential synergy when binding both targets.

FDA anticipates there will be a scientific rationale (e.g., target(s), mechanism(s) of action, decreased dose, or increased safety and/or efficacy as compared to similar monospecific products and available therapies) to support development of a particular bispecific antibody. The data supplied to support the scientific rationale will depend on the particular situation[4] and could potentially be derived from clinical or animal studies[5] or in vitro assays.

C. Regulatory Considerations

FDA's regulation on fixed-combination prescription drugs for humans (21 CFR 300.50) does not apply to the development of bispecific antibodies, which are single molecules. It is not generally expected, but in some cases, FDA may request a comparison of the bispecific antibody to an approved monospecific product(s) directed against the same antigenic target(s) to inform the risk-benefit assessment of the bispecific antibody (see section III.C.2 of this guidance for clinical study considerations).

Bispecific antibodies are subject to all other pertinent laws and regulations for biological products, including those governing product development, testing, and approval. Questions about regulatory requirements for a particular bispecific antibody should be addressed to the appropriate FDA clinical review division.

III. SCIENTIFIC CONSIDERATIONS

Many aspects of a bispecific antibody development program will be similar to monoclonal antibody development programs. This section discusses unique aspects for chemistry, manufacturing, and controls (CMC); nonclinical and clinical pharmacology; and clinical development programs for bispecific antibodies.

[4] See the International Conference on Harmonisation (ICH) guidance for industry *M4E(R2): The CTD — Efficacy* (July 2017) for more information on product development rationale. Also see the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013) for more information on rationale for biological product development. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] FDA encourages sponsors to consult with FDA if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. FDA will consider if such an alternative method could be assessed for equivalency to an animal test method. FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible.

A. CMC Quality Considerations

Bispecific antibodies can exist in many different formats, from tandem monovalent binding fragments to immunoglobulin G (IgG)-based antibodies onto which multiple additional antigen-binding domains are attached. These diverse formats allow bispecific antibodies to be designed to match the proposed mechanism(s) of action and the intended clinical application (Spiess et al. 2015).

There may be unique development considerations for each of these formats, such as stability and production yields, but in general the products should be characterized and the manufacturing processes should be developed in accordance with standard monoclonal antibody development practices.[6] Quality attributes such as antigen specificity; affinity and on- and off-rates; avidity (for bispecific antibodies that target two molecules on the same cell); potency; process-related impurities such as aggregates; fragments/homodimers; stability; and half-life may affect pharmacology and should be studied. For example, in vitro and in vivo pharmacology studies may provide information on the relative binding activity and on- and off-rates for each target. Early in vitro studies may inform selection of an expression construct with optimal affinity and stability properties. The relative amounts of homodimers should be assessed. This is particularly important for effector cell engaging constructs where homodimers of the anti-CD3 or anti-Fc engaging arm may lead to cytokine release. Also, the molecular structure, such as novel epitopes or intact antibody structures with additional domains, could potentially lead to increased immunogenicity.

B. Nonclinical Considerations

Nonclinical studies are generally needed to characterize the pharmacology and toxicology of bispecific antibodies. The scope of the nonclinical program, including pharmacology studies, species selection for toxicology studies, general toxicology, and reproductive toxicology, is expected to be similar to that for monoclonal antibodies directed against a single target.[7,8] Consideration should be given to the expression profile and specificity for each target in nonclinical models in order to design an appropriate toxicological assessment for the bispecific product. Potential safety concerns related to the particular components of the bispecific antibody, if any, may need to be addressed; however, a comparative safety assessment between the bispecific antibody and monospecific product(s) is not typically expected.

---

[6] See *Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use* for more information on product manufacturing and testing (available at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/default.htm).

[7] See the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* for more information (June 2011) (available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm304390.htm).

[8] See the ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010) for more information.

In vitro and in vivo pharmacology studies may also offer the opportunity to generate nonclinical data supporting the scientific rationale of the bispecific antibody (e.g., showing that blocking two targets yields additive or synergistic efficacy compared to a monospecific comparator; showing that simultaneous cross-linking of two receptors offers efficacy that cannot be achieved with a monospecific product; for agonistic products, showing expected activation of the immune system). These studies could also be used to select the first-in-human (FIH) dose.[9]

In general, the standard nonclinical approaches to support the safety of the starting dose in the clinical trial will be appropriate.[10] For bispecific antibodies with agonistic properties, selection of the initial dose using a minimally anticipated biologic effect level (MABEL) should be considered.[11] We recommend discussing dose selection with the appropriate FDA clinical review division.

C. Clinical Considerations

1. Clinical Pharmacology Studies

The clinical pharmacology studies needed for a bispecific antibody development program would be similar to those for monoclonal antibodies and other therapeutic protein products. Pharmacodynamic (PD) assessments may need to take into consideration the binding to each target.

As bispecific antibodies may present as a mixture of biologically active and inactive forms, it is important to identify the bispecific antibody form(s) that is most pharmacologically relevant to pharmacokinetic (PK)/PD assessment and to develop validated assays that measure the appropriate form(s) accordingly. Sometimes more than one assay may be needed to quantify the levels of total, bound, and unbound bispecific antibody (Trivedi et al. 2017).

Bispecific antibodies possess multiple domains that function in different ways to mediate clinical efficacy. An immune response to one domain may inhibit a specific function while leaving others intact. Examination of immune responses to bispecific antibodies may require development of multiple assays to measure immune responses to different domains of bispecific

[9] See *Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use* for more information on product safety data.

[10] See the guidance for industry *Estimating Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005) for more information on product dosing. Healthy volunteers may not be appropriate candidates for initial clinical trials of a particular bispecific antibody because of the potential immunogenicity and toxicity of the bispecific antibody.

[11] See *Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use* for more information on product safety data.

antibodies.[12,13] Sponsors are encouraged to discuss with FDA specific clinical pharmacology development plans for their individual products.

2. Clinical Studies

In many situations, the clinical studies for bispecific antibodies will compare the bispecific antibody to standard of care or placebo. Where there are approved therapies that target the same antigens as those targeted by the bispecific antibody, it may be possible to perform a clinical study comparing the bispecific antibody to the monospecific product(s).

A clinical trial comparing a bispecific antibody to an approved monospecific product(s) directed against the same antigenic target(s) may inform the risk-benefit assessment of the bispecific antibody. FDA may request such studies if the studies could provide valuable information regarding the bispecific antibody's efficacy or safety.[14,15] For example, if both targets are anticipated to be immunosuppressive based on the animal/early human trials suggesting unique or greater safety concerns, a trial comparing the bispecific antibody to the approved monospecific product(s) may be appropriate. Also, if there is a concern that only one of the bispecific antibody's targets was driving the efficacy results, it may be useful to conduct a comparison trial with the relevant monospecific product(s). The studies conducted to support approval will depend on the particular targets and other clinical considerations. Sponsors are encouraged to discuss development plans for their individual products with the appropriate clinical review division within FDA.

[12] See the guidance for industry *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019), where assay development is covered in detail.

[13] See the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) for more information on immunogenicity assessment.

[14] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) for more information on quantity of evidence to support effectiveness.

[15] See *Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use* for more information on product safety testing.

REFERENCES

Brinkmann, U and RE Kontermann, 2017, The Making of Bispecific Antibodies, MAbs; Feb/Mar; 9(2):182–212, doi: 10.1080/19420862.2016.1268307.

Ecker, DM, SD Jones, and HL Levine, 2015, The Therapeutic Monoclonal Antibody Market, MAbs, 7(1):9–14, doi: 10.4161/19420862.2015.989042.

Kontermann R, 2012, Dual Targeting Strategies With Bispecific Antibodies, MAbs, Mar-Apr; 4(2):182–197, doi: 10.4161/mabs.4.2.19000.

Spiess, C, Q Zhai, and PJ Carter, 2015, Alternative Molecular Formats and Therapeutic Applications for Bispecific Antibodies, Mol Immunol, Oct; 67(2 Pt A):95–106, doi: 10.1016/j.molimm.2015.01.003.

Suresh, T, LX Lee, J Joshi, and SK Barta, 2014, New Antibody Approaches to Lymphoma Therapy, J Hematol Oncol, Sep 9; 7:58, doi: 10.1186/s13045-014-0058-4.

Trivedi, A, S Stienen, M Zhu, H Li, T Yraszeck, J Gibbs, T Heath, R Loberg, and S Kasichayanula, 2017, Clinical Pharmacology and Translational Aspects of Bispecific Antibodies, Clin Transl Sci, May; 10(3):147–162, doi: 10.1111/cts.12459.