# Bispecific Antibody Development Programs

## Guidance for Industry

**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)**

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**Pharmaceutical Quality/CMC**

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# TABLE OF CONTENTS

*Contains Nonbinding Recommendations*

# Bispecific Antibody Development Programs Guidance for Industry[1]

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## I. INTRODUCTION

This guidance provides recommendations to assist industry and other stakeholders involved in the development of bispecific antibodies. In addition to general considerations, the guidance provides recommendations for specific regulatory, quality, nonclinical, and clinical considerations for bispecific antibody development programs. Although this guidance is intended for bispecific antibodies, the principles discussed in this guidance may also inform the development of other types of bispecific protein products and multispecific products.[2] This guidance does not discuss development considerations for other multitarget therapies that are antibody cocktails, polyclonal antibody products, or combinations of monoclonal antibodies.[3]

This guidance focuses on a range of regulatory and scientific considerations for bispecific antibodies, but not on development of a particular bispecific antibody. Of note, many aspects of a bispecific antibody development program will be similar to monoclonal antibody development programs. This guidance discusses unique aspects for chemistry, manufacturing, and controls (CMC), as well as nonclinical and clinical development programs for bispecific antibodies. Industry and other stakeholders are encouraged to engage FDA to discuss their individual bispecific antibody development program.

[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] Examples of such products include single domain, antibody mimetics, non-antibody domain, alternative format, T-cell receptor mimetics, non-immunoglobulin (Ig) domain and non-Ig scaffold. Bispecific protein products target two antigens and, as used in this guidance, the term *multispecific product* refers to a therapeutic product that targets three or more antigens.

[3] In an antibody cocktail, different antibodies are mixed together during manufacturing. In a polyclonal antibody, a mixture of antibodies recognizing either specific or diverse targets is obtained by purification of pooled plasma or serum. 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.

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## II. BACKGROUND

### A. Monoclonal and Bispecific Antibody Development

Therapeutic monoclonal antibodies, first commercialized in 1986, 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 warranted 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).[4]

A scientific rationale often exists 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 cell 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). Challenges may arise in developing bispecific antibodies such as immunogenicity related to novel structures and complex structural and functional characterization. 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-

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

associated antigens to facilitate cell killing). This type of bispecific antibodies would require binding to both targets at the same time for efficacy.

(2) Bispecific antibodies with functions not involving bridging two target cells, such as a bispecific antibody that targets two soluble cytokines, binds different epitopes of the same tumor cell or viral antigen, or engages two different targets to mimic the function of an endogenous protein. In this category, the bispecific antibody may sometimes, but not always, be required to bind both targets at the same time for efficacy.

Within each category, potential considerations are relevant to a 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 possible synergy when binding both targets.

FDA anticipates there will be a scientific rationale, including target(s), mechanism(s) of action, or increased safety and/or efficacy as compared to similar monospecific products[5] to support development of a particular bispecific antibody. The data supplied to support the scientific rationale will depend on the particular situation[6] and could potentially be derived from clinical or animal studies[7] 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. Although not generally expected, 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 benefit-risk assessment of the bispecific antibody (see section III.C.2 of this guidance for clinical study considerations).

As noted in section I, this guidance discusses unique aspects of bispecific antibody development programs. Questions about regulatory requirements for a particular bispecific antibody should be directed to the appropriate FDA clinical review division. Sponsors are encouraged to discuss plans for their individual products with the appropriate clinical review division within FDA early in development.

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[5] As used in this guidance, the term *monospecific product* refers to a therapeutic antibody that targets a single antigen.

[6] See the International Council for 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/regulatory-information/search-fda-guidance-documents.

[7] 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 testing method. FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible.

## 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 CMC, nonclinical and clinical pharmacology, and clinical development programs for bispecific antibodies.

### A. CMC Quality Considerations

Bispecific antibodies can exist in many different formats including, for example, tandem monovalent binding fragments as well as immunoglobulin G (IgG)-based antibodies where each arm binds a different antigen or 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).

Unique development considerations may be relevant for each of the formats, such as quality, 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.[8] Quality attributes that may affect pharmacology should be studied, including antigen specificity; affinity and on- and off-rates; avidity (for bispecific antibodies that target two molecules on the same cell); potency; product-related impurities such as aggregates, fragments, homodimers, and other mispaired species; stability; and half-life. 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. Design of the potency assay(s) will depend on the target product attributes. 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 evaluation 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, novel structures 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 and species selection for toxicology studies (including general and reproductive toxicology), is expected to be similar to that for monoclonal antibodies directed against a single target.[9,10]

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[8] See *Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use* (February 1997) for more information on product manufacturing and testing (available at https://www.fda.gov/media/76798/download).

[9] See the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* for more information (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals).

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

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, should be addressed, but a comparative safety assessment between the bispecific antibody and monospecific product(s) will likely not be recommended.

In vitro and in vivo pharmacology studies may also offer the opportunity to generate nonclinical data supporting the scientific rationale of the bispecific antibody. Examples include (1) showing that blocking two targets yields additive or synergistic efficacy compared to a monospecific comparator, (2) showing that simultaneous cross-linking of two receptors offers efficacy that cannot be achieved with a monospecific product, or (3) showing expected activation of the immune system for products that either directly activate the immune system or potentiate that activation. These studies could also be used to select the first-in-human dose.[11]

In general, standard nonclinical approaches to support the safety of the starting dose in the clinical trial will be appropriate.[12] For bispecific antibodies with agonistic properties, selection of the initial dose using a minimally anticipated biologic effect level should be considered.[13,14] We recommend discussing dose selection with the appropriate FDA clinical review division.

## C. Clinical Considerations

### *1. Clinical Pharmacology Studies*

The clinical pharmacology studies for a bispecific antibody development program should be similar to those for monoclonal antibodies and other therapeutic protein products. Pharmacodynamic assessments should take into consideration the binding to each target.

Bispecific antibodies may present as a mixture of biologically active (e.g., unbound and capable of binding a ligand) and inactive forms (e.g., bound and not capable of binding a ligand) in biological matrices. Considerations should be given to identifying the bispecific antibody form(s) most relevant to pharmacokinetic/pharmacodynamic assessment and to develop validated assays to measure the appropriate form(s) accordingly. Therefore, more than one assay may be recommended to quantify appropriate forms. In some instances, pharmacodynamic

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

[12] 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.

[13] See footnote 12.

[14] A retrospective analysis examining toxicity profile and approaches in selecting the first in human (FIH) dose for 17 CD3 bispecific constructs concluded that an FIH dose at 10–30% pharmacological activity was an acceptable approach for all constructs examined (Saber et al 2017).

activity measurements may be considered to develop assays to measure and quantify appropriate form(s) of the bispecific antibody.

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. When examining immune responses to bispecific antibodies, it may be appropriate to develop multiple assays to measure immune responses to different domains of bispecific antibodies.[15,16] Sponsors are encouraged to discuss with FDA specific clinical pharmacology development plans for their individual products.

*2. Other Clinical Studies*

FDA recommends that sponsors define the overall benefit-risk profile of the bispecific antibody. In many situations, the clinical studies for bispecific antibodies will compare the bispecific antibody to standard of care or placebo. If monospecific products approved for the same indication exist and they 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 benefit-risk assessment of the bispecific antibody. 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, if feasible. Also, if there is a concern that only one of the bispecific antibody's targets was driving the efficacy results, to better inform the benefit-risk assessment of the bispecific antibody, it may be useful to conduct a trial with the relevant monospecific product(s). FDA may request such studies in certain cases if they are viewed as potentially providing valuable information regarding the bispecific antibody's efficacy or safety.[17,18]

Overall, studies conducted to inform the benefit-risk assessment and 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.

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[15] 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.

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

[17] 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.

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

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