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# Bispecific Antibody Development Programs

## Guidance for Industry

### ***DRAFT GUIDANCE***

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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**

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*Contains Nonbinding Recommendations*

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# **Bispecific Antibody Development Programs Guidance for Industry<sup>1</sup>**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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.<sup>2</sup> 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.

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<sup>1</sup> 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.

<sup>2</sup> 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.

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### 38 **II. BACKGROUND**

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#### 40 **A. Monoclonal and Bispecific Antibody Development**

41

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

52

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

64

#### 65 **B. General Considerations**

66

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

70

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

74

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

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

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

84  
85 FDA anticipates there will be a scientific rationale (e.g., target(s), mechanism(s) of action,  
86 decreased dose, or increased safety and/or efficacy as compared to similar monospecific products  
87 and available therapies) to support development of a particular bispecific antibody. The data  
88 supplied to support the scientific rationale will depend on the particular situation<sup>4</sup> and could  
89 potentially be derived from clinical or animal studies<sup>5</sup> or in vitro assays.

90

### **C. Regulatory Considerations**

91

92  
93 FDA’s regulation on fixed-combination prescription drugs for humans (21 CFR 300.50) does  
94 not apply to the development of bispecific antibodies, which are single molecules. It is not  
95 generally expected, but in some cases, FDA may request a comparison of the bispecific  
96 antibody to an approved monospecific product(s) directed against the same antigenic target(s)  
97 to inform the risk-benefit assessment of the bispecific antibody (see section III.C.2 of this  
98 guidance for clinical study considerations).

99

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

104

105

## **III. SCIENTIFIC CONSIDERATIONS**

106

107  
108 Many aspects of a bispecific antibody development program will be similar to monoclonal  
109 antibody development programs. This section discusses unique aspects for chemistry,  
110 manufacturing, and controls (CMC); nonclinical and clinical pharmacology; and clinical  
111 development programs for bispecific antibodies.

112

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<sup>4</sup> 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>.

<sup>5</sup> 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.

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### 113 **A. CMC Quality Considerations**

114  
115 Bispecific antibodies can exist in many different formats, from tandem monovalent binding  
116 fragments to immunoglobulin G (IgG)-based antibodies onto which multiple additional antigen-  
117 binding domains are attached. These diverse formats allow bispecific antibodies to be designed  
118 to match the proposed mechanism(s) of action and the intended clinical application (Spiess et al.  
119 2015).

120  
121 There may be unique development considerations for each of these formats, such as stability and  
122 production yields, but in general the products should be characterized and the manufacturing  
123 processes should be developed in accordance with standard monoclonal antibody development  
124 practices.<sup>6</sup> Quality attributes such as antigen specificity; affinity and on- and off-rates; avidity  
125 (for bispecific antibodies that target two molecules on the same cell); potency; process-related  
126 impurities such as aggregates; fragments/homodimers; stability; and half-life may affect  
127 pharmacology and should be studied. For example, in vitro and in vivo pharmacology studies  
128 may provide information on the relative binding activity and on- and off-rates for each target.  
129 Early in vitro studies may inform selection of an expression construct with optimal affinity and  
130 stability properties. The relative amounts of homodimers should be assessed. This is  
131 particularly important for effector cell engaging constructs where homodimers of the anti-CD3 or  
132 anti-Fc engaging arm may lead to cytokine release. Also, the molecular structure, such as novel  
133 epitopes or intact antibody structures with additional domains, could potentially lead to increased  
134 immunogenicity.

### 135 **B. Nonclinical Considerations**

136  
137  
138 Nonclinical studies are generally needed to characterize the pharmacology and toxicology of  
139 bispecific antibodies. The scope of the nonclinical program, including pharmacology studies,  
140 species selection for toxicology studies, general toxicology, and reproductive toxicology, is  
141 expected to be similar to that for monoclonal antibodies directed against a single target.<sup>7,8</sup>  
142 Consideration should be given to the expression profile and specificity for each target in  
143 nonclinical models in order to design an appropriate toxicological assessment for the bispecific  
144 product. Potential safety concerns related to the particular components of the bispecific  
145 antibody, if any, may need to be addressed; however, a comparative safety assessment between  
146 the bispecific antibody and monospecific product(s) is not typically expected.

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<sup>6</sup> 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>).

<sup>7</sup> 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>).

<sup>8</sup> See the ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010) for more information.

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147  
148 In vitro and in vivo pharmacology studies may also offer the opportunity to generate nonclinical  
149 data supporting the scientific rationale of the bispecific antibody (e.g., showing that blocking two  
150 targets yields additive or synergistic efficacy compared to a monospecific comparator; showing  
151 that simultaneous cross-linking of two receptors offers efficacy that cannot be achieved with a  
152 monospecific product; for agonistic products, showing expected activation of the immune  
153 system). These studies could also be used to select the first-in-human (FIH) dose.<sup>9</sup>  
154

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

### **C. Clinical Considerations**

#### *1. Clinical Pharmacology Studies*

162  
163  
164  
165 The clinical pharmacology studies needed for a bispecific antibody development program would  
166 be similar to those for monoclonal antibodies and other therapeutic protein products.  
167 Pharmacodynamic (PD) assessments may need to take into consideration the binding to each  
168 target.

169  
170 As bispecific antibodies may present as a mixture of biologically active and inactive forms, it is  
171 important to identify the bispecific antibody form(s) that is most pharmacologically relevant to  
172 pharmacokinetic (PK)/PD assessment and to develop validated assays that measure the  
173 appropriate form(s) accordingly. Sometimes more than one assay may be needed to quantify the  
174 levels of total, bound, and unbound bispecific antibody (Trivedi et al. 2017).  
175

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

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

<sup>10</sup> 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.

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



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180 antibodies.<sup>12,13</sup> Sponsors are encouraged to discuss with FDA specific clinical pharmacology  
181 development plans for their individual products.

182

### 183 *2. Clinical Studies*

184

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

189

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

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<sup>12</sup> 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.

<sup>13</sup> See the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) for more information on immunogenicity assessment.

<sup>14</sup> 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.

<sup>15</sup> 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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### **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.