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Patent Opportunities In FDA Bispecific Antibody Guidance

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In April 2019, the U.S. Food and Drug Administration published draft guidance entitled "Bispecific Antibody Development Programs Guidance for Industry" that provides "recommendations to assist industry and other parties involved in the development of bispecific antibodies."[1] Based on three issues identified by the FDA as potentially important to regulatory approval of these products, companies may consider aligning their patent strategy with these regulatory requirements to acquire a competitive advantage.

Bispecific Antibodies

Bispecific antibodies are proteinaceous molecules capable of binding to two different antigens. First reported in 1961, early versions were generated from mixtures of two monospecific antibodies (e.g., antibodies that bind to a single antigen) with each having different antigen-binding sites.[2]

Since that time, bispecific antibody engineering has improved substantially, and the class represents a promising area for clinical development. Indeed, these molecules have been used to replace conventional combination therapies in a single molecular entity, bridge effectors of the immune system and tumor cells, provide increased binding specificity to a target and generate a novel function (i.e., a function not possessed by any of the binding specifies taken in isolation). Currently, there are two U.S.-marketed bispecific antibodies with over 85 in clinical development.[3]

Draft Guidance on the Development of Bispecific Antibodies

As with all antibody products, the FDA identifies in the draft guidance three areas for specific focus:

- Immunogenicity,

- Monospecific impurities, and
- Comparator studies.

First, the guidance notes that immunogenicity is a key concern to the FDA because of "significant immunogenicity caused by novel epitopes."[4] It further explains that "an immune response to one domain may inhibit a specific function while leaving others intact" and that multiple assays may need to be developed to measure immune responses to different bispecific antibody domains.[5]

Second, in its chemistry, manufacturing and controls quality considerations section, the guidance provides a laundry list of quality attributes that may impact pharmacology[6]. One specific recommendation is that "[t]he relative amounts of homodimers [in the product] should be addressed," as they could cause adverse reactions.[7] Moreover, the guidance expresses concern that bispecific antibodies will comprise mixtures of biologically active and inactive forms, complicating pharmacokinetic and pharmacodynamic assessments.

Third, in several places, the guidance recommends the use of comparator data relative to monospecific precursors in both nonclinical and clinical studies to support the approval.

Potential Patent Strategies

Although the above three areas of the FDA's focus in the guidance are sparse on details, they nevertheless may highlight opportunities for innovators to wrap additional layers of patent exclusivity around their bispecific antibody assets.

Immunogenicity

The FDA notes that bispecific antibodies may raise immunogenicity concerns that may require development of multiple assays to measure immune responses. Therefore, assay development for immunogenicity assessments, especially for those innovators developing bispecific antibodies that target immune effector cells, may be required and should be considered as part of the innovator's patent strategy. Such a strategy may be used to fence off any key data points that measure immunogenicity as well as proprietary methods developed to evaluate immunogenicity. For example, the guidance notes that the FDA has historically requested assay development for anti-drug antibody detection in therapeutic protein products.

Consequently, if ADA assays were required for approval of a bispecific antibody, the assays may form part of the patent strategy for the antibody. Recently issued U.S. Patent No. 10,295,534 is illustrative of such an approach and generically claims such a method of detecting ADAs against various monoclonal antibodies, such as infliximab or adalimumab.[8] Similarly, U.S. Patent No. 9,759,732 claims a method of detecting ADAs in, e.g., serum, by precipitating them using excess drug as an affinity agent. The patenting of the assays, if required for product approval, could potentially create additional obstacles for a competitive product sponsor, which would then be required to develop its own proprietary assay.

Relatedly, claims directed to a bispecific antibody's efficacy or safety profile may provide an alternative means to address the presence of ADA. For example, the tie between a clinical response and the presence or absence of a level of one or more ADAs may provide a means to pursue a broad antibody claim not limited to a specific amino acid sequence. Further, approval of treatment regimens involving the bispecific antibody that do not produce a certain type of ADA (or level of ADA), and that support method-of-use claims, may create additional challenges to a competitive product.

Monospecific Antibody Impurities

The FDA's potential interest in understanding the presence of monospecific homodimer impurities in a bispecific antibody product may also provide a framework for claiming the product. Again, this may provide an opportunity for assay development, especially if the impurity might affect pharmacokinetic/pharmacodynamic assessment.

Further, claims may be pursued that are directed to the amount of a specific monospecific antibody impurity present in a bispecific antibody product (or the ratio of the monospecific antibody impurity to the bispecific antibody). Such claims may also provide avenues to rebut potential attacks on the patentability of a bispecific antibody particularly where novel manufacturing or purification methods are employed to limit the presence of monospecific antibody impurities.

Moreover, claims directed to the testing methods and endpoints used to measure the presence or absence of these monospecific antibody impurities can be drafted in a manner divorced from the bispecific antibody itself and thus provide an innovator with the ability to lock up a technique that may be useful to other bispecific antibody products.

Comparator Studies

The guidance also states that "[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.[9] Thus, to the extent that comparator studies are required for approval, the data obtained from these studies could be used to support claims directed to the activity of the bispecific antibody relative to its monospecific precursors.

For example, functional claims may be pursued to a bispecific antibody possessing certain functional characteristics, such as wherein the bispecific antibody has X-fold or greater activity (or binding affinity) over a monospecific antibody that binds to the same target. The U.S. Court of Appeals for the Federal Circuit has recently addressed functional claiming in antibody claims in the context of a written description analysis and found this method of claiming viable as long as the patentee shows (1) a representative number of species that fall within the genus of antibodies; and/or (2) common structural features of the genus of antibodies.[10]

Conclusion

The guidance provides a limited and initial view into the FDA's areas of focus for development and approval of an innovator bispecific antibody. As innovators of these products are constructing their development model, negotiating with the FDA about data support for regulatory approval and assessing the competitive landscape, they should consider leveraging these data and assay requirements as part of their overall patent strategy to protect its bispecific antibody asset. Indeed, a robust disclosure around immunogenicity assessments, monospecific impurity detection and comparator studies can provide an innovator with flexibility to pursue a mix of claims each of which can uniquely provide ammunition to fight off potential legal attacks based on novelty or obviousness or fence off competitive products.

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[1] The Guidance also notes that the principles discussed may be applicable to (i) the development of other types of bispecific protein products and (ii) other novel constructs that may have three or more antigen-binding domains. Guidance at 1; 2, n.3.

[2] Nisonoff, A. & Rivers, M., Arch Biochem Biophys., 1961, 93:460-2.

[3] Labrijn A., Janmaat M., Reichert J., & Parren P., Bispecific Antibodies: A Mechanistic Review of the Pipeline, Nat Rev Drug Discov. (forthcoming, epub. before print June 7, 2019).

[4] Guidance at 2.

[5] Guidance at 5-6.

[6] The Guidance lists CMC quality attributes with the potential to affect pharmacology as follows: 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.

[7] Guidance at 4.

[8] See also U.S. Patent No. 9,315,583, claiming methods of detecting ADAs to omalizumab.

[9] Guidance at 6.

[10] See Amgen Inc. v. Sanofi, 872 F.3d 1367, 1373 (Fed. Cir. 2017).