

Inside FDA Regulation Of Antibody Drug Conjugates

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Antibody drug conjugates (ADCs) are therapeutic products that include a monoclonal antibody conjugated to a drug. ADCs are thus a combination of two separate classes of products regulated by the United States Food & Drug Administration: a biologic and a drug. Understanding how the FDA regulates ADCs and how regulatory data exclusivity will likely be awarded for different types of ADCs is of critical importance to life science companies that are developing these new types of innovative and targeted biopharmaceuticals.

The FDA Regulates ADCs as Biologics

Traditionally, the FDA has regulated combination products (e.g., drug/device, biologic/device, drug/biologic) under the statutory framework applicable to the constituent providing the primary therapeutic mode of action. A primary mode of action is defined by 21 C.F.R 3.2(m) as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.”

For example, the FDA regulates the combination product of an insulin injector pen as a drug rather than as a device based on its determination that the drug (insulin) provides the primary mode of action. For typical ADCs, the role of the antibody is to deliver a drug (e.g., a cytotoxin) to specific cells harboring an antigen to which the antibody binds. The question of whether the antibody or the drug provides the primary mode of action in such a scenario has presumptively been answered by the FDA. Indeed, in Draft Guidance for Industry released in May 2015, the FDA declared that as a therapeutic class, ADCs are to be regulated as biologics.

New Biologics Awarded 12-Year Data Package Exclusivity Period

The FDA regulates biologics in accordance with the Public Health Services Act (PHSA). The PHSA was amended by the Biologics Price Competition and Innovation Act (BPCIA) which was enacted on March 23, 2010, as part of the Patient Protection and Affordable Care Act. The BPCIA created an abbreviated approval pathway for a Biologics License Application (BLA) whereby the sponsor of a follow-on product



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can rely on the data package of a previously approved reference product. However, the FDA will not effectively approve an abbreviated BLA until 12 years after the approval of a first licensed reference product (i.e., giving the sponsor of the reference product a 12-year data package exclusivity period).

Importantly, the 12-year exclusivity period only attaches to the “first licensure” of a biologic. For example, supplement or subsequent licensures to the same or a related product by the same sponsor or those simply for new indications, will not receive a new exclusivity period. However, structural modifications to the biologic that result in a change in safety, purity or potency, will be considered as a first licensure eligible for 12 years of exclusivity (FDA Guidance for Industry (August 2014); Reference Product Exclusivity for Biological Products Filed Under 351(a) of the PHS Act).

Many Open Questions on ADC Regulatory Exclusivity

Since 2010, the FDA has approved two ADCs for commercial marketing. SeattleGenetics’ Adcetris (brentuximab vedotin), which contains an anti-CD30 monoclonal antibody conjugated to the cytotoxic monomethyl auristatin E (MMAE) and is used for treatment of relapsed or refractory Hodgkin Lymphoma and anaplastic large cell lymphoma, was approved in 2011. Genentech’s Kadcyla (ado-trastuzumab emtansine), which contains the anti-HER2 monoclonal antibody Trastuzumab (marketed as Herceptin) conjugated to the cytotoxin DM1 and is a treatment for HER2-positive metastatic breast cancer, was approved in 2013. Notably, the only other ADC to be approved, Mylotarg was in 2001 prior to enactment of the Biologics Price Competition and Innovation Act.

Neither constituents of Adcetris (Brentuximab or MMAE) has previously been approved by the FDA as a stand-alone product. The ADC and its individual constituents are therefore all “new” from a regulatory perspective and it appears likely that Adcetris will be awarded 12 years of exclusivity. Despite this, the FDA has not publicly provided such an indication even though Adcetris was approved over four years ago.

Kadcyla presents an interesting alternative. Indeed, although the drug DM1 (N2’-deacetyl-N2’-(3-mercapto-1-oxopropyl)maytansine) has not been approved as a stand-alone product, the antibody (Trastuzumab) was first licensed to Genentech in 1998. Thus, Kadcyla may be viewed as an “old” antibody conjugated to a “new” drug. When Kadcyla was approved, the FDA declined to determine the exclusivity period, stating that the “decision and process will set precedent for biologic reference product exclusivity so there is a need to have agreement from involved parties.”

At that time, drug-drug combination products that included a previously approved drug and a not previously approved drug were not awarded the traditional five years of new chemical entity exclusivity even though the “new” drug in the combination would have been entitled to such exclusivity if approved as a stand-alone product. Of note, the FDA changed this policy after Kadcyla was approved as described in Guidance for Industry (October 2014): New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products. By analogy, this change in policy would seem to favor awarding 12 years of exclusivity in the case of Kadcyla. This would however have the unusual effect of granting 12 years of exclusivity to the ADC when the “new” drug constituent would only receive five years if approved as a stand-alone product (and could be distinguished from the opposite situation where a “new” antibody is conjugated to an “old” drug).

Alternatively and maybe more likely, the FDA may simply treat the conjugation of DM1 as a structural modification that results in a “change in safety, purity, or potency” of the “old” antibody Trastuzumab and award 12 years of exclusivity to Kadcyla on that basis alone. Such an outcome would be particularly

significant for future ADC products that contain an antibody and a drug that have both been previously approved. Indeed, such ADCs that contain an “old” drug conjugated to an “old” antibody will likely need to rely on the structural modification argument in order to obtain 12 years of exclusivity.

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