Orphan Drug Exclusivity Criteria Clarified in *Depomed* Court Decision

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A U.S. District Court has issued a decision that could affect the Food and Drug Administration's (FDA) interpretation and determination in the orphan drug exclusivity area. Specifically, on September 5, 2014, the United States District Court for the District of Columbia issued its memorandum opinion in the case of *Depomed, Inc. v. United States HHS*.[1] The case centered on the Orphan Drug Act, which provides incentives to pharmaceutical companies to research and develop drugs for rare diseases or conditions through, among other benefits, its seven-year period of marketing exclusivity granted to certain drugs.

The central issue in the case was the parties' disagreement over what conditions a drug must satisfy to qualify for marketing exclusivity. The statute sets forth two procedural prerequisites to obtain marketing exclusivity: (1) FDA must "designate" the drug as an orphan drug; and (2) FDA must "approve" the designated orphan drug for marketing. FDA added, in its implementing regulations, that it would not approve another marketing application for the same drug before the expiration of marketing exclusivity, except "if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug."[2]

We will not explain here the Orphan Drug Act or FDA's implementing regulations in detail. We will also not describe every detail of the case. Rather, this Bulletin highlights some of the key points and AGG's observations about the decision.

Background

- In 2002, FDA approved Neurontin (gabapentin) for treatment of post-herpetic neuralgia ("PHN"). PHN qualifies as a rare disease or condition under the statute, but the manufacturer of Neurontin never sought or obtained orphan drug designation for the drug for use in treating PHN and never received the benefit of the exclusivity provision.

- Since 2002, FDA has approved nearly 30 gabapentin products for the treatment of PHN.

- In 2006, Depomed submitted a request to FDA that the agency designate Depomed's own gabapentin product, Gralise®, as an orphan drug for the treatment of PHN. Depomed acknowledged that Neurontin had previously been approved for treatment of PHN. However, the company argued that, because no other gabapentin product had ever been designated as an orphan drug for treatment of PHN, it did not need to provide a plausible hypothesis of clinical superiority in order to satisfy the submission criteria for orphan drug designation applications. FDA denied the designation request, contending that Neurontin had already received marketing approval, even though it was never designated as an orphan product.

1 2014 U.S. Dist. LEXIS 126235.

2 For more information on the Orphan Drug Act, see http://www.fda.gov/forindustry/DevelopingProductsforrareDiseasesConditions/default.htm; see also 21 U.S.C. §§ 360aa-360ee and 21 C.F.R. § 316.3(b)(13).

- In 2010, Abbott Labs, a drug manufacturer that acquired rights to Gralise, renewed Depomed's previous request for orphan drug designation of Gralise. Abbott contended that there was no other drug that "already has orphan-drug exclusive approval" for PHN. FDA rejected the designation request and contended that Gralise was the "same drug" as Neurontin and, therefore, was subject to the clinical superiority standard. Because Abbott failed to provide evidence of clinical superiority, the request was denied.

- In 2010, Abbott submitted an amended designation request, in which it objected to FDA's interpretation, but also presented a clinical superiority hypothesis supported by two studies. FDA granted Abbott's request for designation as an orphan drug for the treatment of PHN and noted that "should [Abbott] obtain marketing approval for [Gralise], [Abbott] will have to prove clinical superiority . . . in order to obtain . . . marketing exclusivity[.]"

- In 2011, FDA granted Abbott marketing approval for Gralise, but maintained it was not entitled to marketing exclusivity because Abbott had not proven clinical superiority to Neurontin.

- In 2011, Depomed reacquired the rights to Gralise and challenged FDA's position in this lawsuit.

Court Decision

- Depomed's motion for summary judgment was granted. The district court found that the plain language of the Orphan Drug Act unambiguously required FDA to recognize that any drug which has been both designated as an orphan drug for treatment of a qualifying disease or condition and also approved for marketing is entitled to an exclusivity period.

- The court examined the statute's exclusivity provision and found that given its "if x and y, then z" formula, exclusivity was clearly required. The court read the statutory language as a limitation on the agency's authority; it is a restriction of FDA's ability to approve the marketing of other such drugs for the same rare disease or condition. No discretion is provided to FDA regarding whether to continue authorizing new drug marketing applications once an orphan drug has been so designated and approved.

- The court interpreted the law to suggest that the intent of Congress was to provide FDA with a merely ministerial role in the exclusivity process and not to grant it the authority to impose additional requirements with respect to a drug that has received designation and approval, i.e., the clinically superior standard.

- The court stated that, in writing the law, there is no suggestion that Congress intended to incentivize only one sponsor to produce a particular drug, and the statute incentivizes investment in these drugs because it prevents new drugs from being adopted and marketed.

- The court did note that FDA's implementation of the statutory provisions lie in its purview and, if it has concerns about a specific outcome, it can address it then.

- At the time of this Bulletin, FDA had not appealed the decision.

AGG Observations

- The case reflects the importance of seeking designation and marketing approval from FDA, and then exclusivity, as soon as possible in the development of an orphan drug. If exclusivity is not sought, a different drug company could receive the benefit.

- The case calls into question FDA's clinical superiority requirement in similar cases, although the court did not seem to reject the standard completely.

- In the future, it is possible that FDA might address this type of issue by not granting designation at the outset. The court stated that:

  > FDA could require designation applicants to show clinical superiority before granting their product orphan drug designation, a change in the regulations that would allow FDA to maintain the benefits of its clinical superiority requirements and also forestall the hypothetical 'serial exclusivity' problem while at the same time avoiding any conflict with the clear language of the statute's exclusivity provision.[3]

- It is unclear whether FDA will retroactively grant exclusivity to drugs that met the criteria, but did not receive exclusivity because of an inability to show clinical superiority. We may see other potential lawsuits against FDA in similarly-situated cases.

- As we have noted in other Bulletins, FDA continues to review orphan drug provisions.[4] While the statute is more than 30 years old, FDA's interpretation continues to evolve as facts dictate.

3 2014 U.S. Dist. LEXIS 126235 at 45.

4 See, e.g., http://www.agg.com/Making-Exclusivity-Less-Confusing-FDA-Establishes-Exclusivity-Board-to-Assist-with-Exclusivity-Determinations-11-14-2012/; http://www.agg.com/FDA-Leaves-an-Orphan-Out-in-the-Cold-09-29-2012/; and http://www.agg.com/FDA-Announces-Proposed-Changes-to-Clarify-Orphan-Drug-Regulations-11-02-2011/.

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