REGULATORY FOCUS

US Orphan Drug Exclusivity Criteria Clarified in Depomed Court Decision

By Alan G. Minsk, JD

A recent US district court decision could affect US Food and Drug Administration (FDA) interpretation and determinations in the orphan drug exclusivity area. Specifically, on 5 September 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 centers on the *Orphan Drug Act*, which provides incentives to pharmaceutical companies to research and develop drugs for rare diseases or conditions including, among other benefits, a 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:

- FDA must "designate" the drug as an orphan drug.
- The agency must "approve" the designated orphan drug for marketing.[2]

In its implementing regulations, FDA added it would not approve another marketing application for a drug with the same active moiety and intended for the same use as the previously approved drug before marketing exclusivity expiration 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."[3,4]

This article highlights some of the key points and observations about the court's 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 (a US patient population of 200,000 or fewer), but Pfizer, Neurontin's manufacturer, never sought or obtained orphan drug designation for the drug for use in treating PHN and, thus, never received the

benefit of the exclusivity provision.[5] Since 2002, FDA has approved nearly 30 gabapentin products for the treatment of PHN.[6] As late as 2010, however, no gabapentin product had received orphan drug designation for treatment of PHN.

In 2006, Depomed Inc. submitted a request to FDA to designate its gabapentin product, Gralise, as an orphan drug for the treatment of PHN. Depomed acknowledged that Neurontin previously had been approved for treatment of PHN. However, the company argued that because no 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 to any previous drug to satisfy the submission criteria for orphan drug designation applications. FDA denied the designation request, contending Neurontin already had received marketing approval, even though it was never designated as an orphan product.[7]

In 2010, Abbott Labs, which had acquired rights to Gralise, renewed Depomed's previous request for orphan drug designation. Abbott contended there was no gabapentin drug that "already has orphan drug exclusive approval" for PHN. FDA rejected the designation request, contending 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.[8]

Abbott subsequently 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 Gralise's designation as an orphan drug for the treatment of PHN but noted "should [Abbott] obtain marketing approval for [Gralise], [Abbott] will have to prove clinical superiority…in order to obtain…marketing exclusivity."[9]

In 2011, FDA granted Abbott marketing approval for Gralise, but maintained it was not entitled to marketing exclusivity because Abbott had not proven the drug's clinical superiority to Neurontin.[10] Later in 2011, Depomed reacquired the rights to Gralise and challenged FDA's position in the lawsuit that is the subject of this article.[11]

Court Decision

Depomed's motion for summary judgment was granted. The district court found the plain language of the *Orphan Drug Act* unambiguously required FDA to recognize any drug designated as an orphan drug for treatment of a qualifying disease or condition and also approved for marketing is entitled to an exclusivity period.[12]

The court examined the statute's exclusivity provision and found, 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.[13]

The court interpreted the law to suggest 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.[14]

The court stated that, in writing the law, there is no suggestion 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.[15]

The court did note FDA's implementation of the statutory provisions lies within the agency's purview and, if FDA has concerns about a specific outcome, it can address it then.[16]

On 3 November 2014, FDA filed a notice appealing the decision to the United States Court of Appeals for the District of Columbia Circuit. FDA then filed an unopposed motion to dismiss the appeal on 6 November 2014. On 7 November, the motion was granted.[17,18]

Observations on the Case at Hand

This case reflects the importance of seeking FDA designation and marketing approval, 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, FDA might address this type of issue by choosing not to grant designation at the outset. The court stated FDA could require designation applicants to show clinical superiority before granting their product orphan drug designation. Such a change in the regulations would allow FDA to maintain the benefits of its clinical superiority requirements and also forestall the hypothetical "serial exclusivity" problem, while avoiding any conflict with the clear language of the statute's exclusivity provision.[19]

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

FDA continues to review orphan drug provisions. While the statute is more than 30 years old, the agency's interpretation continues to evolve as facts dictate.

References

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4. See also 21 U.S.C. §§ 360aa-360ee and 21 C.F.R. § 316.3(b).
5. Op cit 1 at 12.
6. Op cit 1 at 12.
7. Op cit 1 at 13-14.
8. Op cit 1 at 14-16.
9. Op cit 1 at 17-18.
10. Op cit 1 at 18-19.
11. Op cit 1 at 19.
12. Op cit 1 at 3.
13. Op cit 1 at 29-31.
14. Op cit 1 at 37.
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16. Op cit 1 at 44-45.
17. *Depomed Inc. v. United States HHS*, 2014 US App. LEXIS 21700 (DC Cir 2014).
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19. Op cit 1 at 45.

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