

Tissue Agnostic Therapies in Oncology Regulatory Considerations for Orphan Drug Designation

The evaluation of potential tissue agnostic treatments in oncology raises a number of issues for consideration of orphan drug designation such as what factors should be considered in defining a tissue agnostic disease or condition at the time of request for orphan drug designation, how FDA should consider orphan drug designation requests of the same product for a tissue agnostic disease or condition and also for a disease based on traditional disease nomenclature, and how FDA should view orphan drug exclusivity for tissue agnostic indications relative to previous or subsequent approvals for organ specific indications. FDA is holding this public workshop to obtain input on the complex scientific and regulatory issues surrounding molecular targets for drugs and biologics in oncology. This discussion will inform how the Agency can incorporate the evolving science and drug development trends into the implementation of the Orphan Drug Act (ODA).¹

The combination of government incentives, scientific advances, and the promise of commercial opportunity has fueled investment in orphan drugs. Since the ODA was first passed in 1983 there has been tremendous growth in the development of products for rare diseases. Over 650 rare disease indications for drugs and biologics have been developed and approved for marketing, with rare disease drug approvals accounting for approximately 40% of the New Molecular Entities and Therapeutic Biologic Products in Center for Drug Evaluation and Research over the last several years. Additionally, as advances in genomics and precision medicine continue to be made the landscape of product development is changing with an increase in the development of targeted therapies, especially in the oncology space. In 2017, FDA granted its first tissue-agnostic approval (pembrolizumab for patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors) and first tissue-agnostic orphan-drug designations (larotrectinib and entrectinib, each for the treatment of solid tumors with NTRK-fusion proteins). The continued development of targeted

therapies for molecularly defined conditions has the potential to alter the landscape of orphan drug development.

The intent of the ODA was to provide support for the development of drugs or biologics (“drug”) for the diagnosis, prevention, or treatment of rare diseases or conditions, defined by the ODA generally as fewer than 200,000 people in the United States. One method by which FDA provides incentives under the ODA is by granting eligible requests for orphan drug designation. A sponsor may request orphan drug designation at any time in its drug development process prior to submitting a marketing application for the drug for the same rare disease or condition. The granting of orphan drug designation may qualify the sponsor of the drug a waiver of the prescription drug application user fee, tax credits for qualified clinical testing, and potential market exclusivity upon approval.

Whether a given medical condition constitutes a distinct disease or condition for the purpose of orphan drug designation depends on a number of factors including pathogenesis of the disease or condition; course of the disease or condition; prognosis of the disease or condition; and resistance to treatment. These factors are analyzed in the context of the specific drug for which designation is requested. FDA considers the mechanism of action of the drug to determine what distinct disease or condition the drug is intended to treat, diagnose or prevent when reviewing a request for orphan drug designation. The designation request must also include enough information to establish a medically plausible basis for expecting the drug to be effective in the rare disease. This is best supported by clinical experience with the drug in the rare disease or condition, but in the absence of human data may be supported with preclinical data that includes data from the use of the active moiety or principal molecular structure of the proposed orphan drug in a relevant animal model for the rare human disease. Sponsors can also request orphan designation for the use of the drug for the prevention, diagnosis or treatment of an orphan subset of a common disease or condition only if specific regulatory criteria are met for the orphan subset.

Historically, FDA has used a histology based approach, designating and approving oncology drugs for treatment of tumor types based on a single anatomic site. As knowledge of oncogenesis has evolved, oncologists have begun categorizing organ-specific cancers based on molecular markers. For example, decades ago oncologists began identifying breast cancer subtypes based on hormone receptor status. More recently, oncologists have differentiated non–small-cell lung cancer types by specific molecular aberrations, such as *ALK*, *EGFR*, *ROS-1*, or *BRAF*. The rationale for considering the molecular markers of histology based tumor types stems from the valuable information these markers provide in being prognostic indicators based on the target they afford for drug development and treatment. FDA has considered these evolving concepts in implementing the ODA by using such molecular targets to inform orphan designation of an eligible orphan subset within a common disease by the traditional histology-based approach.

Recent developments in the genomics of oncogenesis have opened the possibility of a molecular marker defining a disease that spans multiple histology-based tumors in a tissue agnostic manner. However, it is also clear that tumors represent heterogeneous disease states and that histologic context may be of importance in evaluating potential targeted treatments. These complexities raise a number of issues for consideration of orphan drug designation and orphan drug exclusivity. The discussion and input from this workshop will inform the Agency as it seeks to integrate evolving science in the orphan drug designation of drugs to treat, prevent, or diagnose diseases or conditions in oncology.

¹ Pub. L. No. 97-414, 96 Stat. 2049 (1983), *codified as amended at* 21 U.S.C. §§ 360aa-ee. See also, the Orphan Drug Regulations at 21 CFR Part 316.

² See 21 CFR § 316.3(b)(13) (Orphan subset of a non-rare disease or condition (“orphan subset”) means that use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug).