

August 30, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2010-N-0218: Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases; Public Hearing (June 29-30, 2010)

Dear Sir or Madam:

The Sarcoma Foundation of America is pleased to submit this comment on the Food and Drug Administration's (FDA) review and regulation of articles for the treatment of rare diseases.

The Sarcoma Foundation of America (SFA), a 501(c)(3) nonprofit charitable organization, advocates for increased research to find new and better therapies with which to treat patients with sarcoma. The organization raises money to privately fund grants for sarcoma researchers and conducts education and advocacy efforts on behalf of sarcoma patients. The SFA also interacts with public, private for-profit, and private non-profit entities to educate and raise awareness about the treatment needs of not only sarcoma patients, but also all patients with rare cancers and rare, life-threatening diseases. The SFA, for example, plays an active role in collaborations with the National Organization for Rare Disorders, the Genetic Alliance, the Kakkis EveryLife Foundation, the National Organization Against Rare Cancers, and the American Society of Clinical Oncology.

Unfortunately, despite the efforts of the SFA and related organizations, effective treatments for thousands of rare, life-threatening disorders remain as-yet-unattained. There exists a significant, and currently unmet, need for new therapeutic options. It has become clear, however, that the current drug and biologics approvals process is problematic for therapies intended to treat rare diseases like sarcoma. The nature of rare disorders and their affected patient populations present unique drug development challenges, most notably in recruiting and retaining sufficient patient numbers to produce meaningful clinical trial data. We applaud FDA and its Committee for Rare Diseases for initiating this important regulatory review to enhance development of rare disease treatments.

The SFA believes that broad FDA acceptance of clinical endpoints other than overall survival (OS) could remove many of the present barriers to rare disease drug development. Specifically, progression-free-survival (PFS) and, to a related but lesser degree, time-to-progression (TTP), both provide meaningful metrics for evaluating treatment efficacy while enabling statistically significant results in smaller clinical trial populations. The latter, in particular, possesses applicability far beyond the rare cancer context and could improve treatment prospects for sufferers of innumerable rare, life-threatening diseases. In addition to sarcoma and other rare cancers, Hutchinson-Gilford Progeria, Marfan Syndrome, Epidermolysis Bullosa, Duchenne muscular dystrophy, Sturge-Weber syndrome, Pseudoxanthoma elasticum (PXE), Stiff Person Syndrome, and Progressive Multifocal Leukoencephalopathy are just a few of the many diseases that could benefit from acceptance of PFS and/or TTP as endpoints in lieu of overall survival.

FDA is already familiar with these endpoints, regularly accepts their utilization as an endpoint for full approval and also under the accelerated approval process for certain drugs and biologics, and possesses the regulatory authority to expand their use. However, to the pharmaceutical sponsor wishing to develop a product for a rare, life-threatening disease, with OS being the current default clinical trial endpoint as the measure of clinical benefit, there is no consistent or predictable pathway or policy to follow that provides an incentive for the sponsor to risk initiating the Investigational New Drug (IND) process with FDA. Accordingly, the SFA urges FDA's forthcoming guidance on rare diseases to establish measures such as PFS and/or TTP as societally acceptable endpoints that can alone demonstrate the clinical benefit required for rare, life-threatening disease drug approval.

The SFA looks forward to exploring these issues further and respectfully offers the following comments.

I. General Comments

A. Rare Disease Guidance Issuance

The SFA supports the issuance of rare disease guidance, and we encourage FDA's Committee on Rare Diseases to develop the guidance document(s) referenced in the *Federal Register* notice and required by recent public law.¹

II. Comment to Establish in the New Guidance Alternatives to Overall Survival for Demonstrating Clinical Benefit in Rare Diseases

Although use of PFS and TTP as surrogate endpoints in accelerated approvals is valuable, the SFA believes that meaningful access to rare disease treatments will ultimately not be

¹ See Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2010, Public Law 111-80, section 740.

possible without alternatives to overall survival for demonstrating clinical benefit. Accordingly, we urge FDA to establish progression-free-survival and/or time-to-progression as evidence of clinical benefit in rare diseases sufficient to confer full drug approval.

Section 505(d) of the Federal Food, Drug, and Cosmetic Act (FDCA) requires that, in order to obtain approval, a new drug must be shown to be safe and effective for its proposed use(s).² The FDCA specifies that a drug's effectiveness must be demonstrated by "substantial evidence," which in turn is defined as "evidence consisting of adequate and well-controlled clinical investigations."³ Similarly, the Public Health Service Act requires biological products to be shown to be "safe, pure, and potent" in order to gain approval.⁴ Presently, showings of clinical benefit sufficient for treatment approval include both important clinical outcomes (e.g., increased survival) and effects on established surrogate endpoints (e.g., blood pressure).

Under the current, traditional drug approval process, overall survival is currently the predominant endpoint used to establish clinical benefit for rare solid cancers. Importantly, however, FDA does possess the regulatory authority to establish accepted alternatives to overall survival, including PFS and TTP. The statutory scheme under section 505(d) vests FDA with the authority to determine which clinical outcomes satisfy the "substantial evidence" standard, and as the Agency itself stated recently, "FDA has the flexibility to use its scientific and regulatory expertise to interpret these statutory mandates."⁵ Furthermore, FDA's own industry guidance endorses use of alternative endpoints to overall survival in certain circumstances,⁶ and PFS and TTP have already served, albeit inconsistently, as primary endpoints for drug approval in some oncologic contexts.⁷

Despite FDA's authority to establish alternative endpoints, however, and happenstance occasions when it has done so, a demonstration of overall survival improvement remains the de facto approval endpoint considered by industry should they contemplate

² 21 U.S.C. 355(d).

³ *Id.*

⁴ 42 U.S.C. § 262(a)(2)(C)(i)(I).

⁵ Response to SFA and ASPS Citizen Petition, Docket No. FDA-2007-P-0180, June 28, 2010, at 3.

⁶ See FDA's guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under "Clinical/Medical."

⁷ Examples include, but are not limited to: 2006 approval of lenalidomide (Revlimid) for multiple myeloma based on time-to-progression; 2006 approval of sunitinib (Sutent) for gastrointestinal stromal tumor based on time-to-progression; 2008 approval of bendamustine hydrochloride (Treanda) for chronic lymphocytic leukemia based on progression-free-survival.

developing a new product for most rare solid cancers. Although overall survival certainly represents an ideal endpoint in principle, in reality the extraordinarily small patient populations render it nearly impossible to conduct the trials required for approval. And in the Catch-22 nature of rules required for accelerated approval, these endpoints will never be used as validated surrogate endpoints in such exceedingly rare diseases since it would take a positive efficacy trial in a drug program measuring both PFS (or TTP) and OS to obtain the data necessary to validate the surrogate for use as a subsequent surrogate.

The size and duration of clinical trials statistically necessary for overall survival endpoints are simply not feasible for these rare diseases, particularly those which may prove fatal before studies can even be adequately enrolled. Progression-free-survival and related endpoints like time-to-progression, in contrast, can provide meaningful information about treatment efficacy more quickly and with much smaller clinical studies. Acceptance of these metrics for full approval in lieu of overall survival for rare diseases represents an important and critically necessary regulatory approach. Doing so would maintain sufficient efficacy and patient safety protections while nevertheless acknowledging that risk-benefit considerations are inevitably different for rare disease sufferers than for those afflicted with common, more heavily-researched diseases.

Significantly, it is not only the rare disease research and patient communities who have endorsed PFS and TTP as increasingly desirable alternatives to overall survival. A subject of significant discussion within the scientific community, a growing body of research suggests that PFS can be a suitable, and sometimes even superior, indicator of clinical benefit compared to the traditional endpoint of overall survival.⁸ FDA's own Oncologic Drugs Advisory Committee (ODAC), too, although not opining on the use of alternative endpoints to overall survival specifically, has expressed concern about the requirements for demonstrating clinical benefit and their particular inability to accommodate the limitations inherent to rare cancer research.⁹ As FDA's own guidance states, "Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies."¹⁰ The SFA submits that this risk-benefit analysis, more so than perhaps in any other context, warrants acceptance of PFS for rare disease research, where clinical studies and meaningful treatment options are direly lacking.

The SFA recognizes that PFS and TTP present challenges in their adoption, including greater measurement difficulties and bias risks than using overall survival as a study's primary endpoint. Yet, diagnostic and imaging criteria are continually improving for evaluating disease progression, and FDA already possesses guidance that could help

⁸ See Mary Beckman, *More Clinical Cancer Treatments Judged by Progression-Free Rather than Overall Survival*, 99 JNCI 1068 (2007).

⁹ *Id.*

¹⁰ *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, *supra* note 6, at 8.

ensure objectivity in clinical studies employing tumor progression endpoints.¹¹ In the rare disease setting, however, even if overall survival endpoints may be impossible to implement for the reasons above, on-going studies to confirm efficacy could assume the form of observational or registry-based trials, both of which FDA has recently expressed a willingness to consider more generally for rare cancers.¹² The SFA firmly believes that any initial difficulties are surmountable. Ultimately, FDA can adopt alternative endpoints to overall survival for full drug approval while maintaining appropriate efficacy and safety protections, and this critically-needed regulatory approach promises to produce extraordinary gains in the number of therapeutic options for patients with rare, life-threatening diseases.

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Thank you for the opportunity to comment on FDA's regulation of rare disease treatments. We look forward to a continued dialogue with FDA about the important issues raised at the public hearing and in this review.

Sincerely,

A handwritten signature in blue ink that reads "Mark Thornton". The signature is written in a cursive, slightly slanted style.

Mark O. Thornton, MD, MPH, PhD
President, Sarcoma Foundation of America

¹¹ See generally, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, *supra* note 6.

¹² Citizen Petition Response, *supra* note 5, at 11.