ALLIANCE for Regenerative Medicine

August 26, 2013
Division of Dockets Management (HFA-305)
US Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

Re: Docket No. FDA-2013-D-0575

The Alliance for Regenerative Medicine (ARM) is pleased to comment on the FDA's draft guidance entitled "Draft Guidance for Industry on Expedited Programs for Serious Conditions-Drugs and Biologics", published in the Federal Register on June 26, 2013.

ARM is a multi-stakeholder group comprised of 145 life sciences companies, non-profit research organizations, patient advocacy groups, clinical centers, and investors that have come together to advocate for policies to support research and commercialization of regenerative medicine products. Regenerative medicine represents healthcare related technologies that translate the fundamental knowledge in biology, chemistry and physics into materials, devices and systems through a variety of therapeutic strategies that augment, repair, replace or regenerate organs and tissues.

Regenerative medicine products on the market have already demonstrated the power of this technology to improve clinical care and reduce costs. Hundreds of regenerative medicine products in clinical trials hold the promise to treat unmet medical needs, improve patient care, and bend the health care cost curve in ways that current forms of clinical care have not been able to achieve. Many of the diseases being targeted by regenerative medicine researchers and product developers are chronic diseases that affect millions of American families and are the major cost drivers for Medicare and in our health care system.

General Comments

ARM appreciates FDA's publication of this draft guidance. FDA's expedited programs will speed the availability of safe and effective products to treat unmet medical needs. Many regenerative medicine products are targeted at these conditions and we look forward to working with FDA as the agency implements its programs. This guidance is an important step in the implementation process.

We find the guidance to be clear and comprehensive. It provides drug developers with descriptions and comparisons of the relevant FDA programs -- accelerated approval, breakthrough therapy, fast track designation and priority review. ARM appreciates the guidance's descriptions of the application processes as well as the review process.

Moreover, the guidance provides clarity about key terms such as "unmet medical need", "serious condition", and "available therapy". It discusses considerations for expedited development and review such as manufacturing scale-up and inspections, long-term nonclinical toxicity studies, and review cycle clinical inspections. In addition, this guidance aligns the Center for Drug Evaluation and Research's criteria for priority review designation with the Center for Biologicals Evaluation and Research's criteria. In so doing, it provides important information to drug developers to help them access the federal expedited programs.

We commend FDA for its use of tables and charts which are easy to read and clear and for its use of hyperlinks which facilitate navigation throughout the guidance. We were pleased to see FDA's comprehensive comparative summary of the four expedited programs that includes qualifying criteria, and timelines for the submission and FDA's review, features, and additional considerations in Section IV. The guidance will be an important resource.

Specific Comments

Breakthrough Therapy

ARM seeks clarification on a provision in the section on breakthrough therapies. On page10, lines 282 – 293, the proposal says that this section and other related sections in the document indicate that "…breakthrough therapy designation requires preliminary clinical evidence of a treatment effect…" This is also stated on page 27 in the Appendix. However, other portions of the document indicate that a request for breakthrough therapy designation can be made at the time of IND submission (for example on page 12, which indicates that breakthrough therapy designation enables "intensive guidance on an efficient drug development program, beginning as early as Phase 1" – thus implying designation prior to the Phase 1). These two points appear to be in conflict, but could be explained by several scenarios, such as the generation of prior clinical data ex-U.S., (i.e. not under IND), or preliminary clinical evidence from a different formulation, route of administration or an entirely unrelated indication that might somehow require a separate IND. ARM seeks additional clarity on how this could be achieved.

In addition, in Section VI's discussion of preliminary clinical evidence (lines 263, 280, etc.), FDA should clarify that the "preliminary clinical evidence" should be obtained with the drug product for which the sponsor is seeking breakthrough therapy designation. For example, clinical data obtained with a previous related product would not be considered sufficient to obtain designation.

Moreover, the following requirements are ambiguous and therefore could result in subjective criteria being applied in a non-uniform way within a Center and between Centers.

- Line 291-293: data in a *substantial number* of patients to be considered credible.

- Line295-298: preliminary evidence would be derived from comparison to available therapy in testing and shows *superiority*. The demonstration of superiority from Phase 1 /2 studies would be unexpected. This requirement may be viewed as in conflict with the earlier statement regarding substantial improvement, a potentially lesser burden of proof.

FDA should also acknowledge that for some products addressing orphan indications, it may not be feasible to conduct standard randomized trials and designs such as cross-overs or other within subject comparisons may be considered.

Lines 406-414 of the document indicate that the breakthrough therapy program will involve senior managers and experienced staff. We welcome the assignment of a cross-disciplinary project lead (Section VI.B.3) who will serve as scientific liaison between the members of the FDA review including senior managers; however we would encourage FDA to allow this person to communicate regularly with the sponsor on scientific issues and focus the role of the Project Manager on regulatory issues. ARM is also concerned about how FDA will ensure consistent application of the guidance within Centers and across Centers since several of the qualifying criteria are subjective (i.e., substantial improvement, clinically meaningful endpoints).

Another issue relates to international regulatory harmonization. We can anticipate that when FDA grants a breakthrough designation, the clinical program may be expedited in such a way that the data may not be deemed sufficient by other health authorities. Such a challenge may result in sponsors not pursuing breakthrough designation, keeping the program from achieving its intended benefit of accelerating breakthrough treatments to American patients. Thus, it would be beneficial for FDA to take steps to minimize the possibility that global development considerations will inhibit use of this expedited pathway.

We encourage FDA to work with its health authority counterparts to explain the breakthrough designation program so they understand its benefits and to facilitate acceptance of development programs shaped by breakthrough designation in the US. FDA should consider initiating discussions with the European Medicines Agency to establish a joint assessment and granting process for breakthrough therapy designations.

In addition, we urge FDA to provide additional examples of the types of interactions envisioned with sponsors developing a product designated as a breakthrough therapy.

ARM also calls on FDA to maintain its flexibility in its implementation of the breakthrough designation program. We ask that this be extended to implementation of the PDUFA V New Molecular Entity Program (the Program) for products with breakthrough designation, as the Program goals of "improv[ing] the efficiency and effectiveness of the first cycle review process" and "ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics" are also facilitated by the breakthrough designation process and may be best achieved by continued frequent interactions and flexibility during the review period rather than the approaches called for under the Program.

<u>Unmet medical need</u>

The proposal expands the concept of unmet medical need to include those therapies that address an emerging or anticipated public health need, such as a drug shortage, and also those therapies that, even though they don't show a direct efficacy or safety advantage over available therapy may nonetheless provide an advantage that would be of sufficient public health benefit to qualify as meeting an unmet medical need. It also articulates that a new treatment would qualify as meeting an unmet medical need even if an available therapy exists for a condition. ARM supports this language.

Moreover, the proposal says that where there is an available therapy, a new treatment will be considered to treat an unmet medical need if the treatment "has an effect on a serious outcome of the condition that is not known to be influenced by available therapy (e.g., progressive disability when the available therapy has shown an effect on symptoms but has not shown an effect on progressive disability) or has an improved effect on a serious outcome(s) of the condition compared to available therapy". This would help allow regenerative medicine and other new products that treat underlying causes of disease be appropriately considered as treating an unmet medical need, even if existing treatments exist.

ARM also suggests adding the following language to the bullet point starting on line 179 "[P]rovides similar safety and efficacy as available therapy but with another documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes *or treating a broader segment of the relevant patient population*". Some new therapies will have a comparable benefit to existing treatments, but if they reach a much broader segment of the patient population, that is equivalent to meeting an unmet medial need.

Other Comments

As noted, the guidance includes several key definitions, including serious condition, available therapy, and clinically significant endpoint. However, we encourage FDA to provide more examples and explanation for key definitions that can be applied beyond the oncology and HIV context. For example, the definition of the term "clinically significant endpoint" (lines 345-362) as written is not readily applied to other therapeutic areas. Please consider expanding the bulleted list to be more inclusive of measures of clinical significance for serious conditions other than oncology and HIV.

The two statements in Section III.B lines 134-140 seem inconsistent. ARM suggests providing clarification for the rationale of the second statement beginning on line 136 (i.e. why a drug approved under accelerated approval with restricted distribution would be considered available therapy whereas a drug approved under accelerated approval without restricted distribution would not be considered available therapy).

The guidance states that FDA generally intends to interpret the term "serious" consistent with how the Agency has done so in the past (line 63). However, a portion of the preamble to the proposed accelerated approval rule for determination of the seriousness of a condition contained in the 2006 *Guidance for Industry: Fast Track Drug Development Programs —Designation, Development, and Application Review*[1] is omitted. Please include the following excerpt in this guidance to illustrate the broad spectrum of conditions that have been determined to be serious. As discussed in the preamble to the proposed rule on accelerated approval (57 FR 13234, April 15, 1992), determination of the seriousness of a condition:

> ... is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human

[1] http://www.fda.gov/downloads/Drugs/Guidances/ucm079736.pdf, at 4.

> immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes [such as] ... inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases.

Chemistry, manufacturing and control issues are discussed in general terms with an outline of what should be included in a commercial manufacturing program proposal when an expedited designation (namely breakthrough designation) is received. While we understand the need for sponsors to be proactive in identifying and addressing CMC challenges, it would be helpful for the Agency to provide some examples of the types of flexibility that the Agency's quality review and CMC teams may show teams along with possible acceleration strategies, such as deferring certain process validation requirements until post-approval and leveraging the use of comparability protocols. These issues have been discussed by FDA officials as potentially rate limiting for approval and we urge the Agency to consider addressing them in greater depth in the guidance.

In the context of conducting a confirmatory trial to support accelerated approval, the Agency provides an opportunity for the confirmatory trial to be conducted in a population that differs from the population for which accelerated approval was granted. The guidance does not provide adequate information as to considerations that would be the basis for accepting an alternative population from that which the product received accelerated approval. For certain classes of products, an effectiveness study may provide confirmation of the efficacy of the product and may be a more relevant assessment of efficacy for the approved population rather than that of a different population. The Agency should expand on what guiding principles should be used in identification of an alternative population for the confirmatory trial and whether effectiveness studies would be considered an appropriate design for consideration.

In Section IX (starting line 809), in addition to Manufacturing and Product Quality Considerations and Nonclinical and Clinical Considerations, it would be helpful to add considerations or suggestions for incorporation of pediatric requirements into expedited development programs. It would also be helpful to add considerations for gene therapy products that require long-term follow-up for potential delayed adverse events.

The guidance outlines different considerations for what is required to demonstrate "substantial improvement on clinically significant endpoint" (Section VI., A. 4, lines 304-43) for breakthrough designation and "demonstrating the potential to be a significant improvement in safety and effectiveness" (Section VIII, A., 2, lines 778-802) for priority review designation. However, these two standards are similar and the relationship between the two is not discussed adequately. We suggest that the guidance state the products that have breakthrough designation at the time of submission shall also receive priority review designation.

In addition, FDA should consider replacing "would" by "will" or "should" in the following sentence to make it affirmative instead of conditional starting on line 373: "FDA has determined that it *would* be appropriate for the features of fast track designation to be available to a drug designated as a breakthrough therapy (see Section V.B)."

The document says the term *condition* includes a disease or illness; ARM also wants to reinforce that the concepts in the guidance should also be applied to non-disease conditions, such as traumatic brain injury (TBI) or other forms of trauma that are not diseases *per se*. We urge a modification to page 3, Section III.A.1., line 72: "…or the likelihood that the disease *or condition*, if left untreated…"

Regarding Section VII.D.3., line 742 - 743 "Withdrawal of Accelerated Approval": Under this bullet point, it indicates that the designation may be withdrawn if "…The applicant fails to conduct any post-approval trial of the drug with due diligence." This is a potentially vague standard.

In Section V.B.2, line 254 – 257, the wording "the Agency shall evaluate for filing" is not clear. FDA should clarify this wording.

Thank you for the opportunity to comment. ARM looks forward to working with FDA on ways to ensure that safe and effective products reach patients more quickly.