Biotechnology Industry Organization

August 26, 2013

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2013–D–0575: Draft Guidance for Industry on Expedited Programs for Serious Conditions—Drugs and Biologics; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Expedited Programs for Serious Conditions—Drugs and Biologics*. BIO fully supported the expansion and modernization of FDA's Accelerated Approval pathway and the enactment of the new Breakthrough Therapy Designation Process under the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, P.L. 112-144). BIO believes that these and existing expedited approval pathways will help to foster the development of a new generation of modern, molecularly targeted therapies and provide for earlier patient access to safe and effective new medicines.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO compliments FDA on a well-crafted Guidance on Expedited Programs for Serious Conditions. The FDA Draft Guidance will be helpful to stakeholders in explaining the procedures, eligibility criteria, and general features under each of the four expedited programs: Accelerated Approval, Breakthrough Therapies, Fast Track, and Priority Review. The Draft Guidance is an encouraging step in FDA's implementation of these programs under FDASIA. We welcome an ongoing dialogue with FDA to further evaluate the scientific and medical considerations underlying each respective approval pathway and how to encourage the use of these programs for a broad array of serious and life-threatening diseases and conditions.

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BIO is pleased to provide several general comments on the issues raised by the Draft Guidance, as well as specific line-by-line comments. In particular, we encourage FDA to:

- Elaborate upon the enhanced flexibility provided by FDASIA for Accelerated Approval
- Address unique issues associated with rare diseases under Accelerated Approval
- Establish a systematic framework and evidentiary criteria for discussing Accelerated Approval and endpoint selection earlier in drug development
- For Breakthrough Therapies and expedited program products with companion diagnostics, involve Center for Devices and Radiological Health (CDRH) senior staff in cross-disciplinary engagement during drug development
- Adopt a risk-based, life-cycle approach to review of Chemistry, Manufacturing, and Controls (CMC) data and inspectional activities

A. ACCELERATED APPROVAL:

1. FDASIA Provides FDA and Sponsors with Greater Flexibility than Characterized in the Draft Guidance

BIO was pleased to work with FDA, Congress, and patient stakeholders on the expansion and modernization of Accelerated Approval under FDASIA (Sec. 901). BIO believes the law, both in language and in intent, provides FDA and Sponsors with additional clarity and enhanced flexibility needed to apply the pathway to a broad range of indications using surrogate and intermediate clinical endpoints developed using 21st Century scientific tools and methodologies.

In particular, Congress encouraged FDA "to implement more broadly, effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate." Congress also expressly recognized that this expanded approach "may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs." Through these amendments, Congress intended to "enhance the authority of the FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions."

However, the Draft Guidance appears to understate the degree of enhanced flexibility afforded by the FDASIA provisions. For example, line 444 states that "The FDASIA provisions facilitate *somewhat* broader use of accelerated approval to expedite patient access to important treatments for serious conditions" (emphasis added). The guidance also does not consistently or adequately explain how

FDASIA broadens the program, for example, by clarifying how the available therapy standard is considered relative to the severity, rarity, or prevalence of the condition, how the program applies to rare diseases, or how combinations of drugs would be eligible.

To facilitate such a broader assessment, BIO developed a white paper included in Appendix A of these comments that outlines the key statutory changes made to Accelerated Approval under FDASIA and discusses the intent of these revisions and implications for implementation. Taken in total, it is our view that FDASIA provides significantly broader discretion to utilize these authorities in a variety of serious diseases and conditions. It is our hope that FDA will find the paper useful as the Agency revises the Draft Guidance and continues to put the FDASIA Accelerated Approval provisions into practice.

2. Accelerated Approval Now Balances the Severity, Rarity, or Prevalence of the Condition and the Availability or Lack of Alternative Treatments

As a fundamental premise, biotechnology companies are committed to addressing unmet medical needs for patients and discovering and delivering new therapies to patients with few or no alternative medical options. In that spirit, we agree that unmet medical need is an important concept underlying FDA's expedited approval pathways.

Prior to enactment of FDASIA, FDA regulations addressed "Accelerated Approval of New Drugs for a Serious or Life-Threatening Condition," but there was no statutory language authorizing an Accelerated Approval pathway per se, separate and apart from the Fast Track statutory provision, which made a condition of eligibility that the drug address an "unmet medical need." FDA's own regulations also required that a drug candidate "provide meaningful therapeutic benefit to patients over existing treatments" to be eligible for Accelerated Approval. This restrictive approach led to the imposition of often unduly burdensome obligations – such as comparative head-to-head trials – that undermined the very purpose of this expedited pathway and prevented many therapies and disease areas to qualify, especially for rare diseases.

FDASIA addresses this restrictive reading and expands the availability of the Accelerated Approval pathway. Section 901 of FDASIA codifies Accelerated Approval as a separate pathway, regardless of whether there is a Fast Track designation. "Unmet medical need" remains an important general concept for innovative drug development, but as a matter of statutory construction, it is no longer an explicit eligibility criterion for Accelerated Approval. "Availability or lack of alternative treatments" remains a statutory consideration, although it is not dispositive in determining whether a drug candidate is eligible for the Accelerated Approval pathway.[1] Rather, it is a factor to be balanced along with other factors

[1] We note that, in several places within the Draft Guidance, FDA continues to inaccurately refer to "unmet medical need" as a condition or qualifying eligibility criterion for Accelerated Approval. See, e.g., Lines 482-483 ("accelerated approval is limited to a drug … which appears to provide some meaningful advantage over available therapy"); Line 213 (chart lists same language as a "qualifying criteria" for Accelerated Approval). These references should be corrected in the final guidance.

such as the severity, rarity, or prevalence of the condition when determining whether to grant Accelerated Approval in a particular case.

FDA acknowledges in the Draft Guidance that the new statutory language "may reasonably be interpreted as providing additional flexibility as compared to the regulations," and affirmatively notes that "[s]ection 506(c) broadens use of the accelerated approval pathway to cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective" (Lines 497-501). BIO agrees with this interpretation as far as it goes, but notes that it may be too restrictive if it is meant to signal that the broader use in such particular cases is the only additional flexibility granted by the statute. These important statutory changes should not be minimized; rather, they should be embraced in the Final Guidance and in FDA's relevant regulations.

Specifically, FDA's Accelerated Approval regulations at 21 C.F.R. 314.500 and 21 C.F.R. 601.40 should be revised to reflect that the statute no longer requires as a condition of eligibility for Accelerated Approval that an unmet medical need or "meaningful therapeutic benefit . . . over existing treatments" be demonstrated.

FDA's Draft Guidance must also be revised to reflect these FDASIA changes. BIO's proposed revisions are set forth in detail in the attached chart in the section on "Accelerated Approval" (lines 213 and 440-505).

3. The Draft Guidance Should explicitly Discuss Accelerated Approval for Rare Diseases

BIO also believes that the Accelerated Approval pathway holds great promise for ushering in a new generation of orphan drug products to patients suffering from rare diseases. In fact, FDASIA specifically directs FDA, in developing this guidance, to "specifically consider issues arising under the accelerated approval and fast track processes…for drugs designated for a rare disease or condition," and to "also consider any unique issues associated with very rare diseases" (Sec. 901 (c)(1)).

BIO observes that the Draft Guidance fails to mention rare diseases or discuss how the revised pathway can apply to these rare conditions. It also does not address how flexibility can be applied to cases where small patient populations can benefit from this pathway.[2] This suggests that the FDA guidance is interpreting the Accelerated Approval pathway to apply in the same manner to all conditions that meet the eligibility criteria. However, the very use of the term "rarity" under FDASIA reinforces Congressional intent that FDA should more broadly apply the Accelerated Approval pathway to rare diseases, including low prevalence populations, low prevalence or enriched subpopulations, and genomic subpopulations. In finalizing the guidance, BIO urges FDA to address the unique aspects of rare diseases specifically in this context.

Many rare disease stakeholder groups have been thought leaders on how expedited approval pathways, including Accelerated Approval and Breakthrough

[2] The guidance only mentions 'rarity' in the context of a quote from FDASIA on Line 437

Therapy designation, can apply to rare diseases and orphan products.[3,4] We suggest that the final guidance evaluate stakeholder feedback and suggestions and include more examples of how Accelerated Approval has been and can be used to expedite treatments for rare diseases.

The current Draft Guidance does not address the definitions and thresholds associated with "rarity." Such definition and thresholds for rare diseases are critical for at least two reasons. The first is the need for clarity and consistency among different review divisions as to the number of patients in requests for Expedited Program designations. The second urgent need is for these definitions and thresholds to be consistent across different International Conference on Harmonisation (ICH) regions. The FDA should lead an effort to harmonize these definition and thresholds throughout the ICH regions.

4. Systematic Scientific Framework for Endpoint Selection

We suggest that the Guidance provide a list of possible criteria or a framework to define more clearly the degree of evidence and robustness of data required to justify whether the surrogate or intermediate clinical endpoint is predictive of clinical benefit. This would provide greater consistency and clarity for Sponsors evaluating novel endpoints for use under Accelerated Approval, while maintaining FDA's flexibility to consider various types of evidence to support a particular endpoint.

This Draft Guidance reinforces the idea that proposals for use of surrogate endpoints need to be assessed on a case-by-case basis, with no uniform scientific framework included in the Guidance to specify the types of nonclinical and clinical data that could support the use of surrogate and intermediate clinical endpoints. A statement such as "whether a drug effect on a given endpoint is reasonably likely to predict clinical benefit is a matter of judgment," is not likely to lead to a rigorous scientific framework for the development of surrogate endpoints for accelerated approval of drugs to treat rare diseases.

FDASIA's intent was to address this framework to allow all the scientific data to contribute to the assessment of proposed surrogates. For example, FDASIA states that FDA shall "establish a program to encourage the development of surrogate and clinical endpoints, including biomarkers, and other scientific methods and tools that can assist the Secretary in determining whether the evidence submitted in an application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist." FDASIA further clarifies that FDA may rely upon "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools" as evidentiary criteria to justify the

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[3] EveryLife Foundation for Rare Diseases, "*Accelerated Approval for Rare Diseases: Recommendations on Guidance for Industry for Qualifying Biomarkers as Primary Endpoints in Pivotal Clinical Studies" May 2013* ,http://www.everylifefoundation.org/wp-content/uploads/2013/06/White-Paper-V12-CLEAN.pdf

[4] National Organization for Rare Diseases, *Landmark NORD Study Concludes FDA is Flexible in Reviewing Therapies for Rare Diseases,* October 2011, http://www.rarediseases.org/news-events/news/fda-flexibility-2011

use of a surrogate or intermediate clinical endpoint. (See generally FDASIA Sec. 901.)

The Draft Guidance does not support this intent of FDASIA to establish nonclinical and clinical evidentiary criteria under an established framework to develop new endpoints, and would seem to leave the current practice at FDA regarding Accelerated Approval for rare disease therapies essentially unchanged. BIO proposes the inclusion in this guidance of text that clearly considers the evidentiary standards needed for the acceptance of surrogate and intermediate clinical endpoints for the Accelerated Approval of drugs to treat rare diseases and other serious and life-threatening conditions. We welcome an ongoing dialogue with the Agency around the specifics of such evidentiary criteria for endpoint selection.

5. The Role of Intermediate Clinical Endpoints Should be Further Clarified

BIO appreciates that FDA acknowledges the elevated emphasis of intermediate clinical endpoints under Accelerated Approval. Because BIO members and FDA have mutually limited experience with Accelerated Approvals based on intermediate clinical endpoints, we look forward to an ongoing dialogue with the Agency to clarify further how the endpoints can be consistently utilized under Accelerated Approval, how this can be made clearer in the Guidance.

Accelerated Approval is based on a determination that the product's effect on a surrogate endpoint is "reasonably likely to predict clinical benefit," and the new statutory language provides for more expansive use of non-surrogate clinical endpoints as the basis for granting Accelerated Approval. Specifically, the new language expressly authorizes FDA to grant Accelerated Approval based on the use of clinical endpoints that can be measured earlier in the development process than irreversible morbidity or mortality, and that are reasonably likely to predict an effect on irreversible morbidity or mortality *or other clinical benefit*.

For instance, the President's Council on Science and Technology has cited the following examples of "intermediate" clinical endpoints that could be utilized under an expanded Accelerated Approval pathway.[5]

- "Using improvement in minimal cognitive impairment in likely early-stage Alzheimer's patients as a predictor of delayed progression rather than waiting to assess progression.
- Using improvement in isolated muscle strength in patients with muscular dystrophy as a predictor of benefit, rather than waiting to assess overall deterioration of the patient.
- Using clearance of drug-resistant organisms as a predictor of likely clinical benefit, rather than waiting to measure overall survival rate.

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[5] President's Council on Science and Technology (PCAST), *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation*, September 2012, http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

- Using measures of the amount of air that a patient can exhale by force (a measure of lung capacity known as forced vital capacity) or functional motor tests as an endpoint for predicting a drugs' likely impact on 2 serious diseases lacking good treatments: spinal muscular atrophy, a genetic neuromuscular disease, and amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease."

Other examples of intermediate clinical endpoints may include:

- Reduced kidney function in various kidney diseases, which typically only leads to frank kidney failure over a decade or more; and

- Total kidney volume in polycystic kidney disease - this is a very slowly progressive disease is which the kidney expands and causes a series of progressively worsening symptoms based on expanded volume.

These examples represent "intermediate" clinical endpoints in terms of the speed and efficiency with which therapeutic intervention can be measured and evaluated. However, they are also viewed as neither a surrogate endpoint nor a "hard" clinical endpoint, such as kidney failure or survival. These types of intermediate clinical endpoints are important in that they can be measurable and evaluable earlier, which makes drug development more feasible, faster and more efficient than use of a traditional endpoint that may develop much later in the course of a given disease in a clinical trial.

Under the previously existing law and regulations, there have been few submissions or Accelerated Approvals based on the use of clinical endpoints largely because the statutory framework was unclear and FDA regulations and practice took a narrow approach to the use of such endpoints.

In this respect, the Congressional "findings" that accompanied the FDASIA statutory changes are instructive. They direct the FDA to "implement more broadly effective processes for the expedited development and review of innovative new medicines…using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate." In particular, Congress recognized that this expanded approach "may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs." Through these amendments, Congress intended to "enhance the authority of the FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions."

FDA's regulations and existing guidance should also be revised with regard to the expansion of the "clinical endpoint" provisions. Specifically, 21 C.F.R. 314.510 and 21 C.F.R 601.41, which currently refer to approval based on "an effect on a clinical endpoint other than survival or irreversible morbidity" must be revised to reflect the new statutory language, "effect on a . . . clinical endpoint *that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or morality or other clinical benefit.* . ." *i.e.*, the connection between an observed clinical endpoint (demonstrated

through adequate and well-controlled clinical trials) and the ultimate clinical benefit of a drug may be based on the same "reasonably likely to predict" standard applied to surrogates, and the types of evidence that can support such linkage now expressly include non-clinical data (see below).

And lastly, as discussed in the previous section, it is important that FDA work with stakeholders to develop a uniform scientific framework that specifies the types of nonclinical and clinical data that could support the use of novel surrogate and intermediate clinical endpoints under Accelerated Approval. FDASIA specifically states that evidence to support the use of surrogate or intermediate clinical endpoint may include non-clinical or clinical evidence such as epidemiologic or other evidence developed using biomarkers or other scientific methods or tools.

6. Clear Process for Seeking Accelerated Approval early in Drug Development

We recognize that the Draft Guidance "encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of the drug for accelerated approval, proposed surrogate or intermediate clinical endpoints, clinical trial designs, and study planning and conduct of confirmatory trials (lines 470-472). However, we suggest that FDA also create a clear process to facilitate and document a discussion of an Accelerated Approval development program prior to and after Investigational New Drug (IND) application submission. The Draft Guidance includes appendices outlining the process for seeking designation during drug development for Fast Track, Breakthrough Therapy, and Priority Review, but noticeably absent is a systematic, formalized framework for discussing the use of Accelerated Approval as the basis of approval and the selection of clinical trial designs and surrogate or intermediate clinical endpoints.

We suggest that FDA expand upon this provision and include a procedural section in an Appendix regarding the process for seeking Accelerated Approval. As discussed above, this could include a framework for the scope of evidence used to support Accelerated Approval, rather than on a case-by-case review basis, as is the current practice. Additionally, this framework could include a specific section of what is required to use novel surrogate and intermediate endpoints and the qualification criteria for using them. Finally, this framework could include a section clarifying the degree of data required to consider an endpoint "validated," thereby supporting traditional approval versus the degree of data to consider a biomarker qualified to justify Accelerated Approval.

B. BREAKTHROUGH THERAPY DESIGNATION:

7. Early Discussion of Breakthrough Therapy Designation Potential

BIO suggests that the Guidance should elaborate on the process for discussing potential submissions for Breakthrough Therapy designations. For example, leadership of FDA's Office of Oncology and Hematology Drug Products recently stated that staff advise companies who plan to file for a Breakthrough Therapy designation in cancer to call the office first and schedule a conference call in order

to avoid a situation where designation would not be granted because the company is submitting applications too early and without sufficient data.[6] This type of early and informal advice would help to reduce the workload burden on the Medical Policy Council from premature designation requests that are not ready for review.

8. Process for Cross-Disciplinary, Senior Leadership Involvement in Communication during Development

BIO appreciates the Medical Policy Council's engagement in the Breakthrough Therapy designation process to ensure senior level input. FDA should also adopt a structured process to continue to facilitate senior level input throughout the development process for Breakthrough Therapies that is transparent to the Sponsor. Senior managers and experienced reviewers working in a collaborative, multidisciplinary environment are key to the exchange of information between Sponsor and review team that is timely, efficient, and effective and ultimately will foster innovative drug development. As noted in our comments on cross-Center coordination later in the "General Considerations" section of this document, this approach would include staff from FDA's Center for Devices and Radiological Health to discuss issues related to the expeditious development and approval of companion diagnostic and combination products. We also have provided comments in that section regarding the need for additional consideration by CDRH to ensure that the review and approval of the companion diagnostic would not become a rate-limiting factor for the development of the Breakthrough-designated therapy.

As part of a structured approach on Breakthrough Therapy designation, BIO encourages FDA to consider providing additional detail, in this or subsequent guidance, on the criteria for obtaining Breakthrough Therapy designation. BIO also believes that negative decisions on Breakthrough Therapy designation should be communicated to the Sponsor in writing, with a detailed explanation of FDA's rationale and recommendations on what criteria for efficacy, safety, or other related patient benefit would need to be met to obtain the designation.

9. The Draft Guidance Should Expand Upon the Various Clinical Trial Design Options Available to Sponsors to Expedite Drug Development

We welcome additional clarity on the various clinical options available to Sponsors post-designation to expedite drug development through novel clinical trial designs and approaches. While primary features of the Breakthrough Therapy program include intensive meetings with FDA and organizational commitment to senior managers, these features are merely a means to an end – a more efficient drug development program 'to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment" (FDASIA, Sec. 902). While it is incumbent on the Sponsor to be prepared to discuss with FDA options for streamlining clinical development on a case-by-case basis, we believe

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[6] Forbes, *"The FDA's Cancer Czar Says He Can't Approve New Drugs Fast Enough",* June 23, 2013, http://www.forbes.com/sites/matthewherper/2013/06/23/the-fdas-cancer-czar-says-he-cant-approve-new-drugs-fast-enough/

the Guidance also should provide additional insights on various non-traditional development programs.

The Draft Guidance briefly mentions some of these potential options as "alternative clinical trial designs (*e.g.*, adaptive designs, an enrichment strategy, use of historical controls) that may result in smaller trials or more efficient trials that require less time to complete." (lines 393-395) We encourage FDA to expand upon the Draft Guidance to provide additional examples of alternative trial designs and the relative applicability and merits of each.

Examples for alternative clinical trial designs previously discussed in the Enrichment Guidance published last year represent an excellent baseline for a discussion in the Expedited Programs Guidance. These include the integration of genotypically defined patient populations into larger, phenotypically defined populations that allow properly powered clinical studies. The Expedited Programs Guidance should also discuss clinical study designs, such as crossover and N-of-1 studies, often needed for product registration of rare disease therapies. Future Guidance should also address the use of novel technologies available for continuous and/or home patient monitoring for clinical endpoints, which currently require visits to clinical sites by patients. These technologies are particularly critical in the development and registration of neurodegenerative disease therapies and in many rare disease therapeutic product development programs

FDA also mentions historical controls in this Draft Guidance. However, it has not been clear in practice how and when FDA will accept historical controls and what is required for submission. We welcome additional clarity on this, as well as FDA Guidance on the use of historical controls and alternative clinical study designs.

In addition, we recommend that the Guidance cross-reference recent FDA Guidances on these approaches and that FDA to finalize Draft Guidances on these topics as soon as practicable.[7,8]

Lastly, it is important that the Guidance provide information on how increased interactions between FDA and Sponsors, along with the ability to develop streamlined clinical development programs go beyond such approaches available to drugs eligible for Fast Track. We do not believe that this omission in the Draft Guidance implies that FDA is suggesting that only Breakthrough Therapy designated-products can use novel clinical designs, but it would be helpful if the Guidance clarified this aspect. Additionally, one of the benefits of Fast Track is increased interactions with FDA, and the Guidance should provide information assuring Sponsors that this feature of Fast Track is maintained.

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[7] FDA Draft Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics, December 2010, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf

[8] FDA Draft Guidance for Industry, *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*, December 2012, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf

10. Withdrawal of Designation and Continued Designation

The current language in the Draft Guidance is not sufficiently clear on the process for loss of a Breakthrough Therapy designation. We suggest that the Draft Guidance provide more detail on the process for losing the Breakthrough Therapy designation, including timelines, probationary periods, and review standards.

We understand that the Medical Policy Council will review the continuation of Breakthrough Therapy designation; additional details on the process for this review would be useful. We recommend that FDA provide specific timelines on when it will notify a Sponsor of a Breakthrough Therapy that it is no longer considered Breakthrough-designated due to the approval of another therapy.

FDA may also want to consider introducing a "probationary period" prior to potential withdraw of Breakthrough Therapy designation to preserve active information sharing and data collection, while maintaining the integrity of the development program.

C. FAST TRACK:

BIO would like to have the Guidance more clearly articulate how Fast Track designation will expedite both the development and the review process. This can be accomplished through more frequent interactions with FDA during development and a commitment to review sections of an application if they are submitted through rolling review. These interactions and rolling review will likely lead to optimized drug development and timely reviews, as the Agency will be closely involved in drug development in real-time.

Since one of the features of Fast Track is a rolling submission/review of the New Drug Application (NDA) or Biologics License Application (BLA), we would recommend that FDA commit to reviewing the application under Fast Track as sections are submitted – especially since the Sponsor pays the user fee with the first submission. The Draft Guidance currently states that FDA is not committed to start the review until receipt of a complete submission. FDA indicates that actual commencement and scheduling of review depends on many factors, including staffing, workload, competing priorities, etc. We believe that the intent of the Fast Track provisions is for FDA to start the review prior to a complete submission and address other factors so this can be accomplished. Timelines can be discussed and agreed to at the time of a pre-NDA/BLA meeting. This should be spelled out in Part D of Appendix 2.

We also suggest that FDA consider updating related Manuals of Policies and Procedures (MAPPs) to outline specifically what the Agency will do differently under Fast Track (as opposed to conventional review).

Finally, BIO sees one of the main benefits of Fast Track designation to be more frequent formal and/or informal interactions with the Agency. BIO would like to see the Guidance more concretely discuss how having Fast Track designation will lead to more frequent interactions between the Sponsor and FDA.

D. GENERAL CONSIDERATIONS:

11. The Guidance Should Elaborate on the Cross-Center Process for Expedited Approval of Companion Diagnostics

Diagnostic products "intended to diagnose or detect a serious condition" represent an area that would benefit from additional guidance in either this or a subsequent Guidance document. Specifically, BIO encourages FDA to elaborate in the Guidance on the process for cross-Center collaboration for companion diagnostics and combination products under expedited programs, including Breakthrough Therapies and Accelerated Approval. CDRH plays a primary role in the approval of diagnostic tests, and, therefore, BIO encourages FDA to ensure the coordination of processes in CDRH, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) as regulatory policy evolves. Such coordination will ensure consistent and standardized approaches across Centers, which will facilitate the advance of personalized medicine and innovative targeted therapies. A high percentage of targeted biologic therapies and oncology treatments under development and potentially eligible for expedited programs are being paired with companion diagnostics, which will necessitate a coordinated approach between two or more Centers in many instances.

In particular, BIO recommends that FDA specifically include CDRH staff and senior managers on the cross-disciplinary teams established to accelerate the development of a Breakthrough Therapy. Such an approach – with identified single points of contact for review of the diagnostic (CDRH) and the therapy (CDER/CBER) – will allow the needed coordination to occur on pre-approval inspection plans for both the therapeutic clinical and diagnostic manufacturing sites and advisory committee meeting plans, if one is needed, and for joint communication and discussion of PMRs and PMCs. It would also be helpful if the Agency were to make available best practices for contemporaneous development of drug and diagnostic products, including expectations for Sponsors, as well as detailed process charts that clearly outline the roles, responsibilities, and interactions between CDRH and CDER/CBER staff.

For example, in the section "*Organizational Commitment Involving Senior Managers* (line 404-420), it should be explicitly stated that the suggested members of the cross-functional review team should include staff from CDRH if there is a companion diagnostic. CDRH engagement is critical and in agreement with the current Draft Guidance which indicates the importance of a Sponsor being prepared for other aspects of drug development, including "development of a necessary companion diagnostic." (Line 402)

In addition, it would be helpful if the Agency would issue separate guidance clarifying how diagnostic products under CDRH jurisdiction might be developed under an Expedited Program for Serious Conditions using a risk-based approach for identifying which diagnostic-related requirements might be deferred to post-marketing to facilitate expeditious patient access to the therapeutic. Among some of the specific proposals for contemporaneous companion diagnostic development that FDA should consider if paired with a Breakthrough Therapy are:

- Automatic determination that a companion in-vitro diagnostic (IVD) device for use with a Breakthrough Therapy or drug under Accelerated Approval is eligible for CDRH *priority review.*

- Development by CDRH of a distinct regulatory pathway for companion IVDs similar to that used by CDER for the Breakthrough-designated therapy that would utilize administrative and management strategies and efficiencies to expedite the review (*i.e.*, involvement of senior management, participation in multi-Center cross disciplinary review teams for closer collaboration and coordination between centers, designation of a cross-disciplinary project lead, determination of whether an IND is required in addition to the Investigational Device Exemption (IDE) application, etc.).

- Use by CDRH of risk-based approaches to determine the essential requirements that would be necessary at the time of Pre-market Approval Application (PMA) filing for data and testing related to quality systems, manufacturing processes and software testing and documentation.

12. The Draft Guidance Should Expand on Manufacturing Requirements that Can Be either Accelerated in the Pre-Market or Deferred to the Post-Market

Many expedited development programs can be sought early in drug development, when most companies do not yet have a plan for commercial manufacturing. It is important the FDA and Sponsors coordinate on a mutually acceptable strategy to ensure that an expedited manufacturing program can keep pace with an accelerated clinical program. As noted in the Draft Guidance, the anticipated manufacturing development program could differ based upon the specific expedited development program selected, and the phase of clinical development. We encourage FDA to provide examples that FDA may potentially find acceptable from a CMC perspective to expedite drug development. It may be useful to include scenarios in this guidance or an appendix to the Guidance to help guide manufacturing proposals.

BIO recommends that FDA and Sponsors collaborate to develop a lifecycle management approach for the product and consider both the pre-market and post-market considerations around CMC and manufacturing requirements. This Post-approval Lifecycle Management Plan (PALM) would facilitate responsible product development, FDA evaluation and approval, and patient access to the Breakthrough Therapy-designated product and other expedited approval therapies with an agreed upon path forward for product-lifecycle management that is most desirable for patients seeking access to high quality, Breakthrough Therapies.

Pre-Market CMC Considerations:

BIO recommends that FDA consider risk-based approaches for review of CMC data and for inspectional activities. We suggest the following scenarios be considered as an example for inclusion in a manufacturing development appendix:

- Recommend that for a Breakthrough Therapy, the NDA can be filed with less than 12 months formal stability data on three primary batches. For example, this could include 6 months real time stability data for drug product. Initial product shelf life can be assigned based on a combination of available formal stability data and alternate approaches, such as data from earlier development batches as well as accelerated stability programs.

- Since technology transfer from development to commercial manufacturing requires time to understand and address potential scale-up issues, consider allowing launch of the first commercial batch(es) from manufacturing sites used to supply clinical material without a fully validated process. This could be done with a commitment to complete process and cleaning validation at the commercial sites within a specified number of months after approval.

- In situations where transfer of the manufacturing process to the commercial manufacturing site occurs in time for submission, consider acceptance of concurrent release of process performance qualification (PPQ) batches into commercial distribution prior to completion of validation activities.

- Complete inspections of the proposed commercial sites from an overall quality systems management (ICH Q9, Q10) point of view vs. validation of the specific product (Prior Approval Inspection (PAI)) point of view for simple solid oral dosage forms, such as tablets and capsules. This approach would simplify and lessen the burden of PAI issues at the time of submission. Such inspections can be done 6-12 months prior to the NDA submission and discussed at the same time as Breakthrough designation is being sought from FDA.

- Develop a mechanism for early engagement to align on CMC strategies for Breakthrough Therapies (as early as EOP2). Ideally meetings would include relevant staff from the Office of New Drugs (OND), the Office of Compliance (OC), and the Office of Regulatory Affairs (ORA), as appropriate to address both review and compliance issues. Frequent interactions to discuss potential manufacturing and control issues as they arise can enable more efficient and successful review of NDA submission and successful PAI activities.

Review Period Considerations:

- Additionally, as filing issues related to the submission of a complete application are generally discussed at the pre-NDA/BLA submission meeting, we would encourage FDA to provide feedback earlier, if possible, on potential elements of the CMC section that could be provided within a specified time after filing without negatively affecting the review clock (*e.g.*, human factor summative study, additional stability data).

- We would encourage FDA to commit to reviewing complete sections of the CMC submission as soon as possible and providing feedback to the Sponsor as soon as those sections have been reviewed.

- As Sponsors are prepared for earlier inspections for drugs developed under expedited programs, we would encourage that the scheduling of inspections to occur earlier during the development cycle, especially when various portions of the CMC section are submitted prior to complete NDA submission.

Post-Market CMC Considerations:

In addition to more frequent communication with Sponsors on manufacturing issues, we request that FDA clarify those aspects of manufacturing development that could be negotiated with the Sponsor for completion either during review of the marketing application or as part of a post-approval commitment. This should include the use of a Post-approval Lifecycle Management Plan (PALM) that would be part of the marketing application and provide detailed timelines, deliverables, and types of regulatory filings for completing activities, such as:

- Scale-up Phase III clinical lots to commercial scale for launch with a bridging comparability study

- Launch from a clinical site with clinical Quality Control (QC) release, and transfer to a commercial site and commercial QC post-approval.

- Launch with a provision control system that ensures consistent product followed by upgrades to the control system post-approval after the Sponsor has gained additional manufacturing experience and has completed all aspects of process validation (*e.g.*, filing with more tests initially and justifying elimination of some post-approval, filing with broader IPC and product specification acceptance criteria and tightening specifications that demonstrate process consistency post-approval)

- Launch the commercial process with limited experience and optimize post-approval with a comparability protocol and in vitro/in vivo correlation model as a biomarker for making changes to a small molecule drug post-approval.

- Launch with Phase I to Phase II formulation and optimize post-approval with a comparability protocol and in vitro/in vivo correlation model as a biomarker for making changes to a small molecule drug post-approval.

- Launch with reduced real time stability for commercial material and leverage stability from development lots and predictive modeling of small molecule degradation profiles.

- Leverage life-cycle validation principles “continued verification” to release batches concurrent with manufacture of initial conformance batches.

We recommend the Guidance indicate that FDA is willing to work with a Sponsor to ensure flexibility of its Pharmaceutical Quality System to accommodate the accelerated manufacturing development activities for a Breakthrough product.

13. Potential Abuse Liability Issues

Products that FDA has recommended for scheduling due to their potential for abuse require further review by agencies external to FDA (*i.e.,* National Institute on Drug Abuse (NIDA) and Drug Enforcement Agency (DEA)), which ultimately leads to scheduling by the DEA. These reviews, particularly by the DEA, typically begin after FDA approval, and lead to delays in a manufacturer's ability to market the product. We encourage FDA to open a dialogue as soon as possible with those

other agencies regarding products with potential abuse liability issues that are developed or reviewed under expedited programs. We recommend that FDA provide a commitment in the Guidance to work with other agencies, particularly DEA, as soon as possible to minimize potential delays in the availability of these products due to scheduling issues. Additionally, we recommend that FDA expedite the Agency's internal abuse liability assessment of these products, so that FDA's scheduling recommendation is completed and forwarded to DEA prior to product approval. This timing is critical to avoid, or at least minimize, delays in the availability to patients of important new treatments.

14. Global Harmonization and Convergence

We recommend that FDA become a change agent for global harmonization regarding expectations for data requirements for expedited programs. International divergence on standards for expedited approval creates significant inefficiencies for product development if the Sponsor is required to conduct a single expedited development program for the U.S. and a separate, traditional development program for Europe and other ex-U.S. regions. To the extent practicable, regulatory authorities and Sponsors should strive for a single, expedited clinical development program to demonstrate the safety and effectiveness of a product for a serious and life-threatening condition. Additionally, for companies to utilize their global facilities more effectively and efficiently, the FDA needs to align more with the European Medicines Agency (EMA) and other regulators at this early stage of manufacturing.

One idea, as a starting point, would be a mutual points-to-consider document with the EMA that links into specifics on data expectations for key areas such as historical controls, control groups, rare diseases, long-term outcomes data, CMC attributes such as those listed above, and inspections scheduling/certification. While increasing use of the joint regulatory advice option between the FDA and EMA would be a valuable intermediate step to facilitate harmonization, it would also be useful to initiate an ICH harmonization process for Expedited Programs. Such an process for expedited programs could address issues in the FDA, EMA and the Japanese Pharmaceutical and Medical Devices Agency (PMDA), where there is a common intent in all three ICH regions regarding the goals of Expedited Programs, but where individual process differences among the three regions prevent coherence in product development plans and lead to different submissions in the three regions.

E. CONCEPTS FOR EXPEDITED PROGRAMS

15. Available Therapy Exception for Unapproved Therapies

We note that this Guidance supersedes FDA's 2004 Guidance on Available Therapy,[9] construing FDA policy on the terms and definitions for "*available therapy"* and related terms, such as "*existing treatments"* and "*existing therapy."* However, FDA's stated exception to call, in rare cases, drugs or regimens that are

[9] FDA "Guidance for Industry: Available Therapy", July 2004, Section IV. POLICY: DEFINITION OF AVAILABLE THERAPY, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf

not approved for the relevant indication "available therapy" cuts against the premise that drugs should be proven to be safe and effective. It would be difficult or impossible to predict when FDA would apply this policy, and designing clinical trial programs against unapproved therapies would be a significant challenge. Furthermore, should this policy be adopted, the meaning of "compelling evidence" for unapproved or unlicensed therapies is not clear or predictable.

It is critical that for each of the expedited pathways the emphasis be placed on ensuring expeditious access by patients to innovative drugs. Each pathway calls for a balancing test examining factors such as meeting unmet medical needs with the severity and rarity of the disease or condition, and availability of treatments. This examination and balance should be based on the needs of patients and on scientific and clinical data – not on questions of assumed comparative effectiveness.

We recommend that FDA remove this exception for unapproved therapies to qualify as "available therapy," or, at minimum, clearly define a narrow set of conditions under which unapproved therapies can be considered "available therapy." For example, FDA could include the following text from the 2004 Available Therapy Guidance in the 2013 Expedited Programs Guidance:

> *"Most of the Agency programs that use the term available therapy are intended to encourage the development and expedite the review of innovative drug products. By defining available therapy to focus on approved products with labelling for use in the disease or condition at issue, FDA (1) emphasizes the importance of the approval process for establishing that a drug is safe and effective for a particular use and (2) provides the greatest opportunity for development and approval of appropriately labelled drugs. For these programs, products that are used off-label for the indication at issue and products that have not had formal FDA review are rarely considered available therapy; the definition of available therapy in this guidance provides only a limited exception for particularly well-documented therapies"*

Lastly, BIO would like to suggest that in cases where there is no well-established and documented standard of care (SOC) that FDA, in addition to consulting special government employees or "other experts," consult patients and patient organizations to ensure consideration of the patient perspective on available treatments. BIO would also like FDA to expand on the statement that FDA considers the SOC for the broader population when determining availability of treatments even in the case of a drug that is designed to target a subpopulation.

16. Determination of the Standard of Care

The Draft Guidance notes that "FDA will determine what constitutes available therapy at the time of the relevant regulatory decision for each expedited program the sponsor intends to use (*e.g.*, generally early in development for fast track and breakthrough therapy designations, at time of biologics license application (BLA) or new drug application (NDA) submissions for priority review designation, during BLA or NDA review for accelerated approval)." (lines 127-133)

BIO recognizes that the SOC may change over the course of time and that the Agency will make the determination on what constitutes SOC. However, a decision of what constitutes SOC is needed much earlier in the development program in the context of designing a phase III clinical trial of the experimental treatment versus the SOC (usually at EOP2). Situations can arise, especially in

studies evaluating long-term endpoints such as irreversible morbidity or mortality (IMM), where the standard of care changes during the conduct of the pivotal study. A regulatory determination of a SOC that represents a moving target subject to unforeseen change can pose a considerable challenge for Sponsors making long-term R&D investments and conducting multi-year clinical trials.

BIO suggests that FDA determine SOC at the time of the relevant regulatory *designation period*.

Alternatively, the Draft Guidance should elaborate upon the process and timing for reassessing the standard of care and notifying Sponsors that have previously received designation for expedited development based upon the previous assessment of the standard of care. FDA may be uniquely positioned to play this role given the Agency's access to other development programs in the same disease space.

CONCLUSION:

BIO appreciates this opportunity to comment on the *Draft Guidance for Industry on Expedited Programs for Serious Conditions—Drugs and Biologics*. Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization

Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 2:	"Expedited Programs for Serious Conditions––Drugs and Biologics" FDA should use "serious or life threatening disease or condition" consistently throughout the Draft Guidance. It is more consistent with the FDASIA statute and less confusing to the public to use exact language.	Suggest renaming Guidance: "Expedited Programs for Serious **or Life Threatening Disease or** Conditions––Drugs and Biologics" Additionally, please make conforming edits on lines 59, and on lines 70-72.
III. CONCEPTS FOR EXPEDITED PROGRAM		
A. SERIOUS CONDITION		
1. Whether a Condition Is Serious		
Line 70:	"but the morbidity need not be irreversible if it is persistent or recurrent."	Change to the following to b*roaden the definition of a serious disease or condition by adding in progressive morbidity decline.* "…but the morbidity need not be irreversible if it is persistent, recurrent, **or progressive."**
2. Whether a Drug Is Intended to Treat A Serious Condition		
Lines 93-94:	"A product intended to improve or prevent a serious treatment-related side effect (e.g., serious infections in patients receiving immunosuppressive therapy)" The language should be expanded to consider the potential for a co-development of a drug to mitigate (lower) toxicity cause by the other drug.	"A product intended to improve, **mitigate,** or prevent a serious treatment related side-effect…"

SECTION	ISSUE	PROPOSED CHANGE
Line 96:	In previous Guidance on Fast Track (2006), FDA considered therapies to prevent or treat serious sequelae of nonserious conditions as meeting the "serious condition" eligibility requirement.	Please consider addition of the following text from the 2006 Fast Track Guidance back into the 2013 Draft Guidance: "Many conditions not generally considered to be serious have rare or distant serious sequelae (e.g., urinary tract infections or duodenal ulcers). Product development programs for such conditions could be designated as fast track if the Sponsor specifically designs the development program to demonstrate an effect on those serious sequelae."
B. AVAILABLE THERAPY		
Lines 109-110:	"Approval or Licensure: Only in rare cases will a treatment that is not approved for the indicated use or is not FDA-regulated (e.g., surgery) be considered available therapy." As discussed in our general comments, considering an unapproved therapy to be "available therapy" runs counter to the public health premise that drugs should proven safe and effective.	We suggest removing the allowance for unapproved therapies or qualifying the conditions under which unapproved therapies can be considered "available therapy".
Lines 129-130:	FDA will determine what constitutes available therapy at the time of the relevant *regulatory decision* for each expedited program the sponsor intends to use (e.g., generally early in development for fast track and breakthrough therapy designations, at time of biologics license application (BLA) or new drug application (NDA) submissions for priority review designation, during BLA or NDA review for accelerated approval). *As discussed in our general comments,*	Please replace with "at the time of the relevant regulatory **designation period "** Alternatively, clarify the process and timeline for notifying Sponsors if the SOC shifts prior to product approval.

SECTION	ISSUE	PROPOSED CHANGE
	"Relevant regulatory decision" is ambiguous and subject to unanticipated change. We suggest incorporating a defined time where the status will be determined.	
Lines 134-140:	The first paragraph states that a drug granted accelerated approval is *not* considered available therapy. The second paragraph (starting on line 136), however, implies that a drug granted accelerated approval could be considered available therapy if the drug has a REMS that includes ETASU.	Please clarify whether in determining available therapy, more emphasis is placed on surrogate endpoint being verified for effectiveness or on restricted distribution /REMS for determining safety? Recommend rewording as follows: "A drug approved ~~under accelerated approval~~ with restricted distribution and a drug approved with a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU) under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) would be considered available therapy only if the study population for the new drug **under development** would be eligible to receive the approved drug under the restricted distribution program or ETASU REMS."
Lines 136-140:	*Previous 2004 Available Therapy guidance provided*: "Accordingly, we intend to interpret existing treatment under the accelerated approval regulations to mean, in the context of approval based on a surrogate, a treatment that has demonstrated a clinical benefit under conventional approval standards (21 CFR 314.105, 314.125, 601.2). In the context of a prior approval based on restricted distribution, existing treatment means a treatment approved for the same indication without restricted distribution."	We suggest adding the following clarifying text to align with lines 174-177: "However, in cases where there may be a potential for the new treatment to address an unmet need with similar efficacy without the ETASU REMS/restricted distribution provisions (i.e. safety advantage and/or reduced toxicity), the approved treatment with restricted distribution should not be considered available therapy."

SECTION	ISSUE	PROPOSED CHANGE
	Current Draft Guidance: "A drug approved under accelerated approval with restricted distribution and a drug approved with a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU) under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) would be considered available therapy only if the study population for the new drug would be eligible to receive the approved drug under the restricted distribution program or ETASU REMS." The change in Agency acceptability of this "restricted distribution" from the 2004 guidance could deter development under expedited options for promising drugs that could offer treatment options without any restricted distribution or ETASU REMS. Further clarity should be offered to allow the potential development of promising agents that may not require a restricted distribution utilizing expedited pathways.	
Lines 134-135:	"A drug granted accelerated approval based on a surrogate or clinical endpoint and for which clinical benefit has not been verified is not considered available therapy."	We suggest rewording as follows for clarity: "A drug granted accelerated approval based on a surrogate or **intermediate** clinical endpoint and for which clinical benefit has not been verified **based on appropriate postapproval studies** is not considered available therapy."
C. UNMET MEDICAL NEED		
1. Where There Is No Available Therapy		
Line 152:	"If no therapy exists for a serious condition, there is clearly an unmet	We recommend rewording as follows:

SECTION	ISSUE	PROPOSED CHANGE
	medical need." Available Therapy is a defined term and should be capitalized throughout the Guidance and used exactly to ensure clarity.	"If no **there is no Available T~~t~~herapy ~~exists~~** for a serious **or life threatening disease** or condition, there is clearly an unmet medical need."
2. Where There is Available Therapy		
Lines 162-163	"…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)"	To expand the ability for the new drug to slow disease progression as well as progressive disability, please add the phrase **disease progression** after progressive disability in both locations: "…available therapy (e.g., progressive disability **or disease progression** when the available therapy has shown an effect on symptoms but has not shown an effect on progressive disability **or disease progression**)"
Lines 165-168:	"Has an improved effect on a serious outcome(s) of the condition compared to available therapy (e.g., superiority of the new drug used alone or in combination with available therapy in an active- or historically-controlled trial **assessing an endpoint reflecting mortality or serious morbidity**)" "…assessing an endpoint reflecting mortality or serious morbidity" seems overly restrictive and not with the spirit of FDASIA to provide more flexibility and more focus on intermediate clinical endpoints.	We recommend deleting bolded text so bullet reads as follows: "Has an improved effect on a serious outcome(s) of the condition compared to available therapy (e.g., superiority of the new drug used alone or in combination with available therapy in an active- or historically-controlled trial ~~**assessing an endpoint reflecting mortality or serious morbidity**~~)"
Lines 179-181:	"Provides similar safety and efficacy as available therapy, but with another documented benefit, such as improved	We suggest including the following: "Provides similar safety and efficacy as available therapy,

SECTION	ISSUE	PROPOSED CHANGE
	compliance, that is expected to…" – A therapy like tPA is only used in a small segment of the stroke patient population (~5 – 10%) because of the very short time window for administration (several hours). If you have a therapy that achieves a comparable benefit, but reaches a much broader segment of the patient population, it provides a real benefit.	but with another documented benefit, such as improved compliance, **or the ability to treat a broader segment of the relevant patient population,** that is expected to…"
3. *Where the Only Available Therapy Was Approved Under the Accelerated Approval Program Based on a Surrogate or Clinical Endpoint and Clinical Benefit Has Not Yet Been Verified*		
IV. OVERVIEW OF EXPEDITED PROGRAMS		
Pages 7-8, Line 213 – Breakthrough Designation (BTD)	Qualifying criteria for Breakthrough Therapies: Safety advance listed in guidance isn't listed in table.	Please add safety advance to the table
Pages 7-8, Line 213 - BTD	Under "Features" suggests "beginning as early as Phase 1."	Could the Agency add an example of what constitutes adequate clinical data derived from Phase 1 studies support a BTD for illustration? Please see our additional comments on this issue on line 282.
Line 213 – Accelerated Approval (AA)	As discussed in the general comments, "Meaningful advantage over available therapies" is not a statutory requirement for Accelerated Approval per FDASIA. Rather, FDA must balance "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."	Please strike "~~Meaningful advantage over available therapies~~" and include "**taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.**"
Pages 7-8, Line 213 (table), footnote (b)	"Title VIII of FDASIA entitled "Generating Antibiotic Incentives Now (GAIN)" provides incentives for the development of	Consider adding QIDP designation to this guidance document, particularly if such designation confers no other advantage besides fast track designation and priority

SECTION	ISSUE	PROPOSED CHANGE
	antibacterial and antifungal drugs for human use intended to treat serious and life threatening infections. Under GAIN, a drug may be designated as a qualified infectious disease product (QIDP) if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review. However, QIDP designation is beyond the scope of this guidance." The intent of this guidance document is to create a single resource for programs to "facilitate and expedite development and review of new drugs." As such, it is not clear why QIDP designation is out of scope for this guidance document.	review.
V. FAST TRACK DESIGNATION		
B. FEATURES OF FAST TRACK DESIGATION		
1. Actions to Expedite Development and Review		
Lines 242-246:	"There are opportunities for frequent interactions with the review team for a fast track product. These include FDA-sponsor meetings, including pre-IND, end of Phase 1, and end of Phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, use of biomarkers, and other meetings as appropriate (i.e., to discuss accelerated approval, the structure and content of an NDA, and other critical issues)." This paragraph requires clarity.	We commend the Agency for its efforts in enhancing communication with Sponsors with Fast Track Designation. Historically, Fast Track has not always resulted in frequent interactions between industry and the Agency. We recommend that the FDA have more frequent formal and/or informal interactions with Sponsors for fast track designated products compared with non-FTD products. Informal interactions may include phone calls or email exchanges directly with the review staff, copied to the project manager on a particular program. Additionally, please clarify the additional routes of communication with the Agency in comparison to Breakthrough Therapy Designation.

SECTION	ISSUE	PROPOSED CHANGE
2. Submissions of Portions of an Application (Rolling Review)		
Lines 254-257	As discussed in our general comments, we suggest that FDA should review components of the application as they are submitted.	Please revise the following: "If FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Agency shall evaluate for filing, and ~~may consider~~ **will commit to** reviewing portions of a marketing application **upon submission** before the Sponsor submits the complete application"
VI. BREAKTHROUGH THERAPY DESIGNATION		
A. QUALIFYING CRITERIA FOR BREAKTHROUGH THERAPY DESIGNATION		
3. *Preliminary Clinical Evidence*		
Line 286-289:	"Assessment of the treatment effect for the purposes of breakthrough therapy designation will be based on preliminary clinical evidence, which could include early clinical evidence of both clinical benefit and an effect on a mechanistic biomarker (generally derived from Phase 1 and 2 trials)." Does the biomarker have to be part of clinical evidence? We assume it does not. FDASIA makes no mention of a mechanistic biomarker as having to be part of clinical evidence for breakthrough. Thus, the guidance should be revised to reflect this.	We recommend adding **"with or without"** an effect on mechanistic biomarker "…clinical benefit ~~and an effect~~ ~~on~~ **with or without an effect on a** mechanistic biomarker (generally derived from Phase 1 and 2 trials)."
Lines 282-293:	This section and other related sections in the document indicate that "…breakthrough therapy designation	Additional language that provides greater clarity on how this might be achieved, or how this apparent conflict might be reconciled would be helpful.

SECTION	ISSUE	PROPOSED CHANGE
	requires preliminary clinical evidence of a treatment effect…" However, in other portions of the document, language suggests that a request for breakthrough therapy designation can be made at the time of IND submission (see for example 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 with one another, and some clarity is needed. Note that the apparent conflict 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 use in an entirely unrelated indication that might somehow require a separate IND. Understanding that a request for breakthrough therapy designation may occur at the IND stage, but still requires preliminary clinical evidence (as also stated on page 27 in the Appendix).	
Lines 291-292	Substantial improvement over available therapy should involve a sufficient number of patients to be "considered credible." For orphan products, this may not be possible until the completion of Phase 3 studies.	Please consider revising to specify "sufficient number of **patients based on expected treatable population"** to be considered credible.
Lines 292- 293:	"However, FDA recognizes that the data cannot be expected to be definitive at the time of designation."	Can the FDA clarify in the guidance the expectations about the dose at the time of the designation request? Specifically, is the intended clinical dose expected to be

SECTION	ISSUE	PROPOSED CHANGE
	Clarity regarding dose is needed.	definitive at the time of the request for BTD? This is particularly challenging in the case of a surrogate endpoint, or intermediate endpoint where the disease is prolonged or where there are limited numbers of patients such as in rare diseases. For example: given that early clinical development needed to generate the clinical data and by definition evaluates dose ranges, it would be prudent to mention that the dose chosen for intended breakthrough development has been adequately evaluated or to give some guidance on the expectations about dose at time of submission.
Lines 295- 298:	"Ideally, preliminary clinical evidence would be derived from a study that compares the investigational drug to an available therapy (or placebo, if there is no available therapy) in clinical testing and shows superiority, or from a study that compares the new treatment plus SOC to the SOC alone."	To tie in the types of clinical benefits FDA elucidated in previous sections of the guidance for increased clarity, we recommend rewording as follows: "Ideally, preliminary clinical evidence would be derived from a study that compares the investigational drug to an available therapy (or placebo, if there is no available therapy **or historical controls**) in clinical testing and shows some **clinical benefit such as superiority or improved compliance, toxicity, and/or tolerability;** or from a study that compares the new treatment plus SOC to the SOC alone."
Lines 300-302:	"… (generally, FDA expects such data would be persuasive only if there is a **large difference** between the new treatment and historical experience)." Large difference can be interpreted in different ways so clarity is needed.	Can the FDA provide guidance as to what is a "large difference" between the new treatment and historical experience in the case of rare diseases where comparative data may be challenging and numbers are by definition low? Also, can the FDA provide guidance as to the applicability of the risk-benefit assessment undertaken at the time of a BT application review?
4. *May Demonstrate Substantial Improvement on Clinically Significant Endpoint(s)*		

SECTION	ISSUE	PROPOSED CHANGE
Line 319:	"Approaches to demonstrating preliminary clinical evidence of substantial improvement include:"	We recommend adding a diagnostic bullet where the clinical evidence is considered substantial **when targeted through a companion diagnostic.**
Line 340:	"The new drug reverses disease progression, in contrast to available therapies that only provide symptomatic improvement."	Please add the phrase "or inhibits" to broaden this statement by allowing the new drug to either reverse or inhibit disease progression as opposed to only reversing progression. "The new drug reverses **or inhibits** disease progression, in contrast to available therapies that only provide symptomatic improvement."
Line 342:	"The new drug has an important safety advantage that relates to serious adverse events compared to available therapies and has similar efficacy."	We would welcome additional examples of important safety advantages
Lines 353-355:	"An effect on a surrogate endpoint or intermediate clinical endpoint (see Section VII.B.2) considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)" FDA currently does not make the reasonably likely decision until the review/approval – as previously stated in the document, this would be too late for BT application.	We recommend rewording as follows: "An effect on a surrogate endpoint or intermediate clinical endpoint (see Section VII.B.2) **that may be** considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)"
Line 393-397:	"…sponsor can propose, alternative clinical trial designs (e.g., adaptive designs, an enrichment…"	Would interim analysis of data with use of an external data management board be acceptable? This would allow investigators to use interim data from ongoing trials to achieve breakthrough status without having to design new trials.

SECTION	ISSUE	PROPOSED CHANGE
B. FEATURES OF BREAKTHROUGH THERAPY DESIGNATION		
2. Intensive Guidance on an Efficient Drug Development Program, Beginning as Early as Phase 1		
Line 399:	"FDA anticipates that the review team and the sponsor will meet throughout drug development"	To define the possible amount of communication that can be expected from the FDA, we recommend adding that the **"FDA will be available for more frequent and timely communication."**
5. Organizational Commitment Involving Senior Managers		
Lines 406-414:	As discussed in our general comments, we recommend elaborating on the nature of cross-disciplinary team leads, and include CDRH, DMEPA, and other FDA teams that will be involved. CDRH coordination, in particular, is of high importance.	We suggest further detail regarding cross-disciplinary collaboration, particularly with CDRH coordination. Suggest to include explicitly in the list of potential cross-functional team members a reviewer from CDRH if a companion diagnostic is required for the therapeutic.
VII. ACCELERATED APPROVAL		
Lines 445-446:	"The FDASIA provisions facilitate somewhat broader use of accelerated approval to expedite patient access to important treatments for serious conditions." The underlying intent of FDASIA Sec. 901, as evidenced by the accompanying Sense of Congress, is to provide additional flexibility to apply the Accelerated Approval pathway more broadly and innovatively.	Please strike the term "somewhat" and align the paragraph with the FDASIA Sense of Congress language. "The FDASIA provisions facilitate ~~somewhat~~ broader use of accelerated approval to expedite patient access to important treatments for serious conditions. **In particular, Congress encouraged FDA "to implement more broadly, effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the**

SECTION	ISSUE	PROPOSED CHANGE
		high standards of the FDA for approval of drugs."
Lines 455-456:	"The accelerated approval pathway is most often useful in settings in which the disease course is long and an extended period of time is required to measure the intended clinical benefit of a…"	Examples of certain disease states or disease state markers would be appreciated here. It would be helpful to provide guidance on current FDA thinking for disease states and endpoints this designation is intended for. The context of the guidance should more clearly support broader use of accelerated approval and this should be further explained therein.
Lines 470-472:	"FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of the drug for accelerated approval, proposed surrogate or intermediate clinical endpoints, clinical trial designs, and study planning and conduct of confirmatory trials." It is not always easy to know early if there is an AA potential. As discussed in our general comments, increased communications would benefit this process. Additionally, to conform to FDASIA, please utilize "verification" throughout rather than "confirmatory".	We recommend rewording as follows: "FDA encourages sponsors to communicate with the Agency early and **frequently during the** development concerning the potential eligibility of the drug for accelerated approval, proposed surrogate or intermediate clinical endpoints, clinical trial designs, study planning and conduct of **verification** trials."
Lines 470 – 472:	As discussed in our general comments, although the Agency encourages communication, currently there is no standard process for engagement. A more structured approach could help generate a document that would be	The guidance should include a formal process to communicate with the Agency and document the discussion regarding the development program, both prior to and after submission of an IND.

SECTION	ISSUE	PROPOSED CHANGE
	released post approval providing metrics on how many times FDA was asked if accelerated approval is approved and how often the Agency rejected the proposal. Right now, we have no metrics on how many times accelerated approval proposals are rejected. All we have is a very small number of approvals, we estimate 19 outside of oncology and AIDS; thus, it would be very good to know how many were rejected, and even more importantly why.	
A. QUALIFYING CRITERIA FOR ACCELERATED APPROVAL		
2. Meaningful Advantage over Available Therapy		
Lines 482-505:	As discussed in the general comments, "Meaningful advantage over available therapies" is not a statutory requirement for Accelerated Approval per FDASIA. Rather, FDA must balance "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."	Please revise to place appropriate emphasis on "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." As noted in our general comments, the language on Line 482-483 stating that accelerated approval is "limited" only to those situations where this is a meaningful advantage over existing therapy is inconsistent with FDASIA text and overly restrictive. Similarly, the language on Line499 about broadened use should be referenced as an example, rather than suggesting this is the only flexibility granted by FDASIA.
B. ACCELERATED APPROVAL ENDPOINTS		
1. Surrogate Endpoints		
Lines 529 – 530:	The text speaks to dependency on the 'strength' of supporting evidence but does not provide detail as to what constitutes strong supporting data. There is no criterion provided related to the amount of	Clarify what is considered to be 'strong' supporting evidence. The Draft Guidance should provide a framework addressing how much data is adequate to meet the requirement that a surrogate endpoint is reasonably likely to predict a drug's clinical benefit (*e.g.*, a framework for

SECTION	ISSUE	PROPOSED CHANGE
	data needed to support clinical benefit. There are no specific examples for rare disease.	generating the degree of data required to correlate the surrogate to clinical benefit). Reference(s) of a rare disease(s) example would be helpful. (See general comment XI-iv)
Lines 531-532:	"… (**a validated surrogate endpoint**, which could be used for traditional approval)…"	Can the FDA please define and provide guidance as to what constitutes a validated surrogate marker?
C. EVIDENTIARY CRITERIA FOR ACCELERATED APPROVAL		
1. Whether an Endpoint Is "Reasonably Likely to Predict" Clinical Benefit		
Lines 604 – 607:	Only clinical data is referenced.	We suggest including animal data in addition to clinical data.
Lines 609 – 611:	As discussed in our general comments, FDA should establish a systematic framework and evidentiary criteria for endpoint selection, rather than adopting a case-by-case approach.	The Agency should develop and include data-specific frameworks that can be used as indicators/criteria for the degree of data and robustness of data required for endpoint selection.
Lines 610-611:	"FDA considers all relevant evidence and weighs the uncertainty against the severity of the disease to be treated and the lack of available therapy." This language needs clarity and greater consistency with FDASIA text.	We recommend rewording as follows: "FDA considers all relevant evidence and weighs the uncertainty against the severity, **rarity, or prevalence of the condition** and the lack of available therapy."
D. CONDITIONS OF ACCELERATED APPROVAL		
1. Promotional Materials		
Lines 688-691:	"After 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial	Please clarify.

SECTION	ISSUE	PROPOSED CHANGE
	publication of the **advertisement**." Does this last sentence only apply to "advertisements" or does it apply to other promotional material?	
2. Confirmatory Trials		
Line 693:	Confirmatory should be changed to verification throughout the Draft Guidance. This revised terminology is more expansive, flexible, and consistent with FDASIA.	**Verification** Trials Recommended terminology change throughout guidance.
Lines 700-706:	"Generally, the confirmatory clinical trial would evaluate a clinical endpoint that directly measures the clinical benefit. It is a possibility in some cases, however, that additional evaluation of a surrogate endpoint (e.g., for a longer period), could be persuasive evidence of a clinical benefit. For example, an effect of relatively short duration on a surrogate endpoint may be reasonably likely to predict clinical benefit, supporting accelerated approval. A trial demonstrating that the effect on the same surrogate endpoint persists for an extended duration may be known to reliably predict such clinical benefit." We request more predictability and interpretation from FDA.	There are many examples in oncology from ODAC approvals, and it would be helpful to have more examples of the types of verification trials that the FDA is willing to consider to provide increased predictability. Can FDA provide clear guidance about cases for example where last line therapy in oncology may be suitable for AA, but the verification trial may be in a different line of therapy?
Lines 724-729:	"Another approach is to use an interim analysis of the surrogate endpoint data as the basis for accelerated approval, with **continuation** of the randomized trials	Please consider replacing "continuation" with **"continuation and completion"** so sentence reads: "Another approach is to use an interim analysis of the

SECTION	ISSUE	PROPOSED CHANGE
	during the time period when the surrogate endpoint and interim safety data are being: (1) analyzed, (2) prepared for submission to FDA, and (3) reviewed by FDA. When the ultimate clinical outcome can be expected over this additional timeframe, the data to verify the clinical benefit may be nearly complete by the time of accelerated approval." It may be unclear that the interim analysis and the "continuation of the clinical trials" can come from the same clinical trial.	surrogate endpoint data as the basis for accelerated approval, with continuation **and completion** of the randomized trials during the time period when the surrogate endpoint and interim safety data are being: (1) analyzed, (2) prepared for submission to FDA, and (3) reviewed by FDA."
VIII. PRIORITY REVIEW DESIGNATION		
A. QUALIFYING CRITERIA FOR PRIORITY REVIEW DESIGNATION		
2. *Demonstrating the Potential To Be a Significant Improvement in Safety or Effectiveness*		
Lines 781 to 783:	"On a case-by-case basis, FDA determines whether the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition."	The Priority Review designation is an important way to expedite access for patients. It is understood that there are federal resource issues, but there seems to be no way to predict accurately in many cases if this will apply (as shown in the example). It is challenging to plan for meetings, labeling, promotional material, launch, reimbursement, etc., in the absence of predictability. Can the FDA offer any more predictability as to when PR may be applied? The example given here may be illustrative, but there are still not trends for this. Note, however, that an NDA or BLA Sponsor need not seek Fast Track designation to be eligible for Priority Review. FDA has stated as much in prior guidance and should include such a statement in this guidance as well.

SECTION	ISSUE	PROPOSED CHANGE
IX. GENERAL CONSIDERATIONS		
A. MANUFACTURING AND PRODUCT QUALITY CONSIDERATIONS		
Lines 822-837:	"The Sponsor's product quality team and CMC teams should initiate early communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval…. "	Please see our general comments on manufacturing and product quality considerations in the General Comments section. We request clarity and predictability. For BT and FT designations, there are more clear timelines for FDA communications; however, for AA there is a lack of predictability as to when this pathway will apply. As such, this could affect availability of important therapeutics to patients. It would be helpful if there could be connectivity among the different review groups at FDA when AA is discussed, to lead to greater predictability.
Lines 831-832:	For products that include a drug-device component, human factors (HF) studies are generally performed on the Intended Final Instructions for Use (IFU), and may become rate-limiting to submission.	We suggest that consideration be given to enhanced communication between CDER and CDRH on acceptable development for drug-device combinations, such as assessment of HF studies performed prior to availability of final IFU.
Lines 839-840:	Concerns over inspection readiness of BTD product manufacturing sites.	We suggest that planning be addressed by earlier submission of the facilities section of the 356H form without earlier submission of the CMC section for review, as these activities are carried out by different disciplines of the Agency.
Lines 843-845:	Interactions with FDA regarding the quality aspects of a BTD product.	We suggest that the quality reviewers and coordinators for inspections be present for interactions during the BTD product development meetings. We also recommend having the FDA quality division and the review division work closely together during the conduct of these meetings.

SECTION	ISSUE	PROPOSED CHANGE
C. CLINICAL INSPECTION CONSIDERATIONS		
Lines 859-864:	Inspection schedule	We recommend clarification to state that FDA will schedule manufacturing and clinical inspections early in the application review process for BTD products.
APPENDIX 1: PROCESS FOR FAST TRACK, BREAKTHROUGH THERAPY, AND PRIORITY REVIEW DESIGNATION		
A. PROCESS FOR FAST TRACK DESIGNATION		
Lines 878-880:	"As a practical matter, requests should ordinarily occur no later than the Sponsor's pre-BLA or pre-NDA meeting with the Agency because many of the features of fast track designation will not apply after that time. " This is not always true since one of the more important benefits is rolling submission, which will be available shortly after Pre-NDA/BLA meeting; this is also in line with text in Appendix 2 on line 1142-1150; where formal request comes after the idea of fast track is discussed with the FDA at the pre-BLA meetings.	We request more clarity and predictability from FDA on this issue.
B. PROCESS FOR BREAKTHROUGH THERAPY DESIGNATION		
Lines 982-983:	"Ideally, a breakthrough therapy designation request should be received by FDA no later than the end-of-Phase-2 meetings if any of the features of the designation are to be obtained." FDA policy on late BT applications is inconsistent in the public domain.	1) At the 2013 ASCO meeting, leadership of the Office of Oncology and Hematology Products stated that a BT could be submitted after pivotal data were obtained to take advantage of the potential for priority review. Can the FDA clarify if a BT designation will lead to an increased chance of getting PR designation at the time of filing? 2) Other Agency officials have also commented that BT benefits can be obtained in later files even though the Agency hopes Sponsors will file sooner in the future.

SECTION	ISSUE	PROPOSED CHANGE
		There are benefits for CMC, inspections scheduling, priority review. Can the FDA please clarify these comments?
Lines 1011-1012:	"Proprietary name" and "trade name" are often used interchangeably in industry.	We suggest that the Agency use either "proprietary name" or "trade name" consistently throughout the Guidance or provide clarification if there is a difference.
Lines 1028-1029:	"If applicable, include a list of documents previously submitted to the IND considered relevant to the designation request, with reference to submission dates. Paper submissions can be resubmitted to FDA as appendices to the designation request." The suggested list of documents supporting the breakthrough therapy designation does not call out any related to a potential companion diagnostic. Such documentation would seem to be relevant.	Suggest highlighting inclusion of any pre-Submission or IDE documents if the therapy requires a companion diagnostic.
C. PROCESS FOR PRIORITY REVIEW DESIGNATION		
Lines 1122-1124:	By law, with priority review designation, FDA's goal is to take action on a marketing application within 6 months plus a 2 month validation period for new molecular entities (NMEs).	We would encourage the FDA to use regulatory discretion to complete the review sooner than the PDUFA Priority Review timelines to facilitate patient access
APPENDIX 2: PROCESS FOR ROLLING REVIEW		
A. AGREEMENT ON PROPOSAL		
Line 1135:	"APPENDIX 2: PROCESSES FOR ROLLING REVIEW"	Suggest revising heading to read "APPENDIX 2: PROCESSES FOR ROLLING REVIEW **UNDER FAST TRACK DESIGNATION**"

SECTION	ISSUE	PROPOSED CHANGE
	Since this process is only applicable to Fast Track designation, the heading for this section should be revised to further clarify this condition.	
Lines 1142-1143:	The Guidance indicates that Sponsors should obtain preliminary FDA agreement on the rolling review at the pre-BLA/pre-NDA meeting. This timeline may not be soon enough for products with breakthrough designation.	We suggest that the Agency consider Sponsors requests for rolling review before the pre-BLA/pre-NDA meeting for agents granted breakthrough therapy designation.
Lines 1157-1158:	"FDA responds to Sponsors 'requests for submission of portions of an application by letter."	We acknowledge that rolling NDAs are reviewed as resources permit. However, for BTD products, we recommend that the Agency and Sponsors have certain mutually agreed upon timelines.

APPENDIX A

FDASIA Modernization and Expansion of Accelerated Approval

Key Statutory Changes, Legal Interpretation, and Implementation

June 2013

I. BACKGROUND AND INTRODUCTION:

On July 9th, 2012, President Barack Obama signed the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, P.L 112-144) into law. In addition to reauthorizing FDA's user fee programs, the legislation made significant reforms to help speed the development and availability of innovative new therapies. This includes a modernization and expansion of FDA's existing Accelerated Approval pathway.

First implemented via regulation in 1992 and partially codified in 1997, the Accelerated Approval pathway can facilitate earlier approval of drugs to treat serious and life-threatening diseases or conditions on the basis of the determination that the product has an effect on a surrogate that is reasonably likely to predict a clinical benefit or clinical endpoints other than mortality or irreversible morbidity that can be measured earlier in drug development and reasonably likely to predict a clinical benefit. This is followed by post-marketing clinical trials to verify the anticipated clinical benefit. Accelerated Approval can considerably shorten the time from discovery to FDA approval and provide patients with important medical needs with earlier access to new medicines.

While the legal scope of the Accelerated Approval pathway may include any serious or life-threatening disease with an appropriate regulatory surrogate or clinical endpoint, in practice the pathway has been largely used for approval of HIV/AIDS and oncology therapies. However, modern drug development has changed substantially since 1992 and Congress sought to expand the program to additional diseases and to better leverage recent scientific advancements. For example, the Congressional findings included in FDASIA provide a detailed description of what Congress intends to achieve by expanding Accelerated Approval, and what it expects FDA to accomplish when applying these expanded authorities:

> *"FDA should be encouraged to implement more broadly, effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for approval of drugs."*

Given the general similarities between the FDASIA statutory amendments and the existing regulations governing FDA's Accelerated Approval [21 CFR 314.50 (Subpart H) and 21 CFR 601.41 (Subpart E)], some observers have suggested that FDASIA only codifies FDA's existing authorities and makes little practical change to how FDA interprets and applies the pathway.

However, the intent under these reforms was to apply these authorities more broadly in additional areas beyond just HIV/AIDS and oncology by providing FDA and Sponsors with greater clarity and flexibility to rely upon additional types of data and trial endpoints. Seemingly minor or editorial changes to the underlying statute were in fact deliberate and intentional, and

carry meaning in how Congress expects FDA to implement the pathway. Each change carries significance and should be evaluated as part of the Agency's implementation of FDASIA.

Taken in total and in full context, these changes represent a significant paradigm shift in how the Agency should more broadly and innovatively apply the Accelerated Approval pathway to encourage the expedited development and approval of the next generation of modern therapies for serious and life-threatening diseases intended to address important medical needs. This paper reviews the legal considerations regarding the Congressional intent of specific edits to the underlying statute and issues for FDA implementation.

II. STATUTORY CONSIDERATIONS

The following sections 1) address each specific amendment made to Section 506 of the Food Drug and Cosmetic Act related to Fast Track Products, 2) highlight specific red-line amendments to the statute, and 3) discuss the interpretation and implementation considerations related to each.

A. Designation of a Combination of One or More Drugs:

"(b) Designation of Drug as a Fast Track Product. —

(1) In General. — The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition, or if the Secretary designates the drug as a qualified infectious disease product under section 505E(d). (In this section, such a drug is referred to as a "fast track product".)"

Interpretation:

This provision clarifies that a drug used in conjunction with another new or existing drug or biologic is eligible for fast track designation and consideration under the Accelerated Approval pathway.

Implementation:

Within 12 months of enactment, FDA is required to publish draft guidance addressing implementation of the Fast Track and Accelerated Approval provisions. FDA's current *Guidance for Industry: Fast Track Development Programs* (2006) identifies criteria for a serious or life-threatening condition, as well as the demonstration of unmet medical need. FDA should include in the guidance how a combination of two or more drugs will be evaluated under the expanded Accelerated Approval statutory language. This should include the various scenarios regarding such combinations of drugs (*e.g.*, if one of the products is already approved or if both products are novel), as well as designation of infectious disease products.

B. Clarification and Distinction Between Fast Track Designation and the Accelerated Approval Pathway

"(c) Accelerated Approval of a Drug for a Serious or Life-Threatening Disease or Condition, Including ~~Application for~~ a Fast Track Product. — "

Interpretation:

Prior to enactment of FDASIA, FDA regulations addressed "Accelerated Approval of New Drugs for a Serious or Life-Threatening Condition," but statutory language did not exist authorizing an Accelerated Approval pathway per se, separate and apart from the Fast Track designation. FDASIA now codifies that the Accelerated Approval pathway for products for serious or life-threatening diseases or conditions is separate, regardless of whether there is designation as Fast Track. FDASIA provides both Sponsors and FDA with greater flexibility and statutory support in the application of the Accelerated Approval pathway.

Implementation:

Within 12 months of enactment of FDASIA, the FDA is required to publish draft guidance addressing implementation; accordingly, the 2006 Guidance should be updated for consistency with the new law, and FDA's Accelerated Approval regulations, 21 C.F.R. 314.500 (drugs) and 21 C.F.R. 601.40 (biologics) should also be updated to conform with these FDASIA requirements, as detailed below.

C. Serious or Life-Threatening Disease or Condition

"(1) In General. —

(A) Accelerated Approval. — The Secretary may approve an application for approval of a product for a serious or life-threatening disease or condition, including a fast track product, under section 505(c) or section 351(a) of the Public Health Service Act…

Interpretation:

The language reinforces FDA's authority to grant Accelerated Approval of a drug for a serious or life-threatening disease or condition, regardless of whether the drug meets the eligibility criteria for, or the Sponsor seeks designation of it as, a "fast track" product. Notably, there is no longer any explicit "unmet medical need" criterion to be eligible for Accelerated Approval.

Rather, the availability of alternative therapies is a factor - but not a requirement - balanced along with other factors such as the severity, rarity, or prevalence of the condition that the Agency shall consider when determining whether to grant Accelerated Approval in a particular case (see discussion below). Accordingly, the Accelerated Approval statutory language under FDASIA is now broader and provides the Agency and Sponsors with greater flexibility in utilizing this amended pathway. For example, this provision provides additional clinical options in certain circumstances (consistent with accepted medical practices and ethics) to study a therapy earlier in the disease progression rather than waiting until patients have already progressed through all other alternative therapies in order to demonstrate head-to-head clinical superiority as part of an "unmet medical need" test.

Importantly, FDA's 2004 Guidance on Available Therapy[1] construing FDA policy on the terms and definitions for "*available therapy*" and related terms, such as "*existing treatments*" and "*existing therapy*", appear in a number of regulations and policy statements and should be revised and clarified following the expansion of Accelerated Approval language in FDASIA and modifications to the "*unmet medical need*" standard. For example, in this Guidance, the Agency states that "available therapy (and the terms existing treatments and existing therapy) should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions." The FDA further indicates that "only in exceptional cases will a treatment that is not FDA-regulated (*e.g.*, surgery) or that is not labeled for use but is supported by compelling literature evidence (*e.g.*, certain established oncologic treatments) be considered *available therapy*". To enhance predictability and flexibility in the application of the Accelerated Approval pathway per FDASIA and reflect that the unmet medical need standard is a factor, but not a requirement, the FDA should clarify when a treatment that "is not FDA-regulated" or "that is not labeled for use but is supported by "compelling literature evidence" is applicable and when such "rare exceptions" will apply.

Implementation:

FDA's regulations and existing guidance, including FDA's 2004 Guidance on Available Therapy, need to be amended to reflect these statutory changes, as well as the broader Congressional "findings" that make clear Congress' intent for the Agency to expand the use of Accelerated Approval where appropriate. These revisions should include the fact that there is no longer an explicit "unmet medical need" criterion to be eligible for Accelerated Approval.

Specifically, FDA's Accelerated Approval regulations at 21 C.F.R. 314.500 and 21 C.F.R. 601.40 should be revised to reflect that the statute no longer requires as a condition of eligibility for Accelerated Approval that an unmet medical need or "meaningful therapeutic benefit . . . over existing treatments" be demonstrated. FDA's 2006 Guidance should be revised to reflect that as well. Further, FDA's 2006 Guidance, which currently expands upon whether a condition is considered "serious or life- threatening," should be revised to clarify that this factor applies to Accelerated Approval, in addition to Fast Track.

[1] FDA "Guidance for Industry: Available Therapy", July 2004, Section IV. POLICY: DEFINITION OF AVAILABLE THERAPY, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf

D. "Intermediate" Clinical Endpoints that can be Measured Earlier in Development

…upon a determination that the product has an effect on a ~~clinical endpoint or on a~~ surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit,"…

Interpretation:

Accelerated Approval is based on a determination that the product's effect on a surrogate endpoint is "reasonably likely to predict clinical benefit," and provides for more expansive use of non-surrogate clinical endpoints as the basis for granting Accelerated Approval. Specifically, the new language expressly authorizes FDA to grant Accelerated Approval based on the use of clinical endpoints that can be measured earlier in the development process than irreversible morbidity or mortality, and that are reasonably likely to predict an effect on irreversible morbidity or mortality *or other clinical benefit*.

For instance, the President's Council on Science and Technology has cited the following examples of "intermediate" clinical endpoints that could be utilized under an expanded Accelerated Approval pathway.

- "Using improvement in minimal cognitive impairment in likely early-stage Alzheimer's patients as a predictor of delayed progression rather than waiting to assess progression.
- Using improvement in isolated muscle strength in patients with muscular dystrophy as a predictor of benefit, rather than waiting to assess overall deterioration of the patient.
- Using clearance of drug-resistant organisms as a predictor of likely clinical benefit, rather than waiting to measure overall survival rate.
- Using measures of the amount of air that a patient can exhale by force (a measure of lung capacity known as forced vital capacity) or functional motor tests as an endpoint for predicting a drugs' likely impact on 2 serious diseases lacking good treatments: spinal muscular atrophy, a genetic neuromuscular disease, and amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease."

Other examples of intermediate clinical endpoints may include:

- Reduced kidney function in various kidney diseases, which typically only leads to frank kidney failure over a decade or more; and
- Total kidney volume in polycystic kidney disease - this is a very slowly progressive disease is which the kidney expands and causes a series of progressively worsening symptoms based on expanded volume.

These examples represent "intermediate" clinical endpoints in terms of the speed and efficiency with which therapeutic intervention can be measured and evaluated. However, they are also viewed as neither a surrogate endpoint nor a "hard" clinical endpoint, such as kidney failure or survival. These types of intermediate clinical endpoints are important in that they can be

measurable and evaluable earlier which makes drug development more feasible, faster and more efficient than a traditional endpoint which may develop much later in the course of a given disease in a clinical trial.

Under the previously existing law and regulations, there have been few submissions or Accelerated Approvals based on the use of clinical endpoints largely because the statutory framework was unclear and FDA regulations and practice took a narrow approach to the use of such endpoints.

In this respect, the Congressional "findings" that were enacted along with the FDASIA statutory changes are instructive. They direct the FDA to "implement more broadly effective processes for the expedited development and review of innovative new medicines…using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate." In particular, Congress recognized that this expanded approach "may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs." Through these amendments, Congress intended to "enhance the authority of the FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions."

Implementation:

FDA's regulations and existing guidance should also be revised in regard to the expansion of the "clinical endpoint" provisions. Specifically, 21 C.F.R. 314.510 and 21 C.F.R 601.41, which currently refer to approval based on "an effect on a clinical endpoint other than survival or irreversible morbidity" must be revised to reflect the new statutory language, "effect on a . . . clinical endpoint *that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or morality or other clinical benefit. . .*" *i.e.*, the connection between an observed clinical endpoint (demonstrated through adequate and well-controlled clinical trials) and the ultimate clinical benefit of a drug may be based on the same "reasonably likely to predict" standard applied to surrogates, and that the types of evidence that can support such linkage now expressly include non-clinical data (see below).

E. Severity, Rarity, or Prevalence of the Condition and the Availability or Lack of Alternative Treatments

…"taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

Interpretation:

The language affirmatively directs FDA, in determining whether to grant Accelerated Approval under the statutory standard set forth in this section, to consider the "severity, rarity or prevalence of the condition and the availability or lack of alternative treatments." This supports greater risk/benefit balancing that includes the needs and views of patients suffering from serious or rare conditions, without explicit requirements for direct clinical trial comparisons to other treatments.

The term "rarity" also reinforces Congressional intent that FDA should more broadly apply the Accelerated Approval pathway to rare diseases, including low prevalence populations, low prevalence or enriched subpopulations, and genomic subpopulations.

Implementation:

FDA's regulations and existing guidance need to be amended to include this explicit statutory balancing of factors in FDA decision-making in this area. Specifically, changes are necessary in FDA's regulations at 21 C.F.R. 314.500 and 21 C.F.R 601.40, the "Scope" sections of the drug and biologic Accelerated Approval regulations, which refer to a required demonstration of "meaningful therapeutic benefit over existing treatments." (see section II.C. above)

We also encourage FDA to continue to engage with rare disease stakeholders through a public process to further define and interpret the meaning of the phrase "taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments," and to fully explore the opportunities to utilize Accelerated Approval for rare disease therapies.

F. Evidence to Support an Endpoint

> **"(B) Evidence. —** The evidence to support that an endpoint is reasonably likely to predict clinical benefit under subparagraph (A) may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

Interpretation:

The language provides clear statutory direction to FDA that the evidence to support that *either type of endpoint* is reasonably likely to predict clinical benefit may include non-clinical or clinical evidence such as epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers or other scientific methods or tools.

Implementation:

FDA's current regulations in 21 C.F.R 314.50 and 21 C.F.R. 601.41 state that FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing an effect on a "*surrogate* endpoint that is reasonably likely, *based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit*…" (emphases added). These regulations must be updated to reflect the use of clinical or non-clinical evidence to support the use of a surrogate or clinical endpoint under this new statutory provision.

In addition, surrogate endpoints in Accelerated Approval need not have been previously qualified, nor would their use require a comprehensive qualification as part of a confirmatory study. The confirmatory study will confirm the efficacy and safety of the drug and the qualification of the surrogate limited to the specific accelerated study in which it is used. Data from these studies may also be combined with other data within the FDA to provide cumulative evidence for the qualification of this surrogate in a broader context of use.

A focus on surrogates for the earlier detection of therapeutic benefit is exemplified in both the use of novel surrogates for clinical endpoints as cited in the President's Council on Science and Technology, as well as in the use of novel surrogate platforms to replace current platforms. Noteworthy examples of the application of novel surrogate platforms include:

- Circulating tumor cells (CTCs) use instead of biopsies to assess the efficacy of anti-cancer drugs.
- MRI imaging measurements instead of X-ray radiography.

Use of surrogates such as these should require only an analytical validation with reference to the pre-existing surrogate platform, showing equivalent or superior performance for the same biological measurement of therapeutic efficacy.

G. Post-Approval Verification Studies

"(2) Limitation. — Approval of a ~~fast track~~ product under this subsection may be subject to 1 or both of the following requirements: —

(A) Tt~~t~~hat the sponsor conduct appropriate post-approval studies to ~~validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint~~ verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.~~; and"~~

Interpretation:

The FDASIA language regarding post-approval requirements for Accelerated Approval is amended to provide FDA and Sponsors with greater flexibility as to the type of studies that may be used to verify clinical benefit in the post-approval setting. Specifically, such post-approval

studies may now focus on verifying the predicted clinical benefit, rather than having to validate the surrogate or clinical endpoint. This change was not intended to prevent such post-approval studies, but to provide greater flexibility with respect to the type of studies that could be required. Importantly, as the Senate legislative history on this change makes clear (see Congressional Record – Senate, May 24, 2012, at S3564), the striking of post-approval studies to validate a surrogate endpoint does not signal any intent that surrogate or clinical endpoints be validated prior to Accelerated Approval, or for the Agency to change its historical practice of granting Accelerated Approval based on unvalidated endpoints.

Implementation:

As this provision codified existing FDA practices, no specific regulatory changes are necessary, but it would be useful for FDA to expand upon this provision in Guidance. In particular, in the case of oncology, the FDA should clarify what type of Accelerated Approval verification studies may be appropriate.

H. Awareness Efforts & Development of Surrogate and Clinical Endpoints

"(e) Awareness Efforts. —

The Secretary shall —

(1) develop and disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a description of the provisions of this section applicable to breakthrough therapies, accelerated approval, and fast track products; and

(2) establish a program to encourage the development of surrogate and clinical endpoints, including biomarkers, and other scientific methods and tools that can assist the Secretary in determining whether the evidence submitted in an application is ~~that are~~ reasonably likely to predict clinical benefit for serious or life-threatening conditions for which ~~there exist~~ significant unmet medical needs exist."

Interpretation:

The Secretary's awareness efforts must now extend beyond Fast Track to include the new Breakthrough Therapy designation and enhanced Accelerated Approval pathways. FDA also is required to establish a program to encourage the development of both surrogate and clinical endpoints, including biomarkers and other scientific methods and tools that can assist the Agency in determining whether evidence is reasonably likely to predict clinical benefit.

Implementation:

FDA should implement these new provisions in a transparent manner through a public process that involves relevant stakeholders. FDA should also elaborate upon how the process to engage stakeholders to develop new endpoints is complementary to the PDUFA V and FDASIA programs to advance regulatory science, qualify biomarkers, qualify patient reported outcome tools, and develop new endpoints for rare diseases (PDUFA V commitment letter, sections IX C, D, E; FDASIA §1124, §1102). To the extent practical, the Agency should leverage resources and synergies from these programs to achieve the common goal of developing new endpoints and utilization of modern scientific tools and approaches for a broad range of serious and life-threatening conditions. For example, open stakeholder meetings or hearings to develop a public research agenda of priority disease areas and a list of potential new endpoints would be a welcome element of such a public process.

In particular, the implementation of these provisions should include a viable, efficient regulatory process for the consideration and acceptance of novel surrogates and of novel surrogate platforms. This process must be incremental, matching a qualifiable context of use to the pre-existing data and providing guidance on evidentiary standards needed for increments in the value of the context of use for the surrogate. While pre-qualification is not required to use a surrogate for Accelerated Approval, a viable qualification process will encourage the use of surrogates in drug development and provide uniform guidelines for the interpretation of these results in regulatory review.

I. Rule of Construction

"(f) Construction.---

(1) Purpose. — The amendments made by the Food and Drug Administration Safety and Innovation Act to this section are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."

(2) Construction. — Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well-controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).

Interpretation:

Paragraph one explicitly states that the purpose of these amendments is to encourage the FDA to "utilize innovative and flexible approaches to the assessment of products under accelerated approval," while maintaining safety and efficacy standards.

Paragraph two establishes that the current FFDCA statutory standard – requiring adequate and well-controlled studies showing that the drug is safe for its intended use and that provide substantial evidence that the drug will have its intended effect – applies to Fast Track, Accelerated Approval and Breakthrough Therapies. (However, the new FDASIA provisions do not require that this level of evidence support the relationship between a surrogate or clinical endpoint and the intended clinical benefit of a drug.) This language simply codifies FDA's current practice in evaluating drugs under Accelerated Approval, an approach that requires substantial evidence of the drug's effect on the surrogate or clinical endpoint, but permits other clinical and non-clinical evidence (as described above) to be used to meet the "reasonably likely to predict clinical benefit" part of the approval standard.

Implementation:

Consistent with current law, no implementation is necessary.

J. Publication of Guidance

"(1) DRAFT GUIDANCE.—Not later than 1 year after the date of enactment of this Act, the Secretary of Health and Human Services (referred to in this section as the ''Secretary'') shall issue draft guidance to implement the amendments made by this section. In developing such guidance, the Secretary shall specifically consider issues arising under the accelerated approval and fast track processes under section 506 of the Federal Food, Drug, and Cosmetic Act, as amended by subsection (b), for drugs designated for a rare disease or condition under section 526 of such Act (21 U.S.C. 360bb) and shall also consider any unique issues associated with very rare diseases."

(2) Final Guidance. – Not later than 1 year after the issuance of draft guidance…the Secretary shall –

(A) issue final guidance; and
(B) amend the regulations governing accelerated approval…

(5) NO EFFECT OF INACTION ON REQUESTS. – The issuance (or non-issuance) of guidance or conforming regulations…shall not preclude the review of, or action on, a request for designation or an application for approval" under Section 506 of the FFDCA.

[Note: Included within FDASIA, but not part of the FFDCA]

Interpretation:

FDASIA directs FDA to issue revised guidance and regulations within two years to implement these amendments, including special considerations for the greater use of this pathway for rare, and very rare, diseases. Specifically, the Agency must consider how to "incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence" in instances where "the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical." [FDASIA Sec. 901(c)(3).]

Significantly, the statutory changes made to the Accelerated Approval pathway, Fast Track designation, and Breakthrough Therapy designation are available immediately upon enactment of FDASIA—Sponsors need not wait for FDA guidance to be issued.

Implementation:

FDA is directed to draft guidance(s) on Fast Track, Breakthrough Therapy, Accelerated Approval, and rare disease issues. Specific regulatory and guidance changes are detailed above.

Additionally, it is expected that, among other things, FDA will describe how it intends to incorporate more modern scientific approaches and tools into the Accelerated Approval process, so as to ensure the fulfillment of Congressional intent that these new authorities will help expedite the development and availability to patients of treatments for serious or life-threatening diseases or conditions.

Specifically, we expect that FDA will clarify and broaden the circumstances in which an intermediate clinical endpoint can be used to support Accelerated Approval (that is, to support a determination that the endpoint is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit), across a wider range of diseases or conditions (beyond cancer and HIV/AIDS). Further we expect clarification that the availability of alternative therapies (or lack thereof) is a factor - but not a requirement - balanced along with other factors such as the severity, rarity, or prevalence of the condition that the agency shall consider when determining whether to grant Accelerated Approval in a particular case.

We also expect FDA will describe how it will more explicitly incorporate considerations of disease severity or rarity and the lack of alternative treatments into the risk/benefit analysis for Accelerated Approval. Further, in developing guidance, FDA must consider issues associated with very rare diseases and how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence, especially in instances where there is a low prevalence of the disease and traditional data collection is impractical.

A. Relation of Accelerated Approval to Breakthrough Therapy Designation

(a) Designation of a Drug as a Breakthrough Therapy

(1) In General.-- The Secretary shall, at the request of the sponsor of a drug, expedite the development and review of such drug if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. (In this section, such a drug is referred to as a "breakthrough therapy".)

Interpretation:

In addition to expanding the Accelerated Approval pathway, this provision establishes a new designation for the approval of "Breakthrough Therapies" intended to treat serious or life-threatening diseases where "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." The pathway was established partly in response to the development of new therapies that target the underlying molecular pathways of disease and can demonstrate remarkable efficacy or decreased toxicity in early stage clinical testing, such as in Phase 1 or early Phase 2 of clinical trials. The new provision enables robust FDA-sponsor communications (above and beyond those required for all PDUFA and Fast Track products) to identify an expeditious path for clinical development and minimize patient exposure to ineffective control regimens.

Implementation:

The FDA response to a Breakthrough Therapy designation has informally been described as an "all hands on deck" process. Within 18 months of enactment (January 9, 2014), FDA is required to publish draft guidance addressing implementation of the Breakthrough Therapies provisions; to finalize such guidance within one year of the comment period; and, if necessary, to revise any relevant regulations by July 9, 2014. FDA is also directed to develop and disseminate a description of the Breakthrough Therapies provisions.

FDA should provide additional details regarding the Breakthrough Therapy designation, including: distinguishing Breakthrough designation from Fast Track designation and both of these designations from the Accelerated Approval and Full Approval pathways; options for consolidation of trial phases; clarification of when and what data from Phase 1 or early Phase 2 is acceptable; size of clinical trials, how substantial improvement over existing therapies will be evaluated (for example, direct clinical trial comparisons not necessary) ; how to evaluate "substantial" and clarification of what qualifies as an "existing therapy"; the process/expectations for increased meetings between FDA and sponsors; and further details on the expectations for the amount of data and whether there is a need for a full clinical development plan in the application.

FDA should also elaborate upon what processes it will use to develop cross functional, senior leadership teams across FDA, not just the review division, how it will facilitate interactive communication with the Sponsor, and if/when external expertise or patient input can be imputed

to the process. This is expected to include expedited meeting requests (Type A or B) and additional informal dialogue above and beyond what is expected for all PDUFA products and Fast Track products. The creation of a Breakthrough Designation meeting type would facilitate meeting requests for Breakthrough discussions and the identification of FDA employees required to attend these meetings.

The Agency and industry should also engage in a dialogue in how to address the challenges posed by manufacturing CMC and device-related bottlenecks and how to best harmonize the expedited U.S. development program with other international regions, notably Europe, to achieve a single harmonized development program for a Breakthrough Therapy designated product or any product applicable for expedited development.

Lastly, there needs to be clarity on how this Breakthrough Therapy designation will integrate or not with approval pathways (Accelerated/Full) and FDA processes such Priority Review, etc. In other words, the Agency should clarify how increased communications and involvement of senior level and cross functional FDA teams will actually expedite the development and approval of these products.

III. CONCLUSION

Under the FDASIA expansion of Accelerated Approval, Congress encouraged FDA to "implement more broadly effective processes for the expedited development and review of innovate new medicines… using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate." In summary, FDASIA provides FDA and Sponsors with greater flexibility under Accelerated Approval by:

- Enabling the eligibility of a combination of drugs
- Clarifying the distinction between Accelerated Approval and Fast Track designation
- Replacing the criterion for "unmet medical need" with an evaluation of other factors such as "the severity, rarity, or prevalence of the condition"
- Promoting the use of "intermediate" clinical endpoints, as well as surrogate endpoints, that can be measured earlier in drug development
- Facilitating the use of Accelerated Approval for serious rare diseases, including low prevalence populations, low prevalence or enriched subpopulations, and genomic subpopulations
- Modernizing the type of scientific evidence that can be used to support a determination that a surrogate or clinical endpoint will be "reasonably likely to predict clinical benefit"
- Providing FDA and Sponsors with greater flexibility as to the type of studies that may be used to verify clinical benefit in the post-approval setting
- Establishing a public process to develop and accept novel endpoints
- Establishing a new Breakthrough Therapies Designation process

The hope is that FDA will apply these authorities more broadly and in innovative ways to leverage 21st century advancements in science and drug discovery to help ensure that patients suffering from a broad array of serious and life-threatening condition have timely access to safe and effective new therapies.