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.