

## ***FDA Issues Draft Guidance on Expedited Review Programs, Including Breakthrough Therapy Designations***

***Sponsors seeking expedited review of their drug development programs should conduct a detailed review of the draft guidance, as there is still an opportunity to submit public comment.***

In June 2013, the US Food and Drug Administration (FDA) released its anticipated draft guidance, “Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.”<sup>1</sup> The draft guidance addresses the key features of FDA’s existing expedited review programs and provides FDA’s interpretation of, as well as plans to implement, the new breakthrough therapy designation created by the Food and Drug Administration Safety and Innovation Act (FDASIA). Specifically, the draft guidance sets forth FDA’s interpretation of the fast track, breakthrough therapy, accelerated approval, and priority review programs with a side-by-side comparison of each of the programs’ qualifying criteria and other relevant features, including changes to the programs imposed by FDASIA. Among other things, FDASIA was enacted “to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs.”<sup>2</sup>

It is critical that sponsors understand FDA’s implementation of these expedited review programs in order to take full advantage of the programs’ benefits to expedite clinical development and premarket review. In particular, the draft guidance’s elucidation of the requirements and procedures for breakthrough therapy designation offers sponsors an additional opportunity streamline the drug development and approval process. FDA has requested public comment on the draft guidance by August 25, 2013. To that end, sponsors should be sure to review the draft guidance in detail and submit comments to the docket in an effort to shape the contours of the final guidance, once issued.

### **General Concepts and Considerations**

The draft guidance details FDA’s interpretation of a number of concepts which serve as a foundation for application of FDA’s expedited review programs more generally. Specifically, the draft guidance defines, at the outset, the concepts of a “serious” or life-threatening disease or condition, “unmet medical need,” and “available therapy.”

#### **“Serious” or life-threatening disease or condition**

As explained in the draft guidance, FDA interprets a “serious” or life-threatening disease or condition for purposes of the application of its expedited review programs consistent with its historical interpretation. That is, a “serious” or life-threatening disease or condition is one “associated with morbidity that has substantial impact on day-to-day functioning[, and] [s]hort-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent.”<sup>3</sup> Notably, FDA

regulations state that “[w]hether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”<sup>4</sup> FDA clarifies that a drug is intended to treat a serious disease or condition if it is intended to have an effect on a serious aspect of a disease or condition, “such as a direct effect on a serious manifestation or symptom” of a disease or condition.<sup>5</sup> For example, FDA would view a drug or biologic intended to improve or prevent a serious treatment-related side effect (*e.g.*, serious infection in patients receiving immunosuppressive therapy) or to avoid a serious adverse effect associated with an existing therapy (*e.g.*, less cardiotoxicity than available cancer therapy) to satisfy the criterion that the drug or biologic is intended to treat a “serious” disease or condition.<sup>6</sup>

### **“Unmet medical need”**

The guidance also addresses the concepts of “unmet medical need” and “available therapy” (also referred to as “existing therapy”), which likewise serve as qualifying criteria for FDA’s expedited review programs. An unmet medical need exists where available therapy does not address the treatment or diagnosis for the disease or condition. FDA considers the unmet medical need to include an immediate need for a defined patient population as well as a longer-term need for society; both treatment for a serious disease or condition with no or limited treatment options and the development of products to address resistance to antibacterial drugs would qualify as an unmet medical need.

FDA provides some guidance on how to determine whether an unmet medical need exists if existing therapies exist. Specifically, if an available therapy exists for a condition, a new treatment could still be considered to address an unmet medical need in certain circumstances (*e.g.*, where the treatment has an improved effect on a serious outcome of the disease or condition compared to available therapy, or where the new product has a benefit for patients who are unable to tolerate available therapy or whose disease has failed to respond to available therapy). FDA intends to “consider a range of potential advantages over available therapy beyond those shown in head-to-head comparisons” in making a determination that a product meets an unmet medical need.<sup>7</sup>

### **“Available therapy”**

FDA notes that it considers “available therapy” or “existing therapy” to mean a therapy approved or licensed in the US for the same indication being considered for the new drug and that is relevant to the current US standard of care for the indication. In addition, FDA notes that in certain rare cases, it may deem an unapproved or unlicensed therapy to constitute “available therapy” where compelling evidence supports the safety and effectiveness of the therapy’s use.<sup>8</sup> FDA also acknowledges that the standard of care may evolve for a given disease or condition over the course of drug development, and that the Agency will determine what constitutes “available therapy” at the time of the relevant regulatory decision for the expedited program the sponsor intends to use. However, FDA will not consider a drug that has been granted accelerated approval based on a surrogate or clinical endpoint and for which clinical benefit has not been verified to be “available therapy.” FDA will consider products to address an unmet medical need notwithstanding the availability of therapies with accelerated approval. In addition, FDA will deem a drug subject to a Risk Evaluation and Mitigation Strategy (REMS) that contains elements to assure safe use to be an “available therapy” only where the study population for the new drug under development would be eligible to receive the drug under the REMS.

### **Additional considerations**

The draft guidance also contains some additional considerations for sponsors of expedited review programs. Specifically, FDA notes that the sponsor of a product in receipt of an expedited review designation may require a more rapid manufacturing development program to accommodate the

accelerated pace of the clinical development program. The draft guidance also highlights the importance of communicating early with FDA about non-clinical study programs and about the need for FDA to conduct clinical trial audits, which should be scheduled early in the review process.

## Fast Track

Under the FDCA, FDA is required to grant Fast Track designation to products which are intended — whether alone or in combination with one or more others — for the treatment of a serious or life-threatening disease or condition and that demonstrate the potential to address unmet medical needs for such disease or condition.<sup>9</sup> FDA notes that the type of information it may require to demonstrate this potential to address an unmet medical need may differ based on the product's stage of development. In early development, mechanistic rationale or pharmacologic data could be used to satisfy the statutory criteria, whereas later stage products may require clinical data to meet the requirements.<sup>10</sup>

If a product meets the qualifying criteria for Fast Track designation, the product may be eligible to take advantage of a number of features intended to expedite development and review of the product. Notably, sponsors may enjoy frequent interactions with the review team, including through FDA-sponsor meetings at various stages in the development process. Fast Track products are also eligible for rolling review, which permits the applicant to submit portions of its marketing application in accordance with a schedule to which FDA and the applicant have agreed. In addition, Fast Track products may be eligible for priority review if supported by clinical data at the time of the submission for marketing authorization.

Sponsors may submit requests for Fast Track designation concurrent to submitting the investigational new drug application (IND) or at any point thereafter, but as a practical matter, prior to the pre-biologics license application (pre-BLA) or pre-new drug application (pre-NDA) meeting. The draft guidance sets forth detailed information that sponsors should include in the designation request, including: a cover letter; the IND application number if applicable; the proprietary name and active ingredient or, for biological products, the proper name and trade name; the division or office to which it is being submitted; the proposed indication; a summary of information supporting the request (*i.e.*, how the product meets the criteria for Fast Track); and a list of any previously submitted relevant documents. FDA is required to respond to requests for Fast Track designation within 60 days, and will issue either a designation or non-designation letter. If the product qualifies for Fast Track designation, but subsequently fails to meet the Fast Track eligibility criteria, FDA may issue a notice to the applicant that the development program no longer qualifies.

## Breakthrough Therapy

FDASIA created a “Breakthrough Therapy” designation to expedite review of products intended, — alone or in combination with others — to treat a serious or life-threatening disease or condition and for which “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.”<sup>11</sup> FDA interprets the concepts of “serious” or life-threatening disease or condition and “existing therapy” as described above. However, designation of a product as a Breakthrough Therapy requires more than just theoretical or mechanistic rationale based on non-clinical data to support the designation. In contrast to the Fast Track program, the Breakthrough Therapy designation requires preliminary clinical evidence of a treatment effect that represents substantial improvement over available therapies (generally derived from Phase 1 and 2 trials).

FDA notes that, ideally, the evidence will be derived from a study comparing the investigational product to an available therapy or placebo and the study shows superiority. FDA explains that the demonstration of “substantial improvement,” as required by FDASIA, is ultimately a matter of judgment which depends on

the magnitude, including duration, of the treatment effect and the importance of the observed outcome. In sum, the preliminary clinical evidence should show a “clear advantage” over available therapy, which FDA acknowledges will be more difficult if an effective therapy is currently available in the marketplace.

With respect to the requirement that this data demonstrate substantial improvement over existing therapies on one or more “clinically significant endpoints,” FDA explains that such endpoints refer to measurements of effects on irreversible morbidity or mortality or symptoms that represent serious consequences of the disease. Such endpoints could include effects on established surrogate endpoints, pharmacodynamics biomarkers that do not meet the criteria for acceptable surrogate endpoints, but strongly suggest the potential for clinical meaningful effects in underlying disease, or significantly improved safety profiles with similar efficacy profiles compared to available therapies.

The benefits of Breakthrough Therapy designation include the same benefits that a Fast Track product would receive, plus intensive FDA guidance on the development program (beginning as early as Phase 1 studies) to ensure the design and conduct of the development program are as efficient as possible, while still meeting the statutory requirements for approval. The clinical program may consist of smaller and shorter trials that require less time to complete. Consequently, FDA anticipates that the development program for products with Breakthrough Therapy designation may be significantly shorter than for other products without the designation, products which are intended to treat the disease or condition under study. The Agency will also involve Senior FDA staff for cross-disciplinary review to coordinate internal communications. FDA may suggest that a sponsor submit a Breakthrough Therapy designation request upon review of data submitted to FDA if the sponsor has not requested the designation and FDA believes that product may meet the criteria and the development program may benefit from these features.

Just as a sponsor may submit a Fast Track designation request at the time of an IND submission or any time thereafter, so too may a sponsor submit a request for Breakthrough Therapy designation at this time. However, as noted above, a Breakthrough Therapy designation depends on preliminary clinical evidence to demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Consequently, FDA expects that most requests for designation will be submitted as an amendment to the IND. FDA also suggests that sponsors submit the request for designation no later than the end-of-Phase 2 meeting in order to take advantage of the benefits and design a development program as streamlined as possible. Applications should include the same content as recommended for a Fast Track submission, including a summary of preliminary clinical evidence that the drug may demonstrate substantial improvement. Like FDA’s process for responding to Fast Track designation requests, the Agency is required to respond to Breakthrough Therapy designation requests within 60 days and will issue either a designation or non-designation letter. If at any point after the designation is issued FDA determines that the drug no longer qualifies for Breakthrough Therapy designation, FDA may notify the applicant accordingly.

## **Accelerated Approval**

FDASIA broadened the accelerated approval program to authorize FDA to approve applications for products intended for serious or life-threatening diseases or conditions, including products with a Fast Track designation, “upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict a 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, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.”<sup>12</sup> FDA describes the program as most useful where the disease course is long and when extended periods of time are required to properly measure the intended

clinical benefit; the program is generally less applicable to products intended to treat more acute diseases or where the intended benefit is near-term.

FDA interprets the concept of a serious or life-threatening disease or condition consistent with its other expedited review programs, and the draft guidance provides detail regarding the remaining qualifying criteria under FDASIA. Specifically, FDA notes that regulations implementing the accelerated approval program — which were promulgated prior to FDASIA — limit accelerated approval to products that provide a meaningful therapeutic benefit over existing treatments.<sup>13</sup> FDASIA broadens use of the pathway to situations in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but may be clinically important from a patient and public health perspective. In that sense, FDA acknowledges that FDASIA provides FDA additional flexibility with respect to the accelerated approval program.

In addition, the draft guidance addresses the two types of clinical endpoints that may serve as the basis for accelerated approval: surrogate endpoints and clinical endpoints that can be measured earlier than irreversible morbidity or mortality that are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit (which the draft guidance refers to as “intermediate clinical endpoints”). Surrogate endpoints are markers, such as laboratory measurements, radiographic images, and physical signs, among others, that predict benefits but do not themselves measure the clinical benefits. For example, FDA explains that HIV viral load, as evidenced by a laboratory measure of HIV in plasma, correlates with morbidity and mortality associated with HIV but is not in itself a direct measure of clinical benefit.

An intermediate clinical endpoint is a measurement of a therapeutic effect reasonably likely to predict a clinical benefit. FDA acknowledges it has limited experience with issuing accelerated approval based on such endpoints. FDA, however, identifies a number of examples in which such endpoints could be used to support accelerated approval. For example, FDA believes that where a clinical endpoint demonstrates relatively short-term clinical benefit in a chronic disease setting in which it is essential to confirm longer-term durability of the clinical benefit for traditional approval, but the short term benefit is reasonably likely to predict such benefit, the intermediate endpoint may support accelerated approval.<sup>14</sup>

Finally, the draft guidance addresses the criterion that the endpoint is “reasonably likely to predict clinical benefit.” Ultimately, FDA looks at the plausibility of the hypothesized relationship between the disease, endpoint, the desired effect, and the current supportive evidence. This evidence includes “epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools,” but pharmacologic activity would not be sufficient alone.<sup>15</sup> The draft guidance offers further suggestions as to how best to gather and use evidence for purposes of establishing that the endpoint meets this criterion, and the draft guidance concludes that, whether a drug’s effect on a given endpoint is reasonably likely to predict clinical benefit is a matter of judgment. FDA considers all relevant evidence and makes the determination on a case-by-case basis. Two factors relevant to that determination are the extent to which the pathophysiology of the disease is understood and the extent to which the effect on a surrogate endpoint is known to predict an effect on the disease.<sup>16</sup>

Approval of a product under the accelerated approval program is subject to certain conditions. Under FDA’s accelerated approval regulations, applicants generally must submit to FDA during the preapproval review period all of the promotional materials they intend to disseminate or publish within 120 days after marketing approval. Likewise, applicants generally must submit such materials to FDA 30 days prior to initial dissemination or publication for promotional materials after 120 days following marketing approval.<sup>17</sup> Post-market studies to verify and describe the anticipated clinical benefit or effect on irreversible morbidity

or mortality are also generally required as a condition of approval. Sponsors should submit requests for accelerated approval to the review division during development.

FDA has authority to withdraw approval granted under the accelerated approval program if, among other things, the sponsor fails to conduct any required post-approval study of the drug with due diligence; the post-approval study fails to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit; other evidence demonstrates that the product is not safe or effective under the conditions of use; or the sponsor disseminates false or misleading promotional materials with respect to the product.<sup>18</sup>

## Priority Review

Priority Review is intended for drugs which treat serious or life-threatening diseases or conditions and that, if approved, would provide a significant improvement in safety or effectiveness.<sup>19</sup> As discussed above, the draft guidance adopts FDA's historical interpretation of the "serious" or life-threatening disease or condition criterion. With respect to whether a drug can provide a "significant improvement," the draft guidance explains that FDA makes this determination on a case-by-case basis. The draft guidance provides, as an example, the fact that significant improvement may be illustrated by increased effectiveness in treatment, prevention or diagnosis of a condition; elimination of substantial reduction of a treatment-limiting drug reaction; improved patient compliance that leads to an improvement in serious outcomes; or evidence of safety and effectiveness in a new subpopulation. The priority review designation need not be dependent on evidence from clinical trials comparing a marketed product with the investigational product. That said, FDA suggests that, where possible, sponsors should conduct clinical testing to compare their product to any currently available therapies to demonstrate superiority related to either safety or effectiveness.

The Priority Review designation offers the applicant a shorter review timeline for the application; FDA's goal is to take action on the marketing application within six months as opposed to the traditional 10-month timeline for standard review. FDA reviews all applications to determine whether they qualify for Priority Review, not just applications that request the designation. However, an applicant may specifically request that FDA consider its application for Priority Review, as well. Such designation requests should be made upon submission of the original BLA, NDA, or efficacy supplement, and the request for designation should include a cover letter; the proprietary name and active ingredient or, for biological products, the proper name and trade name; the proposed indication; and a summary of information supporting the request (*i.e.*, how the product meets the criteria for Priority Review). FDA will confirm whether the application is designated Priority Review by Day 60 of the review; the division will inform the applicant in writing of a standard review designation by Day 74 of the review.

## Conclusion

FDASIA's inclusion of the "breakthrough therapy" designation provides drug developers and FDA with a new means to expedite the development and approval of new drugs that may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. Sponsors should understand how this new designation fits with FDA's other tools to expedite clinical development and premarket review, and the draft guidance presents an essential resource for those seeking to account for the various programs, definitions, and concepts which are intended to help streamline the drug development and approval processes. While FDA has been active in granting breakthrough designations — 20 total since enactment of FDASIA<sup>20</sup> — the long-term impact of the law and FDA's implementation remains to be seen, and industry should pay close attention.

If you have questions about this *Client Alert*, please contact one of the authors listed below or the Latham lawyer with whom you normally consult:

**John R. Manthei**

john.manthei@lw.com  
+1.202.637.2211  
Washington, D.C.

**J. Benneville (Ben) Haas**

ben.haas@lw.com  
+1.202.637.1084  
Washington, D.C.

**Elizabeth M. Richards**

elizabeth.richards@lw.com  
+1.202.637.2130  
Washington, D.C.

*The authors would like to thank Bridget Scherbring for her contribution to this Client Alert.*

---

*Client Alert* is published by Latham & Watkins as a news reporting service to clients and other friends. The information contained in this publication should not be construed as legal advice. Should further analysis or explanation of the subject matter be required, please contact the lawyer with whom you normally consult. A complete list of Latham's *Client Alerts* can be found at [www.lw.com](http://www.lw.com). If you wish to update your contact details or customize the information you receive from Latham & Watkins, visit <http://events.lw.com/reaction/subscriptionpage.html> to subscribe to the firm's global client mailings program.

**Endnotes**

- <sup>1</sup> The issuance of the draft guidance was required by the Food and Drug Administration Safety and Innovation Act. Pub. L. No. 112-144, § 901(c), 126 Stat. 993, 1085-86 (2012).
- <sup>2</sup> *Id.* § 901(a)(1)(C), 126 Stat. at 1082.
- <sup>3</sup> 21 C.F.R. § 312.300(b)(1).
- <sup>4</sup> *Id.*
- <sup>5</sup> FDA, Dep't of Health & Human Servs., *Draft Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*, at 3 (June 2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.
- <sup>6</sup> *Id.*
- <sup>7</sup> *Id.* at 5.
- <sup>8</sup> *Id.*
- <sup>9</sup> 21 U.S.C. § 356(b)(1).
- <sup>10</sup> FDA, *supra* note 5, at 9.
- <sup>11</sup> 21 U.S.C. § 356(a)(1).
- <sup>12</sup> 21 U.S.C. § 356(c)(1)(A). Prior to FDASIA, the FDCA authorized FDA to approval a Fast Track product 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. *Id.* § 356(b)(1) (2011). FDA promulgated regulations implementing this former version of the statute, and FDA has not yet amended its regulations to account for FDASIA's amendment to the FDCA.
- <sup>13</sup> 21 C.F.R. §§ 314.500, 601.40.
- <sup>14</sup> FDA, *supra* note 5, at 17.
- <sup>15</sup> 21 U.S.C. § 356(c)(1)(B); New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992).

- 
- <sup>16</sup> FDA, *supra* note 5, at 20.
- <sup>17</sup> 21 C.F.R. §§ 314.550, 601.45.
- <sup>18</sup> 21 U.S.C. § 356(c)(3); 21 C.F.R. §§ 314.530(a), 601.43(a).
- <sup>19</sup> Prescription Drug User Fee Act of 1992. Priority Review is also available for supplements that propose a labeling change pursuant to a report on a pediatric study; applications for drugs that have been designated as qualified infectious disease products; or applications or supplements for drugs submitted with a priority review voucher.
- <sup>20</sup> Janet Woodcock, “Breakthrough” Designation ... Another Powerful Tool in FDA’s Toolbox for Expediting the Development and Review of Promising New Drugs for Serious Conditions, FDA Voice (June 25, 2013), <http://blogs.fda.gov/fdavoices/index.php/2013/06/breakthrough-designation-another-powerful-tool-in-fdas-toolbox-for-expediting-the-development-and-review-of-promising-new-drugs-for-serious-conditions/>.