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FDA Eases Burdens on Expanded Access Use

By Abram Barth, Greg Levine, Leslie Thornton, and Mark Barnes

On Oct. 3, 2017, the Commissioner of the Food and Drug Administration (''FDA''), Scott Gottlieb, M.D., announced in an FDA blog post certain policy changes that ease the process for applying for expanded access use of investigational drugs, devices, and biological products. (FDA Voice Blog, ''Expanded Access: FDA Describes Efforts to Ease Application Process''.) Expanded access programs allow investigational medical products to be made available outside of clinical trials to patients suffering from serious or life-threatening conditions for whom no satisfactory alternative treatment option exists. (*See* 21 U.S.C. § 360bbb.) To obtain an investigational product for a patient under an expanded access program, a physician must, among other prerequisites, obtain approval or permission from FDA, a cognizant institutional review board (''IRB'') (either affiliated with the institution at which the expanded access use will occur or independent), and the manufacturer of the medical product. With its recent initiative, FDA seeks to (i) decrease the administrative burden of IRB review and (ii) address manufacturers' concern that adverse events from expanded access use could impede the company's development program for the investigational product. In light of these changes, drug and device companies, academic medical centers, and hospitals should understand how expanded access programs may now be implemented in a more streamlined manner.

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Expedited IRB Review

Previously, single patient expanded access programs required review by a convened IRB at which a majority of the IRB members are present (known as ''full IRB review''). Expanded access requests often are submitted under time constraints, and convening a quorum of members for full IRB review may have presented an unnecessary administrative delay. FDA's new policy permits a physician who requests a single patient expanded access use to seek FDA authorization of a waiver of full IRB review. The waiver would deem IRB approval to be satisfied by the concurrence of the IRB chairperson or a designated IRB member.

In 2011, FDA requested that the Department of Health and Human Services' Secretary's Advisory Committee on Human Research Protections (''SACHRP'') help address a stakeholder concern that ''administrative burdens associated with IRB review of expanded access are onerous and diminish its practicality, negatively impacting access to investigational drugs for treatment under expanded access protocols, particularly single patient treatment access protocols.'' (SACHRP Recommendations on Single Patient Treatment Use (March 30, 2012).) In response, SACHRP recommended that single patient expanded access programs be eligible for IRB review under an expedited pathway, which FDA has now adopted. Notably, this waiver provision only applies to individual patient expanded access requests and not to intermediate-size expanded access programs (for multiple patients) or to treatment investigational new drug (''IND'') applications (for large cohorts), both of which still require full IRB review.

FDA effectuated this policy change by modifying its Form FDA 3926 for Individual Patient Expanded Access requests for investigational drugs as well as other rel-

evant guidance documents and web pages. Specifically, Form FDA 3926 now includes the following: ''I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.'' FDA's instructions on Form FDA 3296 state that FDA will grant a waiver of full IRB review and approval so long as the requesting physician obtains concurrence by the IRB chairperson or designated IRB member before treatment use begins. (*See* FDA Guidance ''Individual Patient Expanded Access Applications: Form FDA 3926'' (October 2017).) Form FDA 3926 only applies to expanded access requests for investigational drugs; FDA previously had stated that it considered an IRB chairperson's concurrence to be sufficient for medical device expanded access programs. (*See* FDA Guidance on IDE Policies and Procedures (January 1998).)

Sponsor Submission and FDA Use of Adverse Event Data

FDA's announcement also addresses concerns voiced by pharmaceutical and device manufacturers that participation in an expanded access program that yields results inconsistent with the clinical development program may affect the potential commercialization of the product. FDA notes in its blog post that it has ''seen some reluctance among companies to provide investigational drugs for expanded access. This may have been due, in part, to uncertainty about how data for adverse events that occur during treatment under expanded access are viewed by FDA.'' (FDA Voice Blog.) An expanded access program often presents increased risks of adverse events as compared to a clinical trial of the same investigational product because the expanded access patients do not qualify for the ongoing clinical studies, usually due to a more advanced disease stage or additional co-morbidities.

In response, FDA has updated its guidance on ''Expanded Access to Investigational Drugs for Treatment Use'' to explain that the sponsor's written summary of adverse events, which must be submitted at the conclusion of treatment under an individual patient expanded access IND, should include only those events that constitute a ''suspected adverse reaction.'' That is, the event should be reported to FDA ''only if there is evidence to suggest a causal relationship between the drug and the adverse event.'' (*Id*.) This is the same standard for traditional IND safety reporting, and would not sweep in adverse event information for which the available evidence does not provide reason to ''suspect'' that the adverse event was a ''reaction'' to the drug and not simply a temporally related occurrence.

The updated guidance also addresses how FDA intends to use adverse event data reported from expanded access programs. FDA notes the public health importance of early identification of serious adverse events. For example, a relatively rare adverse event that occurs during expanded access may not have surfaced during clinical studies. In fact, FDA states that in a ''very small number of cases,'' adverse event data from expanded access treatment ultimately are reflected in the product labeling. (*Id*.) However, FDA is quick to confirm that it ''is not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug.'' (*Id*.) FDA attributes this to FDA scientific reviewers' understanding that the patient population in expanded access programs is generally sicker and more vulnerable. FDA asserts that it ''is very rare'' to impose a clinical hold due to adverse events observed in expanded access treatment. This suggests that although FDA has placed at least one study on clinical hold as a result of expanded access adverse events, the agency instead is motivated to resolve any problems voluntarily with the sponsor, likely through changes to the protocol or consent form. (*Id*.)

Finally, FDA comments on the collection and use of effectiveness data. FDA acknowledges that although expanded access programs generally are not designed to determine efficacy, the regulations do not prohibit the collection of such data. But FDA concedes that ''it is unlikely that an expanded access'' program ''would yield efficacy information that would be useful to FDA in considering a drug's effectiveness.'' (*Id*.) Even though the efficacy data may not be sufficiently reliable for regulatory purposes because of the uncontrolled nature of expanded access, companies still may seek to collect and analyze effectiveness data for internal research and development purposes. If a company is interested in obtaining efficacy data, we recommend that the expanded access consent form explicitly disclose to the patient that his or her success or failure on the investigational product will be collected and analyzed by the manufacturer for product research and development purposes.

Conclusion

These new policies are part of a larger FDA effort to streamline and reduce administrative burdens and delays in its expanded access programs. For example, in August 2017, FDA drafted a new section to its Manual of Policies and Procedures to set forth the process by which physicians can request emergency use of investigational drugs for individual patient expanded access during and after normal FDA business hours. (*See* § 6030.3.) FDA's activities can be seen as part of a broader discussion ongoing within state legislatures and Congress regarding terminally ill patients' ''right to try'' experimental medical products. As that debate continues, FDA has demonstrated a willingness to take concrete action to facilitate the process for requesting and obtaining expanded access use of investigational medical products.

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