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Client Alert

FDA & Life Sciences Practice Group

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FDA Issues New Form FDA 3926 and Final Guidance for Its Use, a New Approach for Physicians to Request FDA Approval for Expanded Access to Investigational Drugs for Individual Patients

Agency Also Finalizes Additional Guidance Regarding Expanded Access ("Compassionate Use")

On June 2, 2016, the Food and Drug Administration (FDA) issued final guidance "Individual Patient Expanded Access Applications: Form FDA 3926," which explains how licensed physicians may use the simplified application process of new Form FDA 3926 to request FDA approval for expanded access to investigational drugs for treatment use for individual patients.[1] The agency also issued two additional final guidance documents aimed at helping physicians, patients, and industry understand the process for accessing investigational drugs for treatment use ("compassionate use"), where medically appropriate. The guidance "Expanded Access to Investigational Drugs for Treatment Use–Questions and Answers" clarifies how FDA implements its regulations regarding expanded access to investigational drugs for treatment use.[2] The guidance "Charging for Investigational Drugs Under an IND–Questions and Answers" clarifies how patients may be charged for investigational drugs, including drugs for expanded access, under FDA's existing regulations.[3] The new guidance documents do not address expanded access for investigational medical devices.

This client alert focuses on the new and simplified submission process for a licensed physician to request FDA approval for expanded access to an investigational drug for an individual patient because it is a critical advance. The importance of this streamlined process was emphasized in a press release[4] by the FDA Commissioner, Robert Califf, MD:

"As a physician, I understand the importance of being able to access investigational treatments for a patient when there are no other options to treat their serious disease or condition. Access to investigational

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treatments requires the active cooperation of the FDA, industry, and health care professionals in order to be successful. But we know that navigating that process can be challenging and time consuming, and we are committed to reducing the procedural burdens on physicians and patients whenever possible."

As background, on August 13, 2009, FDA revised and consolidated its regulations for expanded access to investigational drugs for treatment use within the Investigational New Drug (IND) regulations at 21 CFR part 312, subpart I. The revised regulations established three categories of expanded access for patient populations based on size: individual patients, including emergency use; intermediate size populations; and larger populations for more widespread use. The regulations define general requirements for expanded access that are applicable to all categories as well as requirements specific to each category, which increase in complexity based on the size of the patient population that will be exposed to treatment use of an investigational product. For each category of expanded access, there are two types of regulatory submissions that may be made: (1) a protocol amendment to the existing IND for treatment use of the investigational drug, or (2) a new IND, which is intended only for expanded access purposes. The latter approach is generally utilized when the sponsor of the existing IND declines to be the sponsor of the drug for expanded access use, or where an IND is not in place at all.

- For intermediate size and larger populations, a treatment protocol amendment is usually submitted to an existing IND by the sponsor (*i.e.*, the drug manufacturer) that holds the existing IND.

- In contrast, for expanded access for a specific individual patient, FDA approval is frequently sought by a licensed physician for a patient under his or her care. In this case, the licensed physician submits a new IND (*i.e.*, an expanded access IND) that is intended to only make the investigational drug available for treatment use for a specific patient, and the physician takes on many of the regulatory obligations of a sponsor-investigator. Because the submission must contain all of the information required for an IND submission under 21 CFR 312.305(b), as well as additional information specific to the expanded access requirements, the licensed physician must also obtain a letter of authorization from the existing IND sponsor (*i.e.*, the drug manufacturer). This letter helps the physician satisfy some of the submission requirements by relying on information in the manufacturer's existing IND, and it allows FDA to access and reference the existing IND.

Since 2009, applications for expanded access have predominantly been IND submissions for single patients. FDA's metrics for approved expanded access submissions for fiscal year 2014 show that nearly 90 percent of all submissions were single patient expanded access INDs, which are submitted by licensed physicians, and of these, 99 percent were approved by FDA.[5] These data underscore the importance of FDA's efforts to streamline the submission process.

INDIVIDUAL PATIENT EXPANDED ACCESS APPLICATIONS: FORM FDA 3926

The new Form FDA 3926 – "Individual Patient Expanded Access Investigational New Drug Application (IND)" – provides a simplified process for the licensed physician to request expanded access to an investigational drug, including emergency use, for an individual patient. The form, which can be accessed on the FDA website, is accompanied by step-by-step instructions. The new form is 2-pages, and FDA estimates that it will require physicians an average of 45 minutes to complete it. Form FDA 3926 is alternative to existing Form FDA 1571, which is used by manufacturers for standard IND submissions for research studies of an investigational drug. Manufacturers who are submitting a protocol to an existing IND for individual expanded access, as well as for all expanded access IND or protocol amendment submissions for intermediate-size or larger populations, must continue to use Form FDA 1571.

Form FDA 3926 contains only ten fields that must be completed by the physician. Notably, it is intended to provide FDA with all of the information that the agency needs to determine if the general requirements for expanded access, the specific requirements for individual patients, and the physician qualifications are met. Among the data that the physician must provide are:

- Clinical information that describes the proposed treatment use (indication), a description of the patient's clinical history, including diagnosis, prior therapy and response to the therapy, and the reason for requesting the proposed investigational treatment, including an explanation as to why the patient lacks other therapeutic options.

- The proposed treatment plan, including the name of the investigational drug, the name of the manufacturer that has agreed to provide the drug, planned dose, duration of therapy, monitoring procedures, and planned modification of the treatment plan if toxicity occurs.

- Documentation of the Letter of Authorization from the drug manufacturer, which is to be attached to Form FDA 3926, granting FDA right of reference to the manufacturer's existing IND.

- Statement of the physician's qualifications.

- Physician's contact information.

- "Authorization to Use Form for Individual Expanded Access." FDA intends to consider a completed form with the box in this field checked to be a formal request by the physician for a waiver of any additional requirements in 21 CFR part 312 for an IND submission.

- Certification statement and signature, whereby the licensed physician certifies that: (1) treatment will not begin until 30 days after FDA receives the completed application and required materials unless

FDA provides earlier notification; (2) the physician will not begin or continue treatment if the FDA places a Clinical Hold; (3) informed consent will be obtained in compliance with the federal requirements; (4) an IRB will be responsible for initial and continuing review and approval of the expanded access use in compliance with the federal requirements; and (5) the physician will conduct the investigation in accordance will all other applicable regulatory requirements. The physician must also acknowledge that in the case of an emergency request, treatment may begin without prior IRB approval provided the IRB is notified of the emergency treatment within 5 working days of treatment.

Form FDA 3926 may also be used for follow-up submissions by the licensed physician, including use as the cover form for the initial written IND safety report, follow-up to a safety report, the annual report, the final summary when treatment is completed, a change in treatment plan, general correspondence, a response to FDA request for information, and a response to a Clinical Hold. Both the actual Form FDA 3926, as well as its guidance document and the new "questions and answers" expanded access guidance document, also clarify that IRB review and approval, as well as informed consent of the patient, are required. Both guidance documents also address that a licensed physician may seek FDA authorization for emergency use of an investigational drug for individual patient expanded access by telephone or other rapid means of communication. If FDA approves emergency use, the physician must submit a request for expanded access authorization to the agency within 15 working days, and may use Form FDA 3926, as well as notify the IRB.

FDA OUTREACH TO PATIENTS AND PHYSICIANS

In the current policy climate where there is intense debate about potential barriers for patient access to investigational drugs for treatment use, FDA has also made new changes to its website landing page for expanded access with intent of making it more accessible and user friendly for patients, including labeling the page as "Expanded Access (Compassionate Use)".[6] In addition to frequent use of the term "compassionate use," FDA repeatedly uses the term "single patient expanded access," which is not included in the regulations, to refer to expanded access for an individual patient that is obtained by a licensed physician. Taken together, the finalization of Form FDA 3926 and the emphasis on "single patient expanded access" throughout the new website suggest that FDA is trying to "re-brand" its public approach to expanded access with a pivot toward enabling patient involvement in obtaining treatment access to investigational drugs through their personal physician. New information pieces include:

- A new patient-targeted webpage that provides patients and their families with extensive information about the expanded access process in non-technical language, including the roles of the patient, FDA, physician and manufacturer. This webpage also includes a new 2-page color brochure that walks the patient through the process for obtaining single patient expanded access through an application submitted to FDA by his or her physician.[7] The brochure presents the patient as having a major role in seeking expanded access through his or her physician, including informing the physician about FDA's tools that enable physicians to request FDA approval for single patient expanded access. It advises that the physician's first step is to contact the drug company to make sure it is willing to provide the

investigational drug, including emphasis that "*FDA cannot make a drug company provide their investigational drug for expanded access; they must do so voluntarily*." The brochure also discloses that the treating physician may request authorization from FDA to charge the patient for the direct costs of making the drug available, and it cautions that the patient and their physician should consider the cost of the investigational drug and any medical services associated with its use that are not covered by third party payers such as Medicare or insurance.

- For physicians, FDA has created a 2-page "how to" color brochure that describes single patient expanded access with a simple step-by-step check list for the physician that intends to seek expanded access for an individual patient. [8] It includes prominently highlighted FDA contact information – including day time and emergency phone numbers. This brochure is a greatly simplified and potentially more accessible guide for physicians than a traditional guidance document. Importantly, the brochure focuses on the application process with little emphasis on the regulatory obligations that the physician will incur as a sponsor-investigator of an expanded access IND for an individual patient.

CONSIDERATIONS FOR DRUG MANUFACTURERS

Manufacturers of investigational drugs should carefully review the new guidance documents, with particular attention to new Form FDA 3926 and its companion guidance document, as well as the updated FDA website landing page for Expanded Access (Compassionate Use). These tools and FDA's new emphasis on "single patient expanded access" are likely to increase patient expectations that their personal physician will seek FDA approval of an investigational drug for treatment use on their behalf. In addition, Form FDA 3926 and its new step-by-step instructions are likely to make it easier and less burdensome for physicians to navigate the process of obtaining FDA approval for expanded access, including emergency use, for an individual patient. Taken together, these developments may increase the number of physician requests for access to an investigational drug for specific patients, including requests for emergency use, and heighten expectations by patients and their families that a manufacturer will voluntarily provide the investigational drug for "compassionate use." Manufacturers should be prepared to handle additional requests by having appropriate protocols and policies in place.

King & Spalding would be pleased to assist in providing you with additional information and considerations about these new developments.

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[1] "Individual Patient Expanded Access Applications" Form FDA 3926. Guidance for Industry" June 2016. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf

Form FDA 3926 – "Individual Patient Expanded Access Investigational New Drug Application (IND)" June 2016. Accessed at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504572.pdf

[2] "Expanded Access to Investigational Drugs for Treatment Use–Questions and Answers. Guidance for Industry." June 2016. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf

[3] "Charging for Investigational Drugs Under an IND–Questions and Answers. Guidance for Industry." June 2016. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351264.pdf

[4] FDA Press Release. Statement from FDA Commissioner Robert Califf, M.D. on the release of the final individual patient expanded access form; June 2, 2016. Accessed at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504579.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

[5] "Expanded Access INDs and Protocols 2009 – 2015." Accessed at http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm443572.htm

[6] FDA website landing page for "Expanded Access (Compassionate Use)". Accessed at http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm

[7] "Single Patient Expanded Access: What YOU Need To Know." Accessed at http://www.fda.gov/downloads/ForPatients/Other/ExpandedAccess/UCM504489.pdf

[8] "Single Patient Expanded Access: Physician Fact Sheet and Application Checklist." Accessed at http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/UCM504494.pdf