Individual Patient Expanded Access Applications: Form FDA 3926

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Additional copies are available from:

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http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
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Contains Nonbinding Recommendations

Individual Patient Expanded Access Applications: Form FDA 3926 Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes Form FDA 3926[2] (Individual Patient Expanded Access – Investigational New Drug Application (IND)), which is available for licensed physicians to use for expanded access requests for individual patient INDs. The terms *compassionate use* and *preapproval access* are also occasionally used in the context of the use of an investigational drug to treat a patient; however, these terms are not defined or described in FDA regulations. Individual patient expanded access allows for the use of an investigational new drug[3] outside of a clinical investigation, or the use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS), for an individual patient who has a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. Form FDA 3926 provides a streamlined alternative for submitting an IND under 21 CFR 312.23 for use in cases of individual patient expanded access, including for emergency use. This guidance and Form FDA 3926 do not apply to other types of expanded access requests, including requests for expanded access for medical devices.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] This guidance has been prepared by the Office of the Commissioner, Office of Policy, Planning, Legislation and Analysis, in cooperation with the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] FDA forms are available on the Internet at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

[3] For the purposes of this guidance, the terms *investigational new drug*, *investigational drug*, *drug*, and *drug product* refer to both human drugs and biological products regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient rather than to obtain the kind of information about the drug that is generally derived from clinical trials. FDA has a long history of facilitating access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions[4] who lack therapeutic alternatives. FDA revised its IND regulations in 2009[5] by removing the existing regulations on treatment use and creating subpart I of 21 CFR part 312 to consolidate and expand the various provisions regarding expanded access to treatment use of investigational drugs.

Subpart I describes the three categories of expanded access:

- Expanded access for individual patients, including for emergency use (21 CFR 312.310)
- Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol — a treatment protocol is submitted as a protocol to an existing IND by the sponsor of the existing IND)[6] (21 CFR 312.315)
- Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations) (21 CFR 312.320)

The revised regulations were, among other things, intended to increase awareness and knowledge about expanded access and the procedures for obtaining investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives. The regulations were also intended to facilitate the availability, when

[4] For the purpose of expanded access to investigational drugs for treatment use, immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether 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 (21 CFR 312.300(b)).

[5] *Federal Register* of August 13, 2009 (74 FR 40900).

[6] For information on the types of regulatory submissions that can be used to obtain expanded access, including treatment INDs or treatment protocols, see the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

appropriate, of investigational new drugs for treatment use while protecting patient safety and avoiding interference with the development of investigational drugs for marketing under approved applications.

The regulations describe criteria that must be met to authorize expanded access use, requirements for expanded access submissions, and safeguards that are intended to protect patients and preserve the ability to develop meaningful data about the safety and effectiveness of the drug through clinical trials or drug development.

A. Expanded Access for an Individual Patient

FDA may permit expanded access to an investigational new drug outside of a clinical investigation, or to an approved drug where availability is limited by a REMS, for an individual patient when the applicable criteria in § 312.305(a) (which apply to all types of expanded access) and § 312.310(a) (which apply specifically to individual patient expanded access, including for emergency use) are met.

Under the applicable criteria in § 312.305(a), FDA must determine that:

- The patient to be treated has a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

- The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

- Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Under the applicable criteria in § 312.310(a):

- The patient's physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

- FDA must determine that the patient cannot obtain the investigational drug under another IND or protocol.

For further information regarding those determinations, please see the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use – Questions & Answers*.[7] In addition, § 312.305(b) of FDA's expanded access regulations sets forth the submission requirements for all types of expanded access requests. Section 312.310(b) contains additional submission requirements for individual patient expanded access requests. A physician submitting a request for individual patient expanded access may satisfy some of the submission requirements by referring to information in an existing IND, ordinarily one held by the investigational drug's manufacturer, if the physician obtains permission from that IND holder (e.g., the drug manufacturer or pharmaceutical company) (§ 312.305(b)(1)). If permission is obtained, the physician should then provide to FDA a letter of authorization (LOA) from the existing IND holder that permits FDA to reference that IND.

One of the requirements under § 312.305(b)(2) is that a "cover sheet" must be included "meeting the requirements of § 312.23(a)." This provision applies to several types of submissions under part 312, ranging from commercial INDs under § 312.23 that involve large groups of patients enrolled in clinical trials to requests from physicians to use an investigational drug for an individual patient. Form FDA 1571 (Investigational New Drug Application (IND)) is currently used by sponsors for all types of IND submissions. However, FDA is concerned that physicians requesting expanded access for an individual patient may have encountered difficulty in completing Form FDA 1571 and providing the associated documents because Form FDA 1571 is not tailored to requests for individual patient expanded access.

To streamline the submission process for individual patient expanded access INDs, FDA developed Form FDA 3926, which is available for physicians to use to request expanded access to an investigational drug outside of a clinical investigation, or to an approved drug where availability is limited by a REMS, for an individual patient who has a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. FDA generally intends to accept submission of a completed Form FDA 3926 to comply with the IND submission requirements in §§ 312.23, 312.305(b), and 312.310(b). FDA intends to consider a completed Form FDA 3926 with the box in Field 10 checked and the form signed by the physician to be a request in accordance with § 312.10 for a waiver of any additional requirements in part 312 for an IND submission, including additional information ordinarily provided in Form FDA 1571 and Form FDA 1572 (Statement of Investigator, which provides the identity and qualifications of the investigator conducting the clinical investigation). FDA concludes that such a waiver of any additional requirements is appropriate for requests for individual patient expanded access INDs because the physician's noncompliance with any such requirements would not pose a significant

[7] For information on expanded access in general, including submitting an expanded access protocol to an existing IND, see the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers*. In a separate guidance, *Charging for Investigational Drugs under an IND — Questions and Answers*, FDA provides answers to questions concerning the regulations on charging for investigational drugs under an IND (21 CFR 312.8). For additional information on expanded access, also see FDA's Web site at http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm.

and unreasonable risk to the individual patient, and the physician's compliance with any such requirements is unnecessary for the Agency to evaluate the IND.

Form FDA 3926 may also be used for certain follow-up submissions to an individual patient expanded access IND, which include the following: Initial Written IND Safety Report (§ 312.32(c)); Follow-up to a Written IND Safety Report (§ 312.32(d)); Annual Report (§ 312.33); Summary of Expanded Access Use (treatment completed) (§ 312.310(c)(2)); Change in Treatment Plan (§ 312.30); General Correspondence or Response to FDA Request for Information (§ 312.41); and Response to Clinical Hold (§ 312.42(e)).

B. Emergency Expanded Access for an Individual Patient

Under § 312.310(d), in an emergency situation that requires the patient to be treated before a written submission can be made, the request to use the investigational drug for individual patient expanded access may be made by telephone (or other rapid means of communication) to the appropriate FDA review division. Authorization of the emergency use may be given by an FDA official by telephone, provided the physician explains how the expanded access use will meet the requirements of §§ 312.305 and 312.310 and agrees to submit an expanded access application within 15 working days of FDA's initial authorization of the expanded access use (§ 312.310(d)(2)). The physician may choose to use Form FDA 3926 for the expanded access application.

III. CONSIDERATIONS AND REGULATORY REQUIREMENTS IN REQUESTING EXPANDED ACCESS FOR AN INDIVIDUAL PATIENT

When a licensed physician would like to obtain an investigational drug outside of a clinical investigation, or an approved drug where availability is limited by a REMS, for an individual patient, the physician should first ensure that the investigational drug can be obtained. If so, the physician should obtain an LOA from the entity that is the sponsor of the IND (e.g., commercial sponsor or drug manufacturer) being referenced. The LOA permits FDA to refer to information that the sponsor of the IND has submitted to FDA (e.g., in a commercial IND). In cases where it is not possible to obtain an LOA (e.g., the entity supplying the drug does not have an IND filed with FDA), the physician should contact the relevant review division at FDA to determine what information is needed to support the expanded access submission. Physicians should also contact the review division if the individual patient expanded access IND is for an approved drug where availability is limited by a REMS. The physician should then submit an individual patient expanded access IND to the appropriate FDA review division and may choose to use Form FDA 3926. Contact information for review divisions may be found on FDA's Web site at http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm.

Under individual patient expanded access INDs, the physician who submits an IND is considered a sponsor-investigator (as defined in § 312.3) and is responsible for complying with the

responsibilities for both sponsors and investigators to the extent they are applicable to the expanded access use, including submitting IND safety reports[8] and annual reports and maintaining adequate drug disposition records. The responsibilities of sponsors and investigators are described in subpart D of 21 CFR part 312 and in related guidance documents, for example, in the guidance for industry *Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects*.

The informed consent requirements in 21 CFR part 50 apply to treatment provided to patients under expanded access INDs, and informed consent must be obtained before initiating treatment, including in the case of emergency use, unless one of the exceptions found in part 50 applies.[9] Additionally, the institutional review board (IRB) requirements found in 21 CFR part 56 apply (see § 312.305(c)(4)), and IRB approval must be obtained before starting treatment under an expanded access IND unless it is for emergency use (in which case the IRB must be notified of the emergency expanded access use within 5 working days of treatment (§ 56.104(c)).[10]

Form FDA 3926 and accompanying instructions may be found on FDA's Web site at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

IV. PROCEDURES AND TIMELINE FOR PROCESSING FORM FDA 3926

In a non-emergency situation, after receiving Form FDA 3926 (i.e., the IND), FDA will assign an individual IND number to the IND and will either allow the treatment use to proceed or put the application on clinical hold (see § 312.42). The IND will go into effect (i.e., treatment with the investigational drug may proceed) after FDA notifies the physician or, if no notification occurs, 30 days after FDA receives the completed Form FDA 3926. FDA generally provides the sponsor with notification acknowledging the complete submission. If the treatment use is not allowed to proceed, FDA generally will notify the physician of this decision initially by

[8] For additional information about FDA's IND safety reporting requirements, please see the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies.*

[9] For information on informed consent in general, see the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet.* When final, this guidance will represent FDA's current thinking on this topic. For additional information on the part 50 informed consent exceptions, see the guidance for institutional review boards, clinical investigators, and sponsors *Exception from Informed Consent Requirements for Emergency Research*.

[10] An IRB means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to assure that the rights and welfare of human subjects are protected, including by determining that informed consent is obtained in accordance with and to the extent required by Federal requirements. Many institutions have their own IRB to oversee human subjects research conducted within the institution or by the staff of the institution. If the physician does not have access to a local IRB, an independent IRB may be used. The Department of Health & Human Services' Office for Human Research Protections maintains a database of registered IRBs. Go to http://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc and click on "Advanced Search." Enter your state to find registered IRBs in your area.

telephone (or other rapid means of communication) and will follow up with a written letter that details the reasons for FDA's decision to place the IND on clinical hold.

If there is an emergency and authorization of the expanded access use is requested before a written submission can be made, the physician must explain how the expanded access use will meet the criteria of §§ 312.305(a) and 312.310(a), as described previously in section II. In these situations, FDA may authorize the expanded access use of the investigational drug, and treatment may begin before FDA's receipt of the written submission (including the LOA), but the physician must agree to submit an expanded access submission within 15 working days of FDA's authorization of the expanded access use (§ 312.310(d)). When treatment involves the emergency use of an investigational drug and approval from an IRB cannot be obtained before treatment, treatment may begin without prior IRB approval provided the IRB is notified of the emergency expanded access use within 5 working days of treatment (§ 56.104).

Secure email between FDA and sponsors is useful for informal communications when confidential information may be included in the message (e.g., confidential patient information). Parties who would like to establish secure email with FDA should email a request to SecureEmail@fda.hhs.gov.

V. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The time required to complete this information collection is estimated to average 45 minutes per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

> Office of Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 51, rm. 6337, Silver Spring, MD 20993-0002

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014.

An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0814 (expires 04/30/2019).