Individual Patient Expanded Access Applications: Form FDA 3926

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Larry Lim, 301-796-3146; or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-7800.

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)

February 2015
Procedural

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Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

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Draft — Not for Implementation

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance introduces and describes draft Form FDA 3926 (Individual Patient Expanded Access—Investigational New Drug Application (IND)). When finalized, draft Form FDA 3926 will be available for licensed physicians to use for expanded access requests for individual patient INDs. Expanded access requests are sometimes referred to as *compassionate use* requests. Individual patient expanded access allows for the use of an investigational drug outside of a clinical investigation 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. When finalized, draft Form FDA 3926 is intended to provide a streamlined alternative for submitting an investigational new drug application (IND) under § 312.23 for use in cases of individual patient expanded access. This draft guidance and draft Form FDA 3926 are not intended to apply to other types of expanded access requests, including requests for expanded access for medical devices.

FDA's guidance documents, including this guidance, 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 the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[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 (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

II. BACKGROUND

On August 13, 2009, FDA published a final rule (74 FR 40900) to amend its IND regulations by removing certain sections of 21 CFR part 312 on treatment use of investigational drugs and adding subpart I of part 312 (21 CFR part 312, subpart I) on expanded access. Subpart I describes the following ways that patients may gain access to investigational drugs through expanded access:

- Expanded access for individual patients, including for emergency use;
- Expanded access for intermediate-size patient populations (smaller than those typical of a treatment IND or treatment protocol); and
- Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations).

The final rule was, among other things, intended to increase awareness and knowledge of expanded access programs 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. It was also intended to facilitate the availability, when 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.

A. Expanded Access for an Individual Patient

FDA may permit expanded access to an investigational new drug for an individual patient when the applicable criteria in 21 CFR 312.305(a) (which applies to all types of expanded access) and 21 CFR 312.310(a) (which applies specifically to individual patient expanded access, including in an emergency) are met. Under the applicable criteria in 21 CFR 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 21 CFR 312.310(a):

- The 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 draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use – Qs & As*.[2] In addition, § 312.305(b)(2) 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. The physician may satisfy some of the submission requirements by referring to information in an existing IND, ordinarily one held by the manufacturer, if the physician obtains permission from that IND holder. 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 licensed physicians to use an investigational drug for an individual patient. FDA is concerned that physicians requesting expanded access for an individual patient may have encountered difficulty in completing Form FDA 1571 (currently used by sponsors for all types of IND submissions) and the associated documents, because it is not tailored to requests for individual patient expanded access.

In an effort to streamline the submission process for individual patient expanded access INDs, FDA intends to make draft Form FDA 3926 (Appendix 1) available, when finalized, for licensed physicians to use to request expanded access to an investigational drug outside of a clinical trial 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 (i.e., for individual patient expanded access, including in emergencies). FDA generally intends to accept submission of draft Form FDA 3926, when finalized, to comply

[2] This guidance (*Individual Patient Expanded Access Applications: Form FDA 3926*) is intended to address the submission of draft Form FDA 3926, when finalized, for an individual patient expanded access IND submitted by a sponsor-investigator. For information on expanded access in general, including submitting an expanded access protocol to an existing IND, see FDA's draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Qs and As*. When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

with the IND submission requirements in §§ 312.23, 312.305(b), and 312.310(b). To the extent that information required under part 312 is not contained in draft Form FDA 3926, FDA intends to consider the submission of that form, when finalized, with the box in item 7 checked and the form signed by the physician, to constitute a request under § 312.10 to waive any other applicable application requirements, including additional information included in Form FDA 1571 and Form FDA 1572 (Statement of Investigator, which provides the identity and qualifications of the investigator conducting the clinical investigation). Although FDA intends to accept draft Form FDA 3926, when finalized, for submitting a new expanded access IND for a single patient, the IND holder (physician) should use Form FDA 1571 for subsequent submissions to his/her IND.

B. Emergency Expanded Access for an Individual Patient

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 over the 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 submission within 15 working days of FDA's initial authorization of the expanded access use (§ 312.310(d)).

III. OVERVIEW OF DRAFT FORM FDA 3926

When a licensed physician would like to obtain an investigational drug for an individual patient, the physician should first ensure that the manufacturer of the investigational drug is willing to provide the drug. If the manufacturer agrees to provide the drug, the manufacturer should provide the physician with a letter of authorization (LOA) that permits FDA to refer to information the manufacturer has submitted to FDA (e.g., in a commercial IND), if applicable. The physician should then submit an individual patient expanded access IND application to the appropriate FDA review division and may choose to use draft Form FDA 3926 (Appendix 1), when finalized, to do so.

Under individual patient expanded access INDs, the physician is considered a sponsor-investigator and is responsible for complying with the responsibilities for sponsors and investigators, including submitting IND safety reports and annual reports and maintaining adequate drug disposition records. The responsibilities of sponsors and investigators are described in subpart D of part 312 (21 CFR part 312, subpart D) and, for example, in the guidance for industry *Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects*.[3]

The informed consent requirements in part 50 (21 CFR part 50) apply to treatment provided to patients under expanded access INDs and protocols, and informed consent must be obtained

[3] This guidance is available at http://www.fda.gov/Drugs/default.htm, under Guidances (Drugs).

before initiating treatment, including in the case of emergency use, unless one of the exceptions found in part 50 applies.[4] Additionally, the institutional review board (IRB) requirements found in 21 CFR part 56 apply (see 21 CFR 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 treatment within 5 working days of treatment).[5]

Draft Form FDA 3926 includes the following information:

Box 1: *Patient's initials* (not the full name, to preserve confidentiality) and *date of submission*.

Box 2: *Clinical information,* including indication, brief clinical history of the patient (age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy), and the rationale for requesting the proposed treatment, including an explanation of why the patient lacks other therapeutic options.

Box 3: *Treatment information*, including the investigational drug's name and treatment plan. This includes the planned dose, route and schedule of administration, planned duration of treatment, monitoring procedures, and planned modifications to the treatment plan in the event of toxicity.

Box 4: *Letter of authorization (LOA)* obtained from the investigational drug's manufacturer and attached to draft Form FDA 3926, when finalized. An LOA grants FDA the right to reference the application for information to satisfy submission requirements, such as a description of the manufacturing facility, chemistry, manufacturing and controls information, and pharmacology and toxicology information. It should include the manufacturer's IND number. In cases where the manufacturer does

[4] For information on informed consent in general, see FDA's draft guidance for industry *Informed Consent Information Sheet – Guidance for IRBs, Clinical Investigators, and Sponsors*. 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*.

[5] 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. In most situations in which patients receive treatment under an expanded access IND, IRB review and approval must be obtained before initiating the treatment. 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.

not have an application already filed with FDA, physicians should consult with the relevant review division to determine what information may satisfy the regulatory requirements. For emergency uses, the LOA and other paperwork may be submitted up to 15 working days after the initial authorization.

Box 5: *Physician's qualification statement* that specifies the medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, the portion of the physician's curriculum vitae (usually the first few pages) may be attached, provided it includes the up-to-date information described in this paragraph.

Box 6: *Physician's name, address, and contact information*, including the physical address, email address, telephone number(s), facsimile number, *and IND number, if known*. If the physician has previously communicated with FDA about expanded access for the individual patient, the physician already may have been issued an IND number by FDA staff. If so, the physician should provide that number. Please note that this is NOT the number for the manufacturer's IND to which the physician has obtained an LOA.

Box 7: *Request for authorization to use Form FDA 3926 for individual patient expanded access* to comply with FDA's requirements for submitting an individual patient expanded access IND. Generally, an IND submission includes additional information, beyond that included in draft Form FDA 3926, which may not be necessary for the purposes of submitting an individual patient expanded access IND. Therefore, consistent with 21 CFR 312.10, FDA intends to consider a completed draft Form FDA 3926, when finalized, with Box 7 checked, to be a request for a waiver of any additional requirements in 21 CFR part 312. FDA concludes that a waiver of any additional requirements is appropriate for individual patient expanded access INDs because the physician's non-compliance with any such requirements would not pose a significant 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. Note that as stated in section II.A of this guidance, after the initial submission of draft Form FDA 3926, when finalized, the IND holder (physician) should use Form FDA 1571 for subsequent submissions to the physician IND.

Box 8: *Certification statement and signature of the physician* certifying that treatment will not begin until 30 days after FDA receives the application unless the submitting physician receives earlier notification from FDA that the treatment may proceed; that the physician will obtain informed consent in compliance with FDA's regulations in 21 CFR part 50; that IRB review of the expanded access use will be obtained in compliance with FDA's regulations in 21 CFR part 56; and 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.

After receiving draft Form FDA 3926, when finalized, (i.e., the IND) in a non-emergency situation, FDA will assign an individual IND number to the IND and will either allow the treatment use to proceed or will put the application on clinical hold (see § 312.42). If the treatment use is not allowed to proceed, FDA generally will notify the physician of this decision initially by telephone and will follow up with a written letter that details the reasons for FDA's decision to place the IND on clinical hold. The IND will go into effect (i.e., treatment with the investigational drug may proceed) once FDA notifies the physician or, if no notification occurs, 30 days after FDA receives the completed draft Form FDA 3926, when finalized.

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. Background. In these situations, treatment with the investigational drug 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 (21 CFR 56.104).

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

APPENDIX 1: DRAFT FORM FDA 3926

Please see attached appendix for draft FORM FDA 3926.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Individual Patient Expanded Access Investigational New Drug Application (IND)

(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. xxxx-xxxx
Expiration Date: Xxxxxxx xx, 201x
See PRA Statement on page 2.

1. Patient's Initials

Date of Submission

2. Clinical Information

Indication

Brief Clinical History *(Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, rationale for request)*

3. Treatment Information

Investigational Drug Name and Manufacturer

FDA Review Division, if known

Treatment Plan *(Including the dose, route of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)*

4. Letter of Authorization (LOA), if applicable *(Obtained from manufacturer of the drug)*

☐ I have attached the LOA from the manufacturer. *(Attach the LOA; if electronic, use normal PDF functions for file attachments.)*

☐ I have not attached the LOA. I commit to providing the LOA to FDA.

5. Physician's Qualification Statement *(Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. (If attaching the CV electronically, use normal PDF functions for file attachments.)*

6. Physician Name, Address and Contact Information

Physician Name *(Sponsor)*		Email Address of Physician
Address 1 *(Street address, No P.O. boxes)*		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		Telephone Number of Physician
City	State	FAX Number of Physician
ZIP Code		Physician's IND number, if known

7. Request for Authorization to Use Form FDA 3926

☐ I request authorization to submit this Form FDA 3926, to comply with FDA's requirements for submitting an individual patient expanded access IND. I will use Form FDA 1571 for subsequent submissions to this IND.

8. Certification Statement: I will not begin treatment until 30 days after FDA's receipt of this application unless I receive earlier notification from FDA that treatment may begin. I also certify that I will obtain informed consent, consistent with Federal requirements, and that an Institutional Review Board (IRB) that complies with the Federal IRB requirements will be responsible for initial and continuing review and approval of this treatment use. I understand 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.

Signature of Physician	**Date**

For FDA Use Only

IND Number	Is this an emergency individual patient IND? ☐ Yes ☐ No	Is this indication for a rare disease (prevalence < 200,000 in the U.S.)? ☐ Yes ☐ No

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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