

## Compassionate Use Navigator Information for Physicians

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As a physician, you must have wished there would be more treatment options for patients who have not responded to available therapies. Thank you for your willingness to seek access to an investigational drug for your patient through compassionate use (expanded access).

### Application Process Overview

- ✓ Identify the investigational drug and the company that makes it.
- ✓ Apply to drug manufacturer: Ask the company to provide the drug for your patient. Secure a Letter of Authorization from the company.
- ✓ Apply to the U.S. Food and Drug Administration for authorization of a compassionate use request for your patient.
- ✓ Apply for IRB approval.
- ✓ Submit required safety reports.

## Apply to a Drug Manufacturer

This is the first and most important step. The drug manufacturer must agree to provide the investigational drug. Without its agreement, you will not be able to proceed and your patient will not receive the drug.

### Who to contact?

You will need to find a point of contact at the drug company to whom you will send a request to provide the drug, along with your patient's medical history.

Your point of contact may be a regulatory affairs official, the chief medical officer, CEO, VP for clinical development, or it may be a general inquiries line.

Some companies post a form on their website for you to complete, others provide a phone number or an email address to send an inquiry. There is no standard industry application form. Most drug manufacturers will consider your request on a case-by-case basis.

There is no legal limit on the time a company can take to respond to a request, and there is no requirement for companies to provide reasons for denials. If the company declines to provide the drug, FDA advises that your options are to use approved treatments, enroll the patient in a clinical trial or an ongoing expanded access program, or to consider designing a new protocol or a new trial.

### Obtain LOA from a drug company

If the company agrees to provide the drug, ask for a letter of authorization (LOA). You will need the LOA to apply for the FDA's authorization.

In most cases, manufacturers will have submitted documentation to FDA, and received permission to study the drug you are requesting. The LOA should reference this documentation, including the number of the investigational new drug (IND), or the New Drug Application (NDA) or Biologics License Application (BLA) number. These numbers are issued by FDA to the company.

If a manufacturer does not have an IND, FDA requires the following information in the letter: chemistry, manufacturing, and controls information, and pharmacology and toxicology information, including a description of the manufacturing facility. The drug manufacturer may prefer that you submit to FDA a separate individual patient IND application. The company will be supplying the drug, but will not itself

be submitting the IND for your patient's access. In this case, you, not the company, will be the sponsor for that IND.

If FDA authorizes the compassionate use request, it will issue another IND number to you. The IND number serves as FDA's authorization for the company to provide the drug. Upon receipt of the IND number from the FDA, you must then provide that number to the manufacturer so the company can ship the drug directly to you.

## Apply for FDA Authorization

After a drug manufacturer has agreed to provide an investigational drug, the next step is to obtain FDA authorization. It is a good idea to call the **FDA Review Division** and describe your patient's situation prior to sending a written application. An FDA official will help you determine whether your patient's condition requires you to follow a non-emergency (individual patient IND) or emergency (emergency IND) pathway, which is used when treatment of the patient must occur within a very limited number of hours or days. FDA authorizes compassionate use in 99.5% of cases.

Your steps will be as follows:

- Call FDA's drug review division to discuss your planned submission.
- Send required paperwork to FDA by fax or email, followed by hard copy.
- Obtain informed consent and IRB approval.
- Receive an IND number from FDA.
- Submit this IND number to the manufacturer.
- Receive the drug from the manufacturer and begin treatment.

### Application paperwork

1. **Form 3926**, Individual Expanded Access Applications. It should take about 45 minutes to complete. Although this form has not been officially approved yet, FDA will accept it. Form 3926 takes less time to complete than the currently used Form FDA 1571 and Form 1572.
2. **Letter of Authorization** from the drug company.
3. A cover letter specifying that this is a request for an individual patient IND or an emergency IND and your contact information.
4. A copy of the **informed consent**.

Information required on Form 3926 includes:

- a. Brief **clinical history** of the patient including:
  - diagnosis,
  - disease status,
  - prior therapy and response to prior therapy,
  - rationale for requesting the proposed treatment. It can include a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug, or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options.
- b. Proposed **treatment plan** including:
  - the dose,
  - route of administration,
  - planned duration,
  - monitoring procedures and modifications (e.g., dose reduction or treatment delay) for toxicity.

- c. **Name of the manufacturer** (drug supply reference statement) and a statement that a Letter of Authorization to cross-reference an appropriate IND of the supplier or Drug Master File (DMF) of the manufacturer is included.
- d. **Informed consent statement** that states that informed consent and approval of an appropriate Institutional Review Board (IRB) will be obtained prior to initiating treatment.
- e. Investigator qualification statement that specifies the training, experience, and licensure of the treating physician. The first two pages of a **Curriculum Vitae** typically contain this information and are usually sufficient.

### Receive FDA approval

In practice, FDA will review the paperwork for oncology patients seeking compassionate use in **about 2 business days**, although by law it has up to 30 days to review the application. If the request is approved, an IND number will be issued by the FDA and you will be contacted by phone or fax, and a letter will follow. It will contain the name and telephone number of the FDA official to whom questions about the application should be directed.

In the unlikely situation when treatment is not allowed to proceed (i.e., a clinical hold is placed on the application), FDA will notify you by phone and in writing.

### Contact information for FDA

The initial request may be made by fax to the appropriate drug review division with hard copies of documentation to follow.

For questions about expanded access for a specific investigational drug, contact the appropriate review division, if known, or CDER's Division of Drug Information (DDI), if not known, at phone:

**301-796-3400 or 855-543-3784; fax: 301-431-6353; or e-mail: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov).**

For questions about expanded access for emergency use for investigational biologics, contact CBER's Office of Communication, Outreach, and Development at phone:

**240-402-7800 or 800-835-4709; or e-mail: [industry.biologics@fda.gov](mailto:industry.biologics@fda.gov).**

For questions about non-emergency individual expanded access for biologics, contact CBER at:

**240-402-8010 or 800-835-4709.**

### **Mailing addresses** (*courier service can be used*)

*For a drug – An original and two photocopies:*

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

*For a biologic product – An original application and a CD with a copy:*

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Document Control Center  
10903 New Hampshire Avenue  
WO71, G112  
Silver Spring, MD 20993-0002

### **Emergency requests**

Your application process will be quicker if the patient needs the drug on an emergency basis because you may proceed before submitting paperwork to FDA or an IRB. FDA defines an emergency as the case in which:

- the physician considers the product is **immediately** needed for the patient's serious or life-threatening condition;
- no satisfactory alternative standard therapy is available;
- the patient cannot receive the product through any existing clinical trials or expanded access protocols;
- access to the drug is needed before the written application can be submitted (approximately within the next 24-72 hours).

Your steps will be as follows:

- Call FDA at the emergency numbers below.
- Receive an IND number from FDA.
- Submit this IND number to the manufacturer.
- Obtain informed consent.
- Notify an IRB of planned emergency use if there is no time to obtain IRB approval.
- Receive the drug from the manufacturer and begin treatment.
- Apply for IRB approval within 5 days of the beginning of treatment.
- Submit required paperwork to FDA within 15 days of the beginning of treatment.

About 30-50% of compassionate use requests FDA receives are considered emergency requests.

## **Emergency contact information at FDA**

Emergency requests may be submitted over the phone, by email or by fax. You will need to explain your patient's situation and agree to submit the required paperwork within 15 working days. An FDA official may provide verbal authorization for compassionate use over the phone.

During **normal business hours** contact Center for Drug Evaluation and Research, Division of Drug Information (DDI) (8am-4:30pm EST weekdays):

Phone: **301-796-3400 or 855-543-3784**

Fax: 301-431-6353

E-mail: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov).

**After hours** – or if you can't reach anyone at DDI – contact the Emergency Call Center (after 4:30pm EST weekdays and all day on weekends) at:

**1- 866-300-4374 or 301-796-8240.**

## **Submit IND number to drug manufacturer and await shipment of the drug**

Upon receipt of the IND number from the FDA, you must then submit the IND number to the manufacturer, and the company will ship the drug directly to you. The IND is considered active as soon as the number was issued.

## Apply to IRB

You must apply for an Institutional Review Board's (IRB) approval for compassionate use prior to initiating treatment. You should specify in the application that the primary intent is treatment, not clinical research.

If your institution does not have an IRB you can:

- Use a for-profit IRB. This is a private IRB that reviews research proposals at a cost.
- Partner with an IRB from your local hospital/institution. Universities that are affiliated with hospitals will most likely have an IRB.
- Start an IRB at your institution.

Some drug companies may require an IRB approval letter before the drug will be shipped. If treatment cannot be delayed, some IRBs have sent manufacturers a written statement indicating that the IRB is aware of the proposed use and considers it to meet the requirements for emergency compassionate use. Although this is not a formal IRB approval, the acknowledgment letter has been acceptable to drug companies.

In an emergency life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval, by law you may begin treatment and report the emergency use of the investigational drug to an IRB within 5 working days (21 CFR 56.104). Some IRBs have specific procedures for approving emergency requests. However, you should notify the IRB right away and follow your institution's procedures for such cases.

Requirements of IRBs differ, but as a general rule you should email the following to the IRB:

- description of case and treatment plan, including justification for compassionate use;
- a proposed consent form;
- any available documentation from the FDA regarding the emergency IND.

## Obtain informed consent

In general, the consent should satisfy federal requirements under **21 CFR 50**.

In a rare situation when it may not be possible to obtain consent from the child's legal guardian, federal regulations (21 CFR 50.23 (a)) may allow for a consent waiver.



## Safety Reports Requirements

FDA requires all sponsors of IND applications, including physicians who administer an investigational drug to a patient, to report adverse events.

### What to report?

As a treating physician you must report any suspected adverse reaction to treatment that is **both** serious and unexpected in an **IND Safety Report**. Before submitting an IND safety report, you need to ensure the event meets all three of the definitions:

- Suspected adverse reaction;
- Serious;
- Unexpected.

*If the adverse event does not meet all three of the definitions, it should not be submitted as an IND safety report.*

**Adverse reaction** is an adverse event where there is a reason to conclude that the drug caused the event. A **suspected adverse reaction** is an adverse event for which there is a reasonable possibility that it is caused by the drug. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.

**Serious adverse event** refers to an event that results in the following outcomes:

- death;
- a life-threatening adverse event (places the patient at immediate risk of death);
- in-patient hospitalization or prolongation of an existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

**Unexpected adverse event** refers to an event that is not consistent with previously described risk information, or occurs at a specificity or severity that has not been previously observed. This definition is also used in the absence of an investigator's brochure in which observed adverse events are described.

Deciding whether an adverse event meets the definition of a suspected adverse reaction can be difficult, but this decision is critical to avoid the submission of uninformative IND safety reports. You should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event.

Any relevant **additional information** which becomes available and is necessary to evaluate the suspected adverse reaction that pertains to a

previously submitted IND safety report must be submitted as a Follow-up IND Safety Report.

### When to report?

- **Serious and unexpected adverse events** that are fatal or life-threatening must be reported to FDA as soon as possible, and **no later than 7 days** after they occur.
- **Suspected adverse reactions** or other safety information that are not serious or life-threatening must be reported **no later than 15 calendar days** after the event.
- A **Follow-Up IND Safety Report** should be submitted as soon as new information is available, and **no later than 15 calendar days** after you receive the information. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.
- At the **conclusion of treatment**, you must provide FDA with a **written summary** of the results of the expanded access use, including adverse effects, the patient's response, drug disposition, and other relevant information. When submitting this summary report, you may request FDA to close the IND application.
- If the investigational treatment continues for a year or longer, there is a requirement to make an **annual report** to FDA for any year during which your patient has received the investigational drug. You will need to submit a brief report of the progress within 60 days of the anniversary from the date when the original IND application went into effect.

### Who to report to?

In addition to reporting to the FDA, you need to report to the drug company and your IRB. The FDA believes that the pharmaceutical company is better positioned than the individual investigator to assess the overall safety of the investigational drug because it has access to serious adverse event reports from multiple study sites and multiple studies and is able to aggregate and analyze these reports. The company is also more familiar with the drug's mechanism of action, class effects, and other information. For these reasons, investigators must immediately **report any serious adverse event to the company**, whether or not the investigator considers the event to be drug related. Drug companies can impose additional reporting requirements when they provide the drug.

You might also have an obligation to report adverse events to your IRB. In general, when an adverse event meets the criteria for reporting it to FDA, it should also be considered an "unanticipated problem" and **reported to the IRB**.

## **How to report?**

Safety reports to FDA must be submitted by email, fax or telephone to the Review Division that authorized the expanded access request. Use FDA Form 3500A together with Form 1571.

## **Protocol amendments**

After an IND application has gone into effect, you may amend the application as needed. You are expected to submit protocol amendments for new protocols or changes to existing protocols before implementation of any changes. Amendments could include any increase in drug dosage or duration of therapy beyond that described in the current protocol, change in the design of a protocol, addition or elimination of a test or procedure, or addition of a new investigator. If the amendment concerns change in application sponsor or addition of a new investigator, Form 1572 should be included in addition to Form 1571.

## **More information**

Please use the Reporting Requirements Chart for links to reporting forms and deadlines.

For detailed explanation of the definitions, requirements, and procedures related to IND application safety reports and the responsibilities of IND applications sponsors with regard to such reporting, see *Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies*.

## Help us build a registry of requests – share your case

To develop effective compassionate use policies, it is necessary to understand the unmet need. Currently, only the number of requests that were granted by both the companies and FDA is known. There is no data on the numbers of applications submitted for pediatric patients, or applications that were denied.

Let us know to which companies you have made compassionate use requests. Let us know the point of contact in the company that you used, whether the company responded and in how much time, and whether your request was ultimately granted. And, please let us know how your patient did – was there any possible benefit from the drug? Were there unexpected toxicities?

Please help us build a registry of compassionate use application outcomes by answering a few questions for our database, or email Elena Gerasimov, Program Director, at [Elena@kidsvcancer.org](mailto:Elena@kidsvcancer.org).

## Thank you!

### COMPASSIONATE USE APPLICATION FLOWCHART

