Compassionate Use Navigator – Information for Physicians

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).

There are currently about 900 cancer drugs in development for adult patients, but almost none are being studied in children. Often children are not eligible for clinical trials of new drugs only because of their age. Sometimes physicians have reasons to believe that a drug being tested for one type of cancer might be of some benefit to a patient with another type of cancer.

Compassionate use is a process that allows patients with a serious or life-threatening disease, such as cancer, to access an experimental drug when they do not qualify for a trial, or when there is no trial.

If you are treating such a patient and know of an investigational drug that might help, we can help you in the application process. Kids v Cancer does not have the medical expertise to guide you in a decision as to whether there is a drug that merits a compassionate use request.

Application process overview

- Identify an investigational drug and the company that makes it.
- Ask the pharmaceutical company – the manufacturer — to provide the drug for your patient.
- Secure a Letter of Authorization from the company.
- Apply for IRB approval.
- Obtain informed consent from your patient.
- Apply to the U.S. Food and Drug Administration for approval of a compassionate use request for your patient, either as a “single patient IND” (Investigational New Drug), also called “individual patient expanded access”, or for an “individual patient expanded access protocol.”
- Submit the IND number received from the FDA to the drug manufacturer.
- Receive the drug from the drug manufacturer and start treatment.

Application steps in depth

Assess the situation

The severity of your patient’s disease or condition is a matter of clinical judgment. However, compassionate use requests are usually associated with life-threatening situations or persistent or recurrent morbidity that has a substantial impact on day-to-day life.
You should establish whether your patient’s situation is an emergency, when the drug is needed immediately, as FDA has a shorter application process for emergencies and may authorize the use of a drug over the phone.

Your patient must be unable to participate in a clinical trial of the drug you are applying for, and there must be no approved therapeutic alternative. You should feel confident that the risks from the disease are higher than the risks from the investigational treatment. The patient, or the patient’s guardian, must be willing to sign an informed consent accepting possible risks of using an investigational product.

**Request compassionate use access from a drug company**

This is the first and most important step. 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. Please search our database of drug manufacturers’ contacts for compassionate use requests (under construction), or contact us for assistance in locating the point of contact at a company. We will do the search for you.

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.

Most drug manufacturers will consider your request on a case-by-case basis. There is no standard industry application form, and different companies will ask for different clinical information about your patient.

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. 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.

Kids v Cancer can assist you in understanding the criteria that the company may consider when reviewing the application, and can review the request before it is sent.

**Obtain LOA from a drug company**

If the company agrees to provide the drug, ask it for a letter of authorization (LOA). You will need to submit the LOA to apply for the FDA’s authorization. Here is a [sample template](#) of LOA.

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 if a BDA or BLA has been submitted. These numbers are issued by FDA to the company.
In a rare case if a manufacturer does not have an IND, FDA needs to have the following information included in the letter: chemistry, manufacturing, and controls information, and pharmacology and toxicology information, including a description of the manufacturing facility. Usually this information is included in the manufacturer’s original IND application.

As the sponsor of the existing IND for the drug, the drug manufacturer may prefer that you submit a separate individual patient IND application for your patient. 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 called a 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 submit that number to the manufacturer so the company can ship the drug directly to you.

**Request FDA authorization**

**Emergency requests**

Your application process will be shorter if the patient’s need for a drug is an emergency. FDA defines an emergency as the case in which access to the drug is needed immediately due to a life-threatening situation and a patient needs to be treated before a written application can be submitted. About 30-60% of the compassionate use requests FDA receives are considered emergency requests.

**Contact the 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 [see non-emergency section below] within 15 working days.

An FDA official may provide verbal authorization for compassionate use over the phone and authorize shipment of the drug.

- During normal business hours contact Center for Drug Evaluation and Research, Division of Drug Information (DDI) (8am-4:30pm EST weekdays):
  
  i. Phone: 301-796-3400 or 855-543-3784
  ii. Fax: 301-431-6353
  iii. E-mail: 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.
Use [this checklist](#) to make sure FDA requirements have been fulfilled.

If FDA authorizes compassionate use – which it does in 99.5% of cases – it will issue an IND number. You will need to submit this number to the drug manufacturer. The drug will be shipped directly to you.

**Non-emergency requests**

Prior to initiating non-emergency use, and within 15 days after starting emergency compassionate use treatment, you will need to submit the following paperwork to the FDA.

In 2015, FDA announced it would dramatically streamline the process for compassionate use applications. Although the FDA’s website states that Form 1571 is needed ([Form 1571](#) and [instructions](#) on how to complete it), in practice FDA will accept the shorter and easier [Form 3926](#), Individual Expanded Access Applications, published at the end of FDA’s draft guidance document. It fulfills the [requirements listed on FDA’s website](#) and should take 45 minutes to complete:

a. Brief clinical history of the patient including diagnosis, disease status, prior therapy, response to prior therapy and rationale for requesting the proposed treatment.
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. Reference a published protocol or journal article if appropriate.
c. Drug supply reference statement which names the supplier or manufacturer 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. The treating physician must contact the supplier or manufacturer for such a statement.
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.

It is not necessary to complete FDA Form 1571 if you are submitting Form 3926 instead.

**Individual patient expanded access IND application.** The vast majority of compassionate use applications to FDA fall into this category. If you have just one patient who needs an investigational drug and you are applying for a drug that you have not administered before, you will be applying for a “single patient IND (Investigational New Drug),” also called “single patient access.” FDA uses the terms “expanded access,” “access,” and “treatment use” interchangeably to refer to the use of an experimental drug. You will become a “sponsor of the emergency IND treatment application,” or “sponsor-investigator.” In practice, a sponsor is either you (the treating physician), or the drug company.
State at the top of the correspondence and on a mailing cover that this is a request for an individual patient IND for treatment use (specifying whether it is an emergency IND or individual patient IND).

Unless FDA notifies you that treatment may begin earlier, there is a 30-day waiting period before treatment with the drug may begin.

*Individual patient expanded access protocol.* If you are already a sponsor of an IND and are applying to add a patient to the existing IND – for instance, you want to treat a second patient with the same investigational drug for which you already have an IND — this is called a “single patient protocol.”

Only the company or individual who holds an IND may apply for a single patient protocol submission. If the company is the sponsor of the existing IND, it can – but rarely does — submit an individual patient access protocol to its existing IND to allow your patient access to the drug. It is also called “protocol amendment” or “access protocol.” In this scenario, the company remains a sponsor of the existing IND, and you are the investigator for the access protocol.

The application process is largely the same as for a single patient IND. Make sure to include a reference to the existing IND in the cover letter. FDA will have assigned you a project manager who can answer your questions.

A Letter of Authorization from a drug manufacturer is not required when submitting an expanded access protocol to an existing IND application.

There is no 30-day waiting period before treatment with the investigational product may begin, but the protocol must be received by FDA and have approval by an IRB before treatment may begin.

Both Single Patient IND and Single Patient Protocol submissions can be emergency or non-emergency.

FDA published [Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use](https://www.fda.gov/drugs/guidance-for-industry/expanded-access-investigational-drugs-treatment-use) that answers frequently asked questions.

**Receive FDA approval**

If the request is approved, an IND number will be issued by the FDA and you will be contacted by phone or fax with a letter to follow. It will contain the name and telephone number of the FDA official to whom questions about the application should be directed.

While generally individual patient access is limited to a single course of therapy for a specified time, FDA may authorize multiple courses of therapy or chronic therapy for individual patient access if a condition requires extended treatment.
If the treatment use is not allowed to proceed (i.e., a \textit{clinical hold} is placed on the application), FDA will notify you initially via a telephone call, and then send a letter that will provide the reasons for FDA’s denial of the request.

\textit{Contact information for FDA}

The initial request may be made by fax to the appropriate \textit{drug review division} with a letter to follow.

For questions about expanded access for a specific investigational drug, contact the appropriate \textit{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.

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.

For questions about non-emergency individual expanded access for biologics, contact CBER at: 240-402-8010 or 800-835-4709.

The initial IND submission should be mailed in triplicate (an original and two photocopies) to:

\begin{quote}
\textit{For a drug:}
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266
\end{quote}

\begin{quote}
\textit{For a therapeutic biological product:}
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
\end{quote}

\textbf{Apply to IRB and obtain informed consent}

\textbf{Emergency}

In an emergency situation where there is not sufficient time to obtain Institutional Review Board’s (IRB) approval, you may begin treatment and report the emergency use of the
investigational drug to an IRB within 5 working days (21 CFR 56 (c)). Some IRBs have specific procedures for approving emergency requests.

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 for treatment use or justification for why informed consent will not be sought; and any available documentation from the FDA regarding the emergency IND.

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.

**Obtain informed consent** from your patient or your patient’s legal guardian. When it may not be possible to obtain consent, federal regulations (21 CFR 50.23 (a)) allow for a consent waiver. FDA may authorize access for an individual patient without written consent if you and a physician not involved in clinical investigation of the drug you are applying for certify in writing that:

- The patient is in a life-threatening situation.
- The physician cannot communicate with the patient.
- Time is not sufficient to obtain consent from the patient’s legally authorized representative.
- No alternative method of approved or generally recognized therapy is available that provides equal or greater likelihood of saving the patient’s life.

If immediate use of a drug is needed to preserve the patient’s life, and there is no time to obtain a determination from a second physician that the conditions listed described above are met, you as the treating physician may administer the treatment. You must have the written determination reviewed and signed by an independent physician within 5 working days after emergency use of the drug.

You can edit this sample informed consent form as needed. In general, the consent should satisfy federal requirements under 21 CFR 50.

**Non-emergency**

You must apply for IRB approval for compassionate use prior to initiating treatment. The full IRB review is required. You should specify in the application that the primary intent is treatment, not clinical research. A sample overview of IRB application procedure is provided here as a guide, but every institution’s IRB rules and requirements are different.

If your institution does not have an IRB you can:
• Partner with an IRB from your local hospital/institution. Universities that are affiliated with hospitals will most likely have an IRB.
• Use a for-profit IRB. This is a private IRB that reviews research proposals at a cost.

You can search the database of registered IRBs [here](#).

**Submit IND number to the 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 so the company can ship the drug directly to you. The IND is considered active as soon as the number was issued.