



MRCT Center

Expanded Access to
Investigational Products

A Practical Approach for
Sponsors, Physicians,
and Institutional Review
Boards



Framework

BIOETHICS COLLABORATIVE



**MULTI-REGIONAL
CLINICAL TRIALS**

THE MRCT CENTER of
BRIGHAM AND WOMEN'S HOSPITAL
and HARVARD

Version 1.1

1 December 2017

Expanded Access to Investigational Products

A Practical Approach for Sponsors, Physicians, and Institutional Review Boards

Table of Contents

1. Resources for Sponsors: Evaluation of Requests for Investigational Products Through the Individual Patient Expanded Access Program.....	2
1.1 Background.....	2
1.2 Overarching Principles for Sponsor Considerations of Expanded Access.....	3
1.3 Considerations for Sponsors in Decision-Making about Expanded Access.....	4
1.4 Transparent Communication of Sponsor Policies and Processes	8
2. Resources for Treating Physicians: Individual Patient Expanded Access to Investigational New Drugs	9
2.1 Introduction.....	9
2.2 Considerations for Physicians in Decision-Making Regarding Expanded Access.....	9
2.3 Regulatory Background	12
2.4 Physician’s Toolkit	16
3. Resources for IRBs/RECs: Evaluation of Requests for Investigational Products Through the Individual Patient Expanded Access Program.....	28
3.1 Background.....	28
3.2 Considerations for IRBs in Decision-Making about Expanded Access.....	29
3.3 Glossary and Definitions.....	30
4. Resources and References	31

Table of Figures

Figure 1: Types of Expanded Access That Occur During the FDA’s Drug Development/Approval Process.....	13
Box 1: Non-Emergency Use and Emergency Use.....	16
Box 2: Necessary Patient and Product Information	17
Box 3: Checklist for Emergency and Non-Emergency Expanded Access Procedures	21

1. Resources for Sponsors: Evaluation of Requests for Investigational Products Through the Individual Patient Expanded Access Program

1.1 Background

The role of the pharmaceutical and device companies is generally to discover, develop and market safe and effective drugs, biologics and devices. The process of drug development—from target identification, lead drug optimization, preclinical development and clinical experimentation, to review and approval by cognizant regulatory authorities—is a long and complex process. The determination of safety and efficacy of an investigational product is typically accomplished through well-designed, prospective, controlled clinical trials. Not all patients, however, have access to those clinical trials, for either clinical, logistical, practical, or other reasons. For seriously ill patients who are unable to participate in a clinical study and for whom no equivalent or satisfactory treatment option is available, access to an investigational product outside of a clinical trial may sometimes be considered. Expanded access (alternatively termed “compassionate use,” “preapproval access,” or “early access”) programs have been developed to provide access to investigational or unlicensed products (drugs, biologics, and devices) to such patients. As described more fully below, sponsor policies regarding expanded access programs should be accessible and clear.

Applicable national laws and regulations govern this process within each country. For example, the European Medicines Agency has described how programs may be created in the European Union (EMA, 2010), as well its own role in these programs (in the EMA termed “compassionate use”) (EC, 2004, Regulation No. 726/2004). Notably, however, each EU Member State is responsible for regulating, coordinating and implementing its own expanded access (compassionate use) programs, including for individual patients on a named basis (EC, 2001, Directive 2001/83). These describe compassionate use programs for groups of individual patients, and access is arranged through their doctor, the product manufacturer and the regulatory authority. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for overseeing the “early access to medicine scheme (EAMS),” a three step process (MHRA, 2014). In India, per the Drugs and Cosmetic Act 1940 and Rules 1945, the Drug Controller General of India (DCGI) provides oversight of use of an unapproved drug in the country by a patient (Rule 36) or by a hospital or institution (Rule 34) (CDSCO, 2014). Codified guidance for expanded access in certain countries such as China does not appear to be readily available. It is, obviously, very important to consult the cognizant national regulatory agency prior to proceeding with expanded access in order to understand specific requirements and regulations.

In the US, on September 16, 2016, the US Department of Health and Human Services (HHS) issued the Final Rule for Clinical Trials Registration and Results Information Submission, referred to as “Final Rule” as required by Title VIII of the Food and Drug Administration (FDA)

Amendments Act of 2007 (FDAAA). Pertaining to expanded access, the Final Rule requires the Sponsor to disclose information about whether expanded access to an investigational product is available on the Study Registration and Results posting on the US portal of www.clinicaltrials.gov. Compliance with regard to Expanded Access will require Sponsors to complete a separate “expanded access registration” record for any unapproved drug product that is available through either a protocol or individual IND expanded access program. April 18, 2017 is the effective date for compliance.

Subsequent to the codification of the Final Rule, the 21st Century Cures Act was signed into law in December 2016. Section 561A of the Act requires drug manufacturers to publicly disclose their expanded access policy and procedures for making a request.

In the US, the Food and Drug Administration (FDA) has defined three variations of the expanded access program: one each for large populations (“treatment IND”), for “intermediate size” populations, and for the individual patient (21 C.F.R. §312 Subpart I). Here we discuss only programs, including those for emergency use, designed to address physician requests on behalf of their individual patients (21 C.F.R. §312.310). We address specifically those programs regulated in the US, although the relevant issues and overarching considerations are applicable to any decision regarding expanded access to investigational products and are common among all countries and their national regulatory agencies. These considerations are discussed further below.

1.2 Overarching Principles for Sponsor Considerations of Expanded Access

As a threshold consideration, the application of certain ethical principles should guide decision making whenever an expanded access request is considered:

- All patients should be treated fairly and equivalently.
- Patients should not be put at risk of unnecessary harm.
 - The risk of potential harm is not greater than the risk of the disease or condition.
 - Some information as to the potential clinical benefit, potential harm, dose and proposed treatment plan is available.
- Adequate supply of the investigational product is or can be made available.
 - The investigational product must be in sufficient supply not only for the treatment program of the patient and for similar future patients, but for the drug development program.
 - Timely completion of appropriately-designed clinical trials is the fastest method to develop data for submission to the regulatory agency for their review and approval, thereby guaranteeing availability of products that are safe and effective to the broadest group of individuals.

1.3 Considerations for Sponsors in Decision-Making about Expanded Access

The sponsor must decide whether to provide the investigational product for the potential benefit of an individual patient in response to a request from a physician. This decision is not always straightforward. As much as the sponsor may wish to assist, there are countervailing considerations. Is there sufficient evidence that the potential benefit of the investigational product balances potential risks and harms? Will provision of the investigational product impede the progress of clinical trials for any reason (e.g., by limiting drug supply or by permitting patients who could be clinical trial participants access to product outside the trial, thereby delaying trial recruitment or even biasing the results)? Will the investigator (here, the treating physician) execute his or her responsibilities so as not to jeopardize the drug development program? Sponsors may have significant data about the investigational products that are not available to the public: what may seem straightforward to the treating physician and to the patient may be far more complex when all the data are known. Here we review considerations of and by the sponsor when approached by an individual physician for individual patient expanded access. For the discussion below, we assume that no intermediate-size expanded access program or treatment IND is open for the investigational product, as that would be the most available and straightforward pathway for access. We intend these considerations to be helpful both for the sponsor as well as for the physician, patient, and institutional review board (IRB)/research ethics committee (REC) to understand the factors that inform these decisions.

1. What is known about the patient, the patient's condition, and the suitability and availability of a clinical trial?

- a. Does the patient have a serious or immediately life-threatening disease or condition? In the absence of a serious or life-threatening disease or condition, the patient has time to wait for definitive data to emerge regarding safety and efficacy.
 - i. *Serious disease or condition* is defined by the FDA as 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 (FDA, 2009, 21 C.F.R. §312.300).
 - ii. *Immediately life-threatening disease or condition* is defined by the FDA as 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 (EMA, 2010).

- b. Has the patient exhausted all other satisfactory or comparable approved treatments for the disease or condition? The risks, safety profile and potential benefits of the investigational product are unknown or incompletely known; all other available approved treatments should be given or considered in advance of the expanded access request.
- c. Are there any suitable and available clinical trials in which the patient could participate?
 - i. Is the disease or condition for which access to the product is being requested already being addressed by an open clinical trial (i.e. a trial actively enrolling) through which the test product (or similar product) could be made available?
 - ii. Is the patient eligible for an ongoing clinical trial? If not, what is the nature of the ineligibility? Is the ineligibility related to the safety or efficacy of the investigational product? For instance, a clinical trial for an investigational agent that is excreted via the kidney or liver may exclude, for safety reasons, individuals with poor renal or hepatic function.
 - iii. If the patient is eligible for a clinical trial, is there an appropriate site to which the patient may be referred? Is referral practical and possible? For instance, significant travel for a seriously ill individual may not be possible, even if all other issues could be resolved. Is it possible and practical to open a site for enrollment that could accommodate the patient and similarly situated patients who may also seek access to the test product?

2. What is known about the investigational product and its availability? It is important to remember that investigational products have not yet been reviewed or approved by the cognizant national regulatory agency. The potential risks and benefits are not yet established and not fully known. Nevertheless, the sponsor may have access to information about the product that the requesting physician does not.

- a. Does the sponsor have safety or risk information about the investigational product, whether published or not, that is applicable to the specific patient and would inform the decision?
 - i. If it is decided that the investigational product would not be appropriate for the disease or condition or for the patient, is it possible to share the explanation with the requesting physician?
- b. If it would be medically justified to provide the investigational product to the patient, is the treatment course known, and is the amount of product required known? Is there sufficient supply of the product so that the progress of ongoing and planned clinical trials will not be adversely affected? If not, can production be increased or scaled to accommodate?

- i. Timely completion of well-designed and executed clinical trials is the most rapid method to assess safety and efficacy of an investigational product; data can then be reviewed by the FDA (or appropriate national regulatory agency). Approval will permit general access by and dissemination to all patients. Any cause of appreciable delay of the drug development program is problematic.
- c. If sufficient drug supply is available, and the patient is an appropriate candidate for the investigational product, is marketing approval likely to be pursued in the United States (or appropriate country)? If not, the sponsor should determine whether the provision of drug would be fair and equitable, as expanded access may need to be continued in that national jurisdiction, for that patient, even though other patients would not have such access. This presents logistical and ethical issues. In any event, the FDA (or the appropriate regulatory authorities of the country in which the investigational product would be supplied) must be consulted and must concur with any decision to offer access.

3. If it is decided that the investigational product can and will be provided, does the treating physician understand his or her responsibilities in the process?

- a. Is the treating physician familiar with the country, region, and/or state specific legal and regulatory requirements for administering the investigational product? Will the treating physician apply for an investigational new drug (IND) application to the FDA?
- b. Is the treating physician aware of his or her responsibilities in the process, including:
 - i. Applying to and obtaining approval from the FDA, if required, and a research ethics committee (REC) or an institutional review board (IRB) prior to any provision of the investigational product?
 - ii. Obtaining and documenting appropriate informed consent from the patient or his or her legally authorized representative prior to treatment?
 - iii. Maintaining accurate records of the case history and observations related to provision of product, including adverse events?
 - iv. Maintaining accurate documentation of the administration of investigational product, including dates, quantity and use?
 - v. Reporting obligations to the regulatory authority? To the IRB/REC? To the sponsor?
 - vi. Communicating with the patient throughout the process?
 - vii. Maintaining confidentiality of information about the patient and about the investigational product?

- viii. Complying with applicable FDA (national) laws and regulations.
- c. If the treating physician will apply to the FDA for permission to administer the investigational product, will the sponsor provide a letter of authorization (LOA) or other documentation (e.g., the investigator's brochure and the IND application)? Will the sponsor allow the treating physician to rely on the information in the existing IND? If not, why not and is it possible to share the explanation with the requesting physician?

4. Are there other considerations (e.g., financial or other resource requirements) before a final decision is made?

When the final decision is made, the sponsor should communicate with the treating physician. If provision of the investigational product is not possible, it is helpful to explain the decision-making process to the physician, as well as any possible alternatives for the patient. For instance, the physician should be informed as to which changes in clinical condition might prompt re-review by the sponsor of the expanded access request for the patient.

If the decision is made to provide expanded access to the investigational product, the sponsor should (1) provide a LOA to the physician, (2) following FDA and IRB/REC approval, arrange for distribution and transport of the product and (b) communicate specific instructions to the treating physician (e.g., timing of reporting of serious adverse events or unanticipated problems, documentation requirements), providing appropriate forms and templates if available. If the sponsor has decided to allow the physician to rely upon the information in the existing IND, the sponsor should (4) provide a copy of the investigator's brochure and the IND application to the physician. It should be clear that the approval is for the specific patient and that remaining product must be returned to the sponsor or destroyed (and documentation provided) and not administered to another individual, even one with a similar clinical history. Further, any limitations to future use should be clarified (e.g. that the sponsor can provide investigational product for the treatment course outlined, but not automatically or necessarily for any changes to that treatment plan).

The sponsor should be aware that provision of expanded access in one set of circumstances implies that the sponsor will consider similar requests in the future. Fairness and equity expectations should be considered in advance.

Finally, the sponsor should consider whether the national regulatory authority permits (or requires) full data gathered during expanded access treatment to be reported to the sponsor and possibly used for later regulatory submissions. Some jurisdictions do not allow such reporting and use of data, while other jurisdictions may not have addressed this issue, and some may require reporting of serious adverse events and unanticipated problems even in the expanded access setting. In any event, it may be important for a sponsor to work with the treating physician and the cognizant regulatory agency to anticipate this issue, and address it explicitly in the application for expanded use and the informed consent.

1.4 Transparent Communication of Sponsor Policies and Processes

The new Final Rule and the 21st Century Cures Act require pharmaceutical and device manufacturers to make their policies for processing, evaluating, and responding to requests for expanded access publicly available. The policy is to outline whether and when expanded access to an investigational product will be considered, and the process by which treating physicians can request access if appropriate. The Act does not require companies to offer expanded access. Companies are mandated to provide, at minimum, the following information:

- a. Contact information for facilitating or submitting a request
- b. Procedures for making a request
- c. Criteria for evaluating a request and responses to a request
- d. Anticipated timeline for acknowledging receipt of a request
- e. Hyperlink or reference to clinical trial record about a requested investigational drug

The availability and accessibility of a clear and transparent process for requests can assure fairness and deliberateness in the process and help to forestall political, media, regulatory and ethical controversies. We recommend that pharmaceutical and device companies make these processes and policies readily accessible in order to aid physicians and patients who are navigating the process of requesting expanded access. We also recommend that pharmaceutical and device companies consider participating in the Reagan-Udall Foundation for the FDA Expanded Access Navigator program (<http://navigator.reaganudall.org>) and for questions email navigator@reaganudall.org.

2. Resources for Treating Physicians: Individual Patient Expanded Access to Investigational New Drugs

2.1 Introduction

The expanded access program has been developed to provide access to investigational or unlicensed products (drugs, biologics, and devices) to seriously ill patients who (1) have no other satisfactory or comparable treatment options and (2) are unable to participate in a clinical study. Generally, the expanded access program (sometimes termed “compassionate use program” or “preapproval access program”) applies to investigational products that are not approved for any purpose in the country where access is sought.¹ Local laws and regulations, as well as manufacturers’ or pharmaceutical companies’ policies, govern the process and approval; any use must conform to such laws, regulations, and policies. Before discussing the process by which a physician requests expanded access to an investigational product (drug, biologic, or device) for an individual patient, it is important to consider whether such a request is reasonable and in the best interests of the patient. Understanding how to approach expanded access has become particularly relevant, as patients are more active participants in their own care and information is more readily available through the Internet and social media, among other methods. Further, in the US, since 2014, the majority of states² have passed what are termed “Right-to-Try” laws that allow patients, under certain circumstances and through their physician, the right to ask a company directly for access to an investigational product, bypassing FDA review and approval. To date, these laws have not been tested in situations FDA has been bypassed to obtain access to an investigational drug. Further, Thus, a physician should understand the issues involved in expanded access in order to be able to advise patients, if asked, and/or to initiate such requests, as appropriate.

2.2 Considerations for Physicians in Decision-Making Regarding Expanded Access

In the US, expanded access to investigational products is only available to patients that (1) have a serious or life-threatening illness, (2) have exhausted all other therapeutic options and have no comparable or satisfactory alternatives, (3) are not eligible for or cannot participate in ongoing clinical trials, and (4) understand and agree to the risks of the investigational product.

Physicians have a fiduciary responsibility to their patients, and in all instances, are motivated to

¹ Generally, an approved product can be prescribed for an individual patient to treat an “off-label” disease or indication; there is no need to engage in an expanded access program. Rarely however, an expanded access program is necessary (e.g. in the US, when product availability is limited by a risk evaluation and mitigation strategy [REMS] program) or preferable (e.g. early use in a neonatal ICU setting in which risk is high and experience is lacking). These special cases follow the same process as that described here.

² As of October 2017, 38 states have passed Right to Try laws. Notably, the Right to Try Laws do not require physicians to prescribe unapproved products, manufacturers or companies to provide investigational products, nor insurance companies to pay for them.

determine what is in the best interest of their patient. In the absence of therapeutic options for a critically ill individual, the choice to pursue expanded access may seem apparent; however, it is important to recognize the risks, both known and unknown, of an investigational product as well as the unknown and uncertain benefit. Indeed, as clinical trials are often ongoing, the relevant data to determine safety and efficacy are still incomplete.

Drug development is a long and complex process. Preclinical studies generally include animal studies and some evaluation for toxicity. Phase I clinical trials assess safety, Phase II trials expose additional patients to the product to refine whether or not there is evidence of efficacy and safety, but it is not until Phase III trials—so called “registration trials”—that sufficient data are collected to determine efficacy and safety with statistical significance. These data are then submitted to the cognizant regulatory authority for its review and approval. Thus administration of an investigational product, whether a drug, biologic, or device, is not without risk: not only may the investigational product not “work” (or be of therapeutic benefit) but it may do harm; toxicity is possible. The physician—and the patient—must appreciate the limitations of current knowledge and the potential harm that administration of the investigational product may cause and know that the majority of investigational products that begin to be tested in humans fail and are never brought to market.³

Notwithstanding this caution, the patient who explores expanded access faces few alternative options: a therapeutic trial of an unknown or incompletely known investigational product, comfort measures, supportive care, or other. In these cases, the physician is responsible for exploring the options with the patient, interpreting what is known and unknown, and educating the patient about the risks and unknown benefits of expanded access. The physician’s role is to be helpful to the patient and to be satisfied that the patient has autonomy and is able to exercise individual choice. Towards that end, the physician is advised to consider the following questions:

1. Regarding the patient:

- a. Does the patient have a serious or immediately life-threatening disease or condition?
If yes, then ask:
- b. Has the patient exhausted all comparable or satisfactory alternative approved therapies?
If yes, then ask:
- c. Is the patient a candidate for any ongoing clinical trial, considering the inclusion and exclusion criteria, the location of the trial, and other practical and logistical challenges?

If there is an appropriate clinical trial, the request for expanded access is likely to be

³ McKee, A. E., Markon, A. O., Chan-Tack, K. M., & Lurie, P. (2017). How Often Are Drugs Made Available Under the Food and Drug Administration's Expanded Access Process Approved? *Journal of Clinical Pharmacology*, 57(S10).

denied. As part of the drug and device development process, sponsors generate data to help regulators determine whether or not an investigational product is safe and effective. Regulatory agencies are obligated in turn to review the submitted data and render a decision regarding safety and efficacy. If approved, the product will then be made generally available. While the fiduciary responsibility of a physician is to the individual patient, the responsibility of regulatory agencies is to the health of its population, and of the sponsor for making products available for societal benefit. Therefore, expanded access should only be considered when the product cannot be provided within an ongoing and enrolling clinical trial.

2. Regarding the investigational product:

- a. What is known about the risks, toxicities, and potential benefit of the investigational product?
 - i. It may be helpful to ask the patient for any information that he or she may have.
 - ii. The medical literature may be helpful, but may not reflect information from on-going or recent studies.
 - iii. The sponsor may have information not available in the literature or other means. It is always worth trying to contact the company to access information that they may have (see below).

The sponsor may decline to offer expanded access to the investigational product for a number of reasons including (1) information that it has obtained from other trials, (2) lack of sufficient product availability such that provision to the individual patient may or will compromise completion of a clinical trial or the drug development program, or (3) logistical, financial or other reasons. The company may not release, and is under no obligation to release, information, particularly if incomplete.

3. Regarding treatment and subsequent steps:

- a. If the patient is an appropriate candidate and the risks of administration of the investigational product is acceptable in light of the alternatives, then:
 - i. Does the patient understand the risks of the treatment and is he or she willing to proceed?
 - ii. Is the planned course of treatment defined? Generally, the “course” of treatment is determined as a component of the approval process with the FDA after all the data from the product development program has been analyzed. In expanded access programs, however, this information is not yet available. Physicians will find it helpful to extrapolate from the treatment plan of an ongoing clinical trial with inclusion and exclusion

criteria that most nearly match the patient and to discuss the plan with the sponsor. That said, it is important to outline the individualized treatment plan, as well as the outcome measures that will be used to continue or discontinue treatment, to the extent possible in advance of initiating the expanded access program.

- b. The physician will have significant responsibilities in his or her role not only as the treating physician but also as the sponsor-investigator in this context.⁴ It is important to know those responsibilities and the various processes and procedures that are necessary, involving the institutional review board (IRB)/research ethics committee (REC), the sponsoring company, and the regulatory agency. The discussion below and the delineation of the steps involved are meant to be helpful in that regard.

2.3 Regulatory Background

We will focus on the processes and regulations in the US although local laws, regulations and guidance⁵ as well as sponsor requirements must be consulted in advance of proceeding with any request. In the US, the US Food and Drug Administration (FDA) has developed programs and processes to assist patients, physicians and the industry in the provision of investigational products when there is no comparable or satisfactory therapy available to diagnose, monitor or treat the patient's disease or condition (21 C.F.R. §312 Subpart I). As use of an investigational product is envisioned in all programs, submission of an "investigational new drug (IND)" or "investigational device exemption (IDE)" application to the FDA is required. As a general matter, the purpose is to provide access to products for patients that are seriously ill or have life-threatening diseases or conditions, not to develop generalizable knowledge regarding the safety or efficacy of a product.

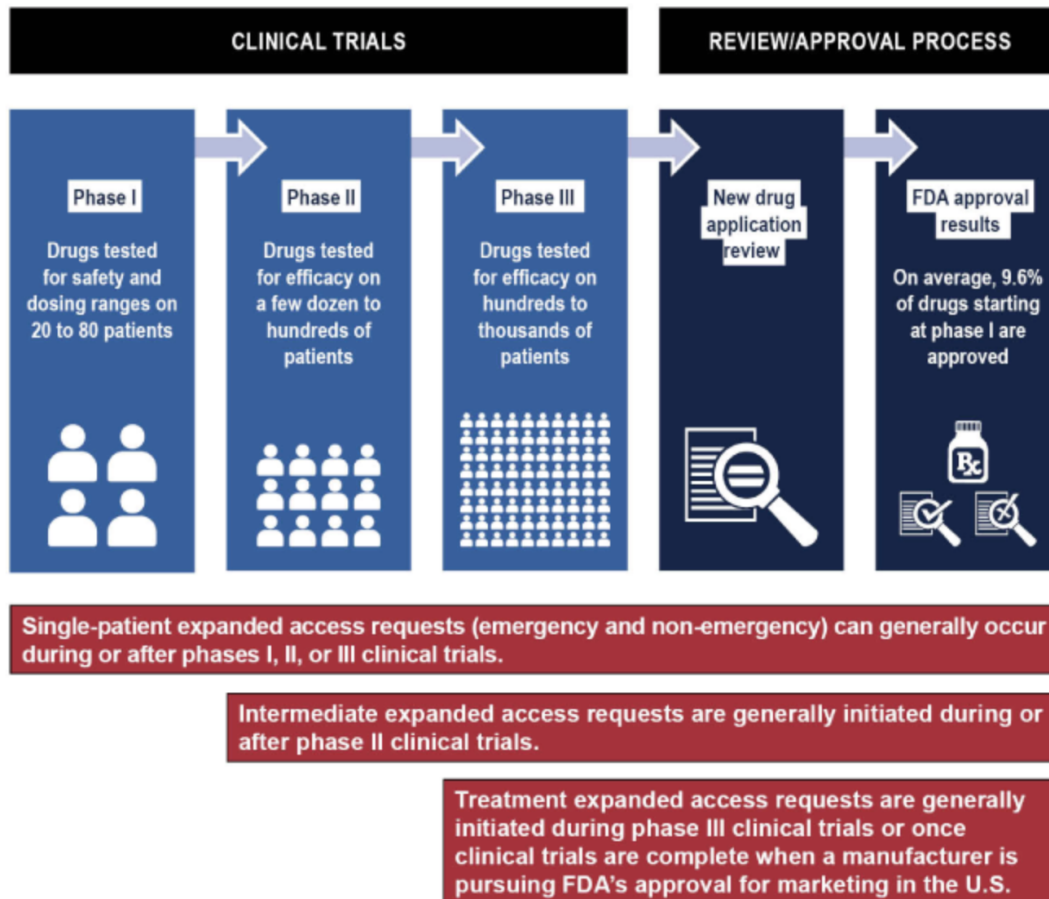
The FDA has developed programs for widespread treatment use of products (a "**treatment IND**"), intended for patients with serious or immediately life-threatening diseases or conditions usually during the time period when clinical trials have been completed and the sponsor is pursuing regulatory approval (21 C.F.R. §312.320) and for **intermediate-size patient**

⁴ Because the treating physician will be functioning as a sponsor-investigator, and in this case, prescribing the product under an individual patient IND/IDE, we advise the physician to ensure that prescribing the unapproved product is a "covered" activity under the doctor's professional liability policy.

⁵ Other jurisdictions have specific regulations. The European Medicines Agency, for instance, has described how programs may be created in the European Union; however, each EU Member State is responsible for coordinating and implementing its own program (EMA, 2010). In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for overseeing the "early access to medicine scheme (EAMS)," a three step process (MHRA, 2014). In India, per the Drugs and Cosmetic Act 1940 and Rules 1945, Drug Controller General of India (DCGI) provides oversight of an unapproved drug in the country by a patient (Rule 36) or by a hospital or institution (Rule 34) (CDSCO, 2014.) Codified guidance for expanded access in certain countries such as China does not appear to be readily available. It is always important to consult local regulatory agencies prior to proceeding with expanded access. The considerations discussed here are applicable to the evaluation of the appropriateness of expanded access to investigational products for any individual patient.

populations in settings in which the FDA has received multiple expanded access requests for the same indication (21 C.F.R. §312.315). These two programs differ from the program of expanded access to INDs for an individual patient in that the FDA has already approved the program and a clinical research protocol has already been written, reviewed and approved by one or more IRBs/RECs.⁶ (see Figure 1).

Figure 1. Types of Expanded Access That Occur During the FDA’s Drug Development/Approval Process



Source: GAO analysis of FDA data. | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and when a new drug is being tested for a life-threatening ailment, the drug development process may be expedited by going through only one or two phases of clinical trials before an application is submitted to FDA for marketing approval.

From: US Government Accountability Office. FDA has taken steps to improve the expanded access program but should further clarify how adverse events data are used. GAO 17-564. Released July 11, 2017. <https://www.gao.gov/products/GAO-17-564>. Accessed November 25, 2017

⁶ Institutional policy may require that the physician nevertheless have the protocol reviewed by his or her local IRB/REC, but the process is usually much simpler to execute.

The program of **expanded access to INDs for an individual patient**, including that for emergency use, is given in 21 C.F.R. §312.310. Only expanded access programs for an investigational product to be used for the treatment of an individual patient by a licensed physician, will be discussed here.

The treating physician should be aware that there are several steps in obtaining expanded access for an individual patient. These include patient assessment and evaluation; contact with the product manufacturer or drug supplier (the “sponsor” and usually the pharmaceutical or device company)⁷ with or without a request for a letter of authorization (LOA); submission of an individual patient expanded access IND or IDE supplement to the FDA, and FDA review and approval; submission of a protocol and informed consent document submission to an institutional review board (IRB), and IRB review and approval; and reporting and follow up obligations. We recommend that the physician contact the sponsor immediately after a decision is reached to request expanded access and, if the supplier agrees to provide the product, that both FDA and IRB/REC applications be submitted essentially concurrently. Recent experience has shown that FDA approves >99% of all expanded access requests for individual patients it receives and in a timely fashion.⁸ IRB review and approval may take longer than, and may follow, the process at the FDA. Note, however, that the product may not be given to the patient until both FDA and IRB approvals have been obtained.

There are two types of individual patient expanded access requests: (1) Non-Emergency and (2) Emergency requests. For all non-emergency cases, the FDA and IRB must receive a written application in advance. When a patient’s condition is dire and there is insufficient time to submit a written application, a physician can request expanded access from the FDA over the phone (see below). At that time, the FDA will decide whether or not the expanded access request can proceed as an emergency request. Nevertheless, the requesting physician must submit the application to the FDA within 15 working days of approval; the processes therefore are not different in substance, only in timing. The IRB may also review an application as an emergency; follow up written documentation must be submitted within the time period specified by institutional policy of the responsible IRB (usually 5 days).⁹

⁷ We use the general term “sponsor” to denote that entity that has the ability to review and approve the provision of the investigational product, and can supply the product if approved. Generally, this is the pharmaceutical or device company that manufactures the product, but may be a drug or device supplier or designee. Occasionally other entities (e.g. government agencies) will be the cognizant agency able to review, approve, and release the product. The term “sponsor” used here should not be confused with the “sponsor” of the individual patient expanded access IND application to the FDA.

⁸ Jarow, J. P., Lemery, S., Bugin, K., Khozin, S., & Moscicki, R. (2016). Expanded access of investigational drugs: the experience of the Center of Drug Evaluation and Research over a 10-year period. *Therapeutic innovation & regulatory science*, 50(6), 705-709.

⁹ We recommend that the treating physician contact his or her institutional IRB or an independent or recommended IRB as soon as possible after the sponsor agrees to make the investigational product available. (see Section 2.4 below)

The treating physician may submit FDA Form 3926¹⁰ to the FDA in order to request individual patient expanded access IND/IDE. Released in June 2016, Form FDA 3926 is an electronic, streamlined application for requesting individual patient expanded access, for which detailed instructions for completion have been made available.¹¹ If for some reason Form 3926 cannot be used, the individual patient expanded access IND may be submitted, per Forms FDA 1571¹² and 1572,¹³ as a protocol amendment to an existing IND if amenable to the sponsor (usually the pharmaceutical company). Alternatively, the IND/IDE may be submitted as a new application by the treating physician “under whose immediate direction an investigational drug is administered or dispensed for an expanded access use.”¹⁴ We recommend that the treating physician utilize Form FDA 3926 whenever possible.

For expanded access to a device, the sponsor will have to submit an IDE supplement to the FDA (21 C.F.R. §824.35). In cases where a device does not have an IDE filed with the FDA, the physician and sponsor will need to contact the FDA (See Steps 2 and 3, below).

The treating physician serves as the IND sponsor-investigator (21 C.F.R. §312.305(c)(3)) and should be familiar with his or her roles and responsibilities, including securing informed consent from the patient after review and approval by an institutional review board (IRB); maintaining and reporting, as required, case reports, drug disposition and adverse event records; and other responsibilities. Often, the new IND will reference an existing IND with permission of the sponsor. **The checklist and tools provided here are meant to assist the treating physician in pursuing expanded access for the patient.**

Several resources for requesting expanded access currently exist for patients, patient advocates, and physicians, including:

- Kids v Cancer (<https://www.kidsvcancer.org/>) has created a [Compassionate Use Navigator](#)¹⁵ that aims to assist the pediatric oncology community in understanding and applying for expanded access. In addition, Kids v Cancer also provides personalized assistance to patients pursuing expanded access and to physicians submitting requests and reports to the sponsor, FDA, and IRB.

¹⁰ <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504572.pdf>

¹¹ Instructions for filling out form FDA 3926 – Individual Patient Expanded Access, Investigational New Drug Application (IND). Available at:

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504574.pdf>. Accessed November 25, 2017.

¹² HHS FDA Investigational New Drug Application.

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf>, and instructional directions for completion:

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM182850.pdf>

Accessed November 25, 2017.

¹³ HHS FDA Investigational Statement of Investigator.

<https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

¹⁴ <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.305>

¹⁵ See Kids v Cancer, “Compassionate Use Navigator.” <http://www.kidsvcancer.org/compassionate-use/>. Accessed November 25, 2017.

- The Regan-Udall Foundation (<http://reaganudall.org/>) for the Food and Drug Administration has drafted plans for an [Expanded Access Navigator](#),¹⁶ which will aim to be an educational resource for patients and healthcare providers as well as a centralized resource for information about requesting individual patient expanded access.
- The Regulatory Affairs Professional Society (RAPS; <http://www.raps.org>) has created a [guide](#)¹⁷ to the FDA’s regulations on expanded access.
- Harvard Catalyst, the Harvard Clinical and Translational Science Center, has created a Physician Checklist to Obtain Expanded Access IND for Treatment of the Individual Patient.¹⁸

2.4 Physician’s Toolkit

Step 1. Patient Assessment

- Patient Evaluation:** When considering expanded access to an investigational product, a physician must evaluate the risks of providing the investigational product against the risks of the patient’s disease or condition. The patient must have a serious disease or condition, for which no alternative comparable treatment exists. Additionally, any extant clinical trials should be closed or inaccessible to the patient (see <https://clinicaltrials.gov>).
- Determine patient eligibility (21 C.F.R. §312.300) and whether emergency or non-emergency indication (Box 1):

Box 1: Non-Emergency Use and Emergency Use

- The patient has an “serious disease or condition.”** (See Appendix I: Glossary and Definitions)
- There are no alternative comparable or satisfactory treatments that are approved and available to the patient.**
- There are no clinical trials open or accessible to the patient.**¹⁹
- The potential benefits of providing the investigational product to the patient outweigh the potential risks.**

¹⁶ See Regan – Udall Foundation for the Food and Drug Administration, “Draft Project Proposal: Expanded Access Navigator for Individual Patient Access.” <http://navigator.reaganudall.org/about>. Accessed November 25, 2017.

¹⁷ See Regulatory Affairs Professional Society (RAPS), “Regulatory Explainer: FDA’s Expanded Access (Compassionate Use) Program.” <http://www.raps.org/Regulatory-Focus/News/2015/02/04/18343/Regulatory-Explainer-FDAs-Expanded-Access-Compassionate-Use-Program/>. Accessed January 10, 2017.

¹⁸ Harvard Catalyst. Harvard Clinical and Translational Science Center. Physician Checklist To Obtain Expanded Access IND For Treatment Of Individual Patient. https://catalyst.harvard.edu/pdf/regulatory/Single_Patient_IND.pdf. Accessed November 25, 2017.

¹⁹ Please see ClinicalTrials.gov, an online database of clinical trials worldwide, to determine whether or not any clinical trials are open to the patient. <https://clinicaltrials.gov>. Accessed January 10, 2017.

Emergency Use Only

- Is the patient’s disease or condition “immediately life-threatening”?** (See Appendix I: Glossary and Definitions)
- Is there insufficient time for FDA submission and IRB review?**

If the patient meets the criteria above, the physician must then request the sponsor to provide the product, providing sufficient information for the sponsor to make an appropriate decision.

In order to request a **Letter of Authorization** (Step 2) from a Sponsor and in order to complete **FDA Form 3926** (Step 3), the **following information about the patient and product is needed and should be collected** (Box 2):

Box 2: Necessary Patient and Product Information

Patient Information:	Product Information
<ul style="list-style-type: none"> <input type="checkbox"/> Age <input type="checkbox"/> Gender <input type="checkbox"/> Weight <input type="checkbox"/> Allergies <input type="checkbox"/> Diagnosis <input type="checkbox"/> Clinical history <input type="checkbox"/> Prior therapies and responses: <input type="checkbox"/> Explanation of why patient’s lack other therapeutic options <input type="checkbox"/> Rationale for requesting expanded access 	<ul style="list-style-type: none"> <input type="checkbox"/> Product Name <input type="checkbox"/> Manufacturer <input type="checkbox"/> Indication <input type="checkbox"/> Treatment Plan (Dosage; Means of Administration; Duration; Monitoring Procedures)

Step 2. Approval from Supplier/Manufacturer (the “sponsor,” usually the pharmaceutical or device company)

The physician must contact the supplier/manufacturer (“sponsor”) to ensure that the sponsor will agree to provide the investigational product, if approved by the FDA and IRB. It is often advisable to contact the sponsor early in the process of considering expanded access for the patient: the sponsor will generally have information about the investigational product that is difficult to access by any other means. The sponsor will also be able to inform the physician of ongoing clinical trials that may be appropriate for the patient, of intermediate-size or treatment IND availability, or of prior experience with expanded access (and potential IRB and FDA contacts). Please note that a sponsor may not, and is under no obligation to, approve the request even if the patient meets eligibility for expanded access.

In both emergency cases and non-emergency cases, the supplier must agree to provide the investigational product.

- ❑ **The physician contacts the sponsor:** The physician must contact the sponsor to ensure that the sponsor will provide the investigational product. The 21st Century Cures Act, passed in December 2016, requires sponsors to make their policies for processing, evaluating, and responding to expanded access (also termed ‘compassionate use’) publicly available. The policy will detail the terms of access, criteria for review and approval, and processes by which treating physicians can request access if appropriate.

The requesting physician may be required, for example, to submit a form online or to contact a sponsor representative directly. **Please note that policies, processes, and points of contact will vary from sponsor to sponsor.**
- ❑ **The sponsor agrees to provide expanded access.** For factors considered by sponsors when deciding whether or not to provide expanded access, see the MRCT Center’s Resources for Sponsors Providing Expanded Access to Investigational Products (Section 1).
- ❑ **For drugs and biologics, the physician requests a Letter of Agreement (LOA) from the sponsor:** The LOA (which will be included in the FDA submission for approval) should list the **sponsor’s IND number**. In the event that the product does not have an IND application already submitted to the FDA, the physician should contact the FDA for guidance on what information to provide about drug supply and safety.
- ❑ **For devices, the physician requests the sponsor to submit an IDE Supplement:** In the case of investigational devices, the sponsor will usually have an investigational device exemption (IDE) filed with the FDA (21 C.F.R. §812). The sponsor will then submit an IDE Supplement to the FDA (21 C.F.R. §812.35). In cases where the sponsor does not have an IDE application at the FDA, the physician and sponsor will need to contact the FDA directly. (See Step 3).

Step 3. FDA Submission:

To submit a **non-emergency request for individual patient expanded access to an investigational drug**, the physician must submit either

- **Form 3926 (preferred)**

Link:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504572.pdf>

Please note Form 3926 must be opened in Internet Explorer, and it may be necessary to download in order to be opened and completed. Attend to the boxed “Important information” at the top of the page.

Instructions:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504574.pdf>

Guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf>

For submission of Form 3926, the following information is necessary (and see Box 2 and 3):

- A concise clinical history of the patient
- The entity (usually the manufacturer) that will supply the investigational product and the name of the product
- The treatment plan, including dose, route and schedule of administration, duration of therapy, planned monitoring procedures, and planned modifications to therapy in the event of toxicity
- Letter of authorization (LOA) from the entity providing the product
- Information concerning your education, training, specialty, licensure (including number), experience, current employment and job title. A curriculum vitae (CV) may be supplied instead, if it contains the required information
- Signature to indicate you will fulfill all applicable regulatory requirements, including:
 - That you will not begin treatment until 30 days after receipt of the application by the FDA, unless notified by the FDA otherwise
 - That you will not begin or cease treatment if the investigation product is put on clinical hold
 - That you will not begin treatment prior to IRB review and approved of the treatment use, and that the IRB will be responsible for initial and continuing review
 - That you will obtain informed consent from the patient
 - That, in the event of emergency use, you will abide by the emergency use requirements

- **Forms 1571 and 1572**

Link (1571):

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf>

Instructions:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM182850.pdf>

Link (1572):

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Instructions:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM223432.pdf>

Form 3926 is a shorter, streamlined document designed specifically for single patient requests, and **we recommend treating physicians use Form 3926**. If for some reason Form 3926 cannot be used, Forms 1571 and 1572 may also be submitted for single patient IND request.

When medical necessity dictates that there is insufficient time to prepare and submit Form 3926 (or Forms 1571 and 1572), the physician may submit **an emergency request for individual patient expanded access to an investigational drug** by contacting the FDA directly (see chart, below). If the request is approved, the physician is expected to submit Form 3926 (or Forms 1571 and 1572) within 15 working days of the initial approval.

For more information about expanded access to investigational drugs for treatment use, please see: <http://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>

To submit a **non-emergency request for individual patient expanded access to an investigational device**, the sponsor (usually the device manufacturer) must submit to the FDA an **IDE supplemental request** for expanded access (21 C.F.R. §812.35(a)).²⁰

In the case of **an emergency request for individual patient expanded access to an investigational device**, the unapproved device may be used **without** prior approval by the FDA. Even in these cases, however, the treating physician is expected to follow appropriate measures to respect the patient's autonomy, including informed consent, the concurrence of the IRB chairperson or designee (see Section XX, Resources for IRB), assessment by an uninvolved physician, sponsor authorization to provide the device, and any local institutional approvals that are required. The institutional process for emergency approval of investigational products is usually outlined in institutional policies; the treating physician should contact the appropriate institutional resource. The sponsor must still report the emergency use within 5 days to the FDA, filling out the IDE Supplement (21 C.F.R.

§812.35(a(2)). **If no IDE exists**, the treating physician must submit a report on emergency use of the device to:

Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave
Document Control Center
WO66 Rm G-609
Silver Spring, MD 20993

For a complete list of contact information for submitting a request for expanded access to the FDA, please see:

<http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm>

²⁰ For guidance on requesting expanded access to devices, please see FDA, "Expanded Access for Medical Devices." <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>. Accessed November 23, 2017.

Box 3: Checklist for Emergency and Non-Emergency Expanded Access Procedures

Non-Emergency Cases	Emergency Cases
<p><input type="checkbox"/> FDA Form 3926, Individual Patient Expanded Access Application To complete, you will need the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Indication <input type="checkbox"/> Patient history and information (patient initials, indication and proposed treatment use, brief clinical history including age, gender, weight, allergies, diagnosis, prior therapies and responses, reason for request, explanation of lack of other treatment options) <input type="checkbox"/> Investigational drug name <input type="checkbox"/> Manufacturer/supplier name <input type="checkbox"/> Applicable FDA review division, see http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm <input type="checkbox"/> Treatment plan (planned dose, route and schedule of administration, planned duration of treatment, monitoring procedures, and any planned modifications in the event of toxicity) <input type="checkbox"/> Physician's qualification statement / physician's CV <input type="checkbox"/> Physician contact information <input type="checkbox"/> Letter of Authorization (LOA, referencing the sponsor's IND number). <input type="checkbox"/> Check box 10A on Form 3926, indicating a request for authorization to use Form 3926. <input type="checkbox"/> Check box 10B on Form 3926, indicating a request for authorization to use alternative IRB review procedures. <p>Or:</p> <p><input type="checkbox"/> FDA Form 1571: Investigational New Drug Application. <i>We do not recommend Form 1571 and 1572 in place of Form 3926.</i> The physician should select "Individual Patient,</p>	<ul style="list-style-type: none"> <input type="checkbox"/> During business hours (8 AM – 4:30 PM EST weekdays), the treating physician should contact the following departments at the FDA: <input type="checkbox"/> Investigational Drugs CDER's Division of Drug Information (DDI) Phone: 855-543-3784 or 301-796-3400 or the appropriate CDER Review Division (see Appendix B.) <input type="checkbox"/> Investigational Biologics CDER's Office of Communication, Outreach, and Development Phone: 240-402-7800 or 800-835-4709 Email: industry.biologics@fda.gov <input type="checkbox"/> Investigational Devices Center for Devices and Radiological Health (CDRH) Phone: 301-796-5640 Fax: 301-847-8120 <input type="checkbox"/> Outside of business hours (weekends; after 4 PM (EST) on weekdays), the treating physician requesting expanded access for emergency use of drugs, biologics, and devices should contact The FDA Emergency Call Center Phone: 866-300-4374 <p>Electronic and facsimile communications are not monitored during this time.</p>

Non-Emergency” or “Individual Patient, Emergency” in Section 12. Additionally, the physician must provide:

- Single patient request statement
- Patient history
- Treatment plan
- Product information
- Informed consent

- FDA Form 1572: Statement of Investigator:**
This must accompany Form 1571.

To submit for expanded access to an investigational drug, physicians should

- Call CDER Division of Drug Information (DDI) at 855-543-3784 or
- Email CDER DDI at druginfo@fda.hhs.gov
- Mail request to
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

To submit for expanded access to an investigational biologic, physicians should either

- Call CBER 240-402-8010 or 800-835-4709;
or
- Email CBER at ocod@fda.hhs.gov
- Mail request to:
Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

- The decision to authorize or deny emergency expanded access will be communicated by telephone.**

Note additional requirements:

- All necessary forms and information must be submitted to the FDA within 15 working days of FDA authorizing access
- Emergency use must be reported to the IRB within 5 working days of treatment initiation

Please also see updated FDA CDER processes and procedures at

<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM572098.pdf>.

IDE Supplemental request for expanded access (21 C.F.R. §812.35(a)).²¹

- Patient condition
- Rationale for requesting expanded access (lack of alternative approved treatments; benefit-risk analysis of using the investigational device.)
- Deviations from the clinical trial protocol as described in the IDE.
- Informed consent document
- Institutional clearance
- IRB chairperson approval (Please see Step 4, below).
- Independent assessment of an uninvolved physician
- Authorization of device manufacturer

In instances where the sponsor does not have an IDE with the FDA, the sponsor must also include:

- Description of device

To submit, physicians should

- Call the Center for Devices and Radiological Health (CDRH) at 301-796-5640.
- Fax the request to CDRH at 301-847-8120
- Email request to CDRHExpandedAccess@fda.hhs.gov
- Mail request to:
Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave
Document Control Center
WO66 Rm G-609
Silver Spring, MD 20993

²¹ For guidance on requesting expanded access to devices, please see FDA, “Expanded Access for Medical Devices.” <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>. Accessed January 5, 2016.

FDA Response

Approval: If the FDA approves an **emergency IND request**, treatment with the drug can begin once the physician has obtained informed consent from the patient or legally authorized representative. Note: the physician should contact the IRB, however, to ensure conformance with institutional policies and follow-up with the IRB appropriately thereafter. In **non-emergency cases of expanded access requests to INDs or IDEs**, the FDA will notify the requesting treating physician (sponsor-investigator) in a timely manner, often within days of submission. However, the physician may begin treating the patient with the investigational product 30 days after the FDA receives the request if there is no response from the FDA. The treating physician should feel free to contact the FDA directly if no response is received and further delay would be detrimental to the patient. If the application is approved, an IND number will be assigned. That IND number should be supplied to the manufacturer (sponsor) so that the investigational product can be shipped. Treatment may begin after FDA review and approval (or the FDA has not responded 30 days following submission), IRB review and approval of the protocol, and the patient has given their voluntary informed consent.

Disapproval: If treatment use is not approved, FDA will generally notify the physician by telephone, followed by written communication.

Step 4. IRB Submission, review and approval:

When the physician submits a request to the FDA, the physician agrees that an IRB will review, approve, and oversee the provision of the investigational drug, biologic, or device. Recently, and in response to the 21st Century Cures Act, the FDA modified its expectation that a convened IRB will review expanded access requests for drugs and biologics and an IRB chairperson will review requests for devices. As of October 2017, **an IRB chairperson or other appropriate designee can now approve the treatment request**. We recommend that a physician contact the reviewing IRB as soon as a decision to pursue expanded access is made. Each IRB should have written procedures regarding their processes for reviewing expanded access requests, and, as a result, IRB requirements may differ.

Drugs and Biologics (INDs)

In non-emergency cases, a treating physician requesting expanded access to an investigational drug or biologic should submit the following to the IRB:

- Explanatory letter with rationale for requesting expanded access including sufficient clinical and medical information that a reasonable person is able to form an independent opinion, proposed treatment plan, outcome measures that will be used for evaluation, and monitoring plan
- Informed consent document
- FDA Form 3926
- Investigators Brochure

- Sponsor LOA
- Any additional materials that the reviewing IRB requires according to its written procedures

In emergency cases, where the FDA had determined the provision of the drug or biologic can occur immediately, the physician is required to report to submit the same documentation to the IRB within 5 working days of beginning treatment with the investigational product (21 C.F.R. §56.104(c)).²² Nevertheless, a physician should engage with the IRB as early as possible, as the responsible IRB can assist a physician with navigating its specific procedures and review process.

Devices (IDEs)

In non-emergency cases, the treating physician must seek the concurrence of the IRB chairperson concurrently with the application to FDA. If the IRB chairperson will not approve the use of the device prior to FDA approval, the treating physician should indicate that IRB approval will be obtained prior to administering the device. This approval must then be submitted in a follow-up report to the FDA.

In emergency cases, and similar to the expectations for drugs and biologics, the treating physician is expected to respect the patient's autonomy, including informed consent, the concurrence of the IRB chairperson, assessment by an uninvolved physician, sponsor authorization to provide the device, and any additional local institutional processes and approvals. The treating physician must report the use of an IDE to the IRB within 5 working days.

For physicians without access to an IRB, submissions can be filed with an independent IRB. To find a local IRB, the [OHRP Database of Registered IRBs](#) may be helpful. The IRB will determine whether the treatment plan, planned approach, informed consent document, and proposed follow up plan is approved. Only with IRB approval may the investigational product be administered.

Step 5. Obtain Informed Consent from the Patient or Legally Authorized Representative.

The informed consent should fulfill the requirements established by the FDA (21 C.F.R. §50 Subpart B). Please see:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.20.2>.

²² Of course, IRBs/RECs may have institutional policies that require submission of written materials sooner than 5 working days. The written procedures and policies of the reviewing IRB should be followed if more restrictive.

Step 6. Physician Responsibilities:

When a physician submits a request for expanded access to an investigational product on behalf of a patient, the physician is considered the sponsor-investigator. As such, the physician is responsible for ensuring that the provision of expanded access is executed as proposed in the Form 3926 (or Form 1571 and Form 1572), and for **recording and reporting**:

Product access:

The physician must arrange with the sponsor to receive the investigational product.

- Create plan, with sponsor, for obtaining the investigational product
- Maintain product disposition records, including return or destruction of unused product and issuance of a certificate of destruction if required

Maintenance of adequate records of (1) case history and observations related to provision of product, including adverse events; and (2) disposition of investigational product, including dates, quantity and use. See: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362663.htm>

Safety reports for adverse events

- To the FDA (see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362555.htm>)
 - Serious and unexpected adverse reactions must be reported as a suspected adverse reaction only if there is evidence that there is a causal relationship between the investigational product and the adverse event (21 CFR 312.32(c)).
- To the IRB
 - Written IRB procedures should be followed

Treatment plan amendments

- To the FDA (see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362503.htm>)
- To the IRB
 - Written IRB procedures should be followed

IND Annual reports if the treatment use extends beyond one year

- To the FDA (see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362663.htm>)
- ☐ IRB continuing review report if the treatment use extends beyond one year
 - Application for continued review, per written IRB procedures
- ☐ For IDE, a semi-annual progress report:
 - To the FDA and IRB (see: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046717.htm>)
- ☐ Summary report to sponsor and FDA
 - Since the treating physician is functioning as the sponsor-investigator, he or she assumes the responsibility to provide FDA a written summary of the results of the expanded access use, including adverse effects, as detailed in the regulations (§ 312.310(c)(2)).

3. Resources for IRBs/RECs: Evaluation of Requests for Investigational Products Through the Individual Patient Expanded Access Program

3.1 Background

In addition to physician determination of need and appropriateness, manufacturer or company review and approval of a request for the investigational medicine, and FDA review and approval of a single-patient IND or a protocol amendment to an existing IND, expanded access to a drug for an individual patient requires IRB/REC review and approval of an application for use. In the US, the latter requirement is a consequence of FDA regulations regarding oversight of the administration of the (IND-authorized) investigational product. IRB review is intended to assure that the rights and welfare of the potential participant are protected, including that informed consent is voluntary, informed, and obtained in advance of treatment. In this situation, the purpose of IRB review is to ensure that the patient understands that treatment will consist of an investigational product about which safety and efficacy have not been established. The purpose is not for the advancement of generalizable knowledge.

Over the last several years, the FDA has made significant efforts to reduce the barriers to expanded access including the requirements for IRB review and approval. In October 2017, the FDA amended its guidance to allow a physician submitting an individual patient expanded access IND application to elect to request a waiver, under 21 CFR § 56.105, for review by a convened IRB at which the majority of members were present. Instead of requiring “full” board review, the IRB chairperson or a designated IRB member may review and approve the application.²³ If the physician uses FDA Form 3926, Box 10b should be checked; if the physician submits FDA Form 1571, a separate waiver request must be submitted. The waiver will be granted if the physician attests that he or she will obtain approval by the IRB chairperson or designated IRB member, and informed consent by the patient, in advance of treatment.²⁴

Because applications for an individual patient expanded access IND are relatively rare for an IRB, it is worth considering the limited aspects of review that are necessary. Here we examine the scope of responsibilities of the IRB in expanded access programs and suggest measures for simplification and process improvement. The FDA regulations (21 CFR part 56) must be followed. Physicians are permitted by both FDA and the Office of Human Research Protections

²³ The waiver provision only applies to IRB of an individual patient expanded access application, not an intermediate-size expanded access program or treatment IND.

²⁴ Expanded Access to Investigational Drugs for Treatment Use. Questions and Answers. Guidance for Industry. Question 6. <https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>. Accessed November 23, 2017.

regulations to access their own institutional IRB, an independent IRB, or a central or single IRB to oversee human subjects research. The physician should be aware of their institution's policies in this regard.

3.2 Considerations for IRBs in Decision-Making about Expanded Access

As mentioned, the purpose of IRB review is not the ascertainment of generalizable knowledge, but rather the assurance that the individual patient is aware of the potential risks and uncertain benefits of the planned treatment using an investigational product. The IRB should consider:

- That the purpose of the activity is clinical care, not research.
- That a single patient will be treated, and therefore no inclusion/exclusion criteria, nor statistical analysis, are anticipated.
- That the clinical course of the patient is described in adequate detail to justify use of the individual patient expanded access application. Submission of the materials presented to the FDA are often adequate.
- That the treatment plan makes provisions to ensure the safety of the patient, including expectations for monitoring and planned modifications of the treatment plan in the event of toxicity or unanticipated problems that are thought to be causally related to the investigational product.
- That the informed consent document and process explain the uncertainty of the proposed treatment plan, uncertain benefits and potential risks including serious harms, all research-related procedures, and the voluntary nature of consent.
- That special protections are in place to ensure adequate understanding of the informed consent, acknowledging that the patient is vulnerable,
- That the privacy interests of the patient will be protected to the extent possible and that the requirements of HIPAA will be followed.
- That the rights and welfare of the patient are protected.
- That the physician understands his or her responsibilities in obtaining informed consent, monitoring and reporting to all offices and agencies and to the entity that provided the investigational product. Any special reporting requirements should be outlined.

Following IRB review (or expedited review by the IRB chairperson or his or her designee), the IRB will determine whether the application is approved, modifications required, deferred, or disapproved. Note, research cannot be disapproved by expedited review, and should be referred to a convened IRB.

3.3 Glossary and Definitions

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. ([21 C.F.R. §312.300](#))

Investigational device: is a device, including a transitional device, that is the object of an investigation. ([21 C.F.R. §812.3](#))

Investigational new drug: means a new drug or biological drug that is used in a clinical investigation. ([21 C.F.R. §312.3](#))

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 C.F.R. §312.300](#))

4. Resources and References

21 C.F.R. §312: Investigational New Drug Application

<https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=3b47469566c47db3234b52059e48d203&mc=true&n=pt21.5.312&r=PART&ty=HTML>

Accessed November 27, 2017

21 C.F.R. §312 Subpart I: Expanded Access to Investigational Drugs for Treatment Use

<https://www.ecfr.gov/cgi-bin/text-idx?SID=c859616b5a665bbcda13092d0c1c063d&node=sp21.5.312.i&rgn=div6>

Accessed November 27, 2017

21 C.F.R. §812: Investigational Device Exemptions

<https://www.ecfr.gov/cgi-bin/text-idx?SID=404baf05c26922d7542aec17055068ef&mc=true&node=pt21.8.812&rgn=div5>

Accessed November 27, 2017

Ainge, D. et al. (2015). Global Access Programs: A Collaborative Approach for Effective Implementation and Management. *Pharmaceut Med*, 29(2), 79–85.

<http://doi.org/10.1007/s40290-015-0091-9>

Accessed January 10, 2017

Central Drugs Standard Control Organization (CDSCO) (2014), Procedure for permission to Import Small Quantities of Drugs for Personal Use.

<http://cdsco.nic.in/forms/list.aspx?lid=1852&ld=30>

Accessed January 10, 2017.

European Commission (EC) (2001), Directive 2001/83/EC of the European Parliament and of the Council. On the Community code relating to medicinal products for human use.

http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf

Accessed January 10, 2017.

— — — (2004), Regulation No. 726/2004 of the European Parliament and of the Council.

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20090706:EN:PDF>

Accessed January 10, 2017.

European Medicines Association (EMA) (2007). Committee for Medicinal Products for Human Use (CHMP). Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) No 726/2004. 2007.

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf

Accessed January 10, 2017.

European Medicines Association (EMA) (2010). “Questions and answers on the compassionate use of medicines in the European Union.”

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500069898.pdf

Accessed January 10, 2017.

Food and Drug Administration (FDA) (2009), Expanded Access to Investigational Drugs for Treatment Use, 21 C.F.R. Sect. 312 Subpart I.

<http://www.ecfr.gov/cgi-bin/text-idx?SID=c859616b5a665bbcd13092d0c1c063d&node=sp21.5.312.i&rgn=div6>

Accessed January 10, 2017.

Food and Drug Administration (FDA) (2017) Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers. Guidance for Industry

<https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf>

Accessed November 25, 2017

Food and Drug Administration (FDA) (2017) Individual Patient Expanded Access Applications: Form FDA 3926 Guidance for Industry

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM432717.pdf>

Accessed November 25, 2017

Medicines and Healthcare Products Regulatory Agency (MHRA) (2014), Early Access to Medicines Scheme (EAMS).

<https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams>

Accessed January 10, 2017.

Patil, S. (2016). Early access programs: Benefits, challenges, and key considerations for successful implementation. *Perspectives in Clinical Research*, 7(1), 4–8.

<http://doi.org/10.4103/2229-3485.173779>

Accessed January 10, 2017.

Rahbari, M. and Rahbari N.N. (2011). Compassionate use of medicinal products in Europe: current status and perspectives. *Bull World Health Organ*, 89(3), 163.

<http://doi.org/10.2471/BLT.10.085712>

Accessed January 10, 2017.

Section 801 of the Food and Drug Administration Amendments Act (FDAA 801)

<https://clinicaltrials.gov/ct2/manage-recs/fdaaa#DevelopmentOfRegulations>

Accessed March 25, 2017.

Sou, H. (2010). EU compassionate use programmes (CUPs): regulatory framework and points to consider before CUP implementation. *Pharm Med*, 24(4), 223–229.

<http://doi.org/10.1007/BF03256820>

Accessed January 10, 2017.

United States. Cong. House of Representatives. *21st Century Cures Act*. 114th Cong. H. Res 6 (2016).

<https://www.congress.gov/bill/114th-congress/house-bill/6/text>

Accessed January 27, 2017.