Issuing Department: Human Subjects Protection Program
Policy Number: 2011-022.2
Policy Title: Investigational Drug/Biologic - Expanded Access for Treatment Use, Including Single Emergency Use

Purpose

The purpose of this policy is to set for the requirements that investigators, sponsors, Institutional Review Boards and the FDA must fulfill when an investigational new drug or biologic is to be used in a therapeutic manner.

Definitions

See policy 2011-007.0 for definitions of the following terms:

Emergency Use	Investigational New Drug	Immediately Life Threatening
Noncompliance, Serious	Test Article	Seriously Debilitating
Serious Disease or Condition	Investigator	Sponsor

Policy

FDA regulations permit expanded access to an investigational drug or biologic for treatment use, including emergency treatment for an individual patient, providing certain criteria, submission requirements, and safeguards are met before beginning treatment.

In all cases of expanded access use, investigators must be aware of their obligations; including, but not limited to, the obligation to obtain IRB review and informed consent when possible.

Per 21 CFR 312.305(a), for all expanded access requests sufficient information must be provided to the FDA such that the FDA can determine that:

- The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
- Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Per 21 CFR 312.305(b) an expanded access submission is required for each type of expanded access request. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants the physician a right of reference to the IND. If the physician obtains permission to reference the existing IND, the holder of the IND (typically the manufacturer) should provide the physician with a letter of authorization (LOA) to refer to that IND and that LOA would be included in the submission to the FDA.

All expanded access submissions must include the points noted below. For individual patient expanded access requests (emergency or non-emergency) an appropriately completed and signed Form FDA 3926 is

recommended in place of the Form FDA 1571 and will be considered by the FDA to comply with the submission requirements.

- A cover sheet (i.e. Form FDA 3926 for Individual Patient Expanded Access or Form 1571 for other types of Expanded Access Requests);
- The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
- The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;
- The method of administration of the drug, dose, and duration of therapy;
- A description of the facility where the drug will be manufactured;
- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and
- A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." The type of expanded access request must be delineated in the applicable box on Form FDA 1571.

In all cases of expanded access, an investigator (i.e. a licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use) must comply with the responsibilities for investigators set forth in 21 CFR 312 subpart D to the extent they are applicable to the expanded access use. Investigators are responsible for reporting adverse drug events to the sponsor, and, with the possible exceptions for emergency use noted below, ensuring that informed consent requirements are met and that IRB review of the expanded access use is obtained prior to use of the investigational agent. Investigators are also responsible for maintaining accurate case histories and drug disposition records and retaining records.

In all cases of expanded access, the sponsor (i.e. the individual or entity that submits an expanded access IND or protocol) must comply with the responsibilities for sponsors set forth in subpart D to the extent they are applicable to the expanded access use. Sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records.

A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a *sponsor-investigator*, and must comply with the responsibilities for sponsors and investigators set forth in subpart D to the extent they are applicable to the expanded access use as described above.

With the exception of expanded access for emergency use, an expanded access IND goes into effect 30 days after the FDA receives the IND or on earlier notification by FDA that the expanded access use may begin. Per 21 CFR 312.42, the FDA may place any expanded access IND or protocol on clinical hold.

Additional requirements for each specific type of Expanded Access request are as follows:

Expanded Access - Single Patient (SP), Including Emergency Use (21 CFR 312.310)

SP Additional Criteria: FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician. The criteria noted above per 21 CFR 312.305(a) must be met and the following additional determinations must be made:

- The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and
- FDA must determine that the patient cannot obtain the drug under another IND or protocol

SP Submission Requirements: The submission requirements noted above per 21 CFR 312.305(b) apply. FDA will accept completion of Form FDA 3926.

- If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.
- A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.
- A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

SP Safeguards: Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy. At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects. The FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration. When a significant number of similar individual patient expanded access requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under 312.315 or 312.320.

SP Emergency Use Procedures. An individual treated through emergency use is considered a research subject as defined in FDA regulations. An individual treated through emergency use is not considered a research subject under DHHS regulations unless IRB approval of an emergency use protocol was obtained prior to the use.

Emergency Use requires authorization from the FDA. If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone. Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. See Appendix A for FDA Contact Information. Expanded access use under the emergency procedures may begin when the use is authorized by the FDA reviewing official.

The licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

Informed consent of the subject shall be obtained unless, per 21 CFR 50.23: the investigator and a physician who is not otherwise participating in the intervention certify in writing that all of the criteria noted below are met.

- the subject is confronted by a life-threatening or severely debilitating situation necessitating the use of the test article;
- informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- time is not sufficient to obtain consent from the subject's legal representative;
- no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination noted above in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

When IRB review cannot be obtained prior to the emergency use of a test article for a single patient, per 21 CFR 56.104 and 21 CFR 50.23 such use of a test article, and the documentation described above, must be reported to the IRB within 5 working days after use of the test article. Any subsequent use of the test article is subject to IRB review.

Expanded Access - Intermediate-size Patient Populations (IPP) (21 CFR 312.315):

FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use. Expanded access under this section may be needed in the following situations:

- *Drug not being developed.* The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.
- *Drug being developed.* The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.
- *Approved or related drug.* The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or the drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

IPP Criteria: In addition to the criteria required per 21 CFR 312.305(a) and described above, the FDA must determine that:

- There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and
- There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

IPP Submission Requirements: In addition to the submission requirements required per 21 CFR 312.305(b) and described above:

- The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated.
- If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.
- If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

IPP Safeguards: Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section. If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use. If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug. As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under 312.320.

The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

Treatment IND (TI) or Treatment Protocol (TP) (21 CFR 312.320)

Criteria TI/TP: FDA may permit an investigational drug to be used for widespread treatment use providing certain criteria are met. In addition to the criteria required per 21 CFR 312.305(a) described above the FDA must determine that the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or all clinical trials of the drug have been completed; and the sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence;

When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials.

When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk

of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

Submission Requirements TI / TP: The expanded access submission requirements per 21 CFR 312.305(b) described above apply.

Safeguard TI / TP: The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators. Expanded access use for a treatment IND or treatment protocol (21 CFR 312.320) may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

Procedure

Expanded Access Request for Emergency Use for A Single Patient:

The physician should first contact the holder of the IND to confirm that the investigational agent will be made available under the company's IND.

If so, approval from the FDA must then be obtained. If time permits, a written submission should be made to the FDA using FDA Form 3926. If time does not permit, the request to use the investigational agent for an individual patient may be made by telephone (or other rapid means of communication) to the appropriate FDA review division. (See Appendix A for FDA Contacts) The physician must be prepared to explain how the expanded access use will meet the requirements of 312.305 and 312.310 noted in the policy section above. The physician must commit to making a submission to the FDA within 15 working days of the FDA's authorization.

If time permits, the prescribing clinician should notify the IRB Office in writing of his/her intent to utilize an investigational drug for a therapeutic reason at least 24 hours prior to the planned date of the first administration of the drug. An email notification should be sent to a Regulatory Specialist (RS) within the office (IRB contact information available at http://research.uchc.edu/rcs/hspp/) to alert the IRB of the situation, and the RS will contact an IRB Chair to review the material.

The information provided to the IRB for the emergency use of this investigational drug should include the following information:

- assurance from the prescribing person that this use is NOT part of a project that is currently awaiting IRB approval;
- assurance that the use of the drug(s) or biologic is primarily to treat a patient with a specific, clinically urgent, condition; and that the patient is not a research subject;
- a brief written statement explaining the rationale for the use of the investigational drug or biologic;
- a copy of the consent form that will be used by the prescribing person to obtain informed consent from the patient or the patient’s legally authorized representative. Such consent form to include a description of the clinical protocol (length of administration, dosage, method of evaluation of efficacy, side effects, etc.);
    - a consent form is required unless the investigator/clinician and a licensed physician who is not otherwise participating in the intervention certify in writing that the four criteria for not obtaining consent as noted above in the policy section are met.

- a formal statement from the manufacturer (or distributor) of the investigational drug , that the prescribing person has received approval for use of the investigational agent (e.g. Letter of Authorization from the sponsor of the IND).
- If a submission has been made to the FDA, the completed submission materials. If a submission was not made, a statement or documentation noting the date of the FDA's authorization.

If prospective review from the Chair was not obtained due to the emergent nature of the situation, the clinician must submit the material noted above for review and evaluation by the IRB Chair within 5 working days after the use of the article.

- If consent was not obtained, the clinician who performed the intervention must obtain the written opinion of an independent physician as to whether consent could have been obtained based upon the four criteria in the policy section.
- If in the course of conducting a retrospective review the Chair determines that the investigator was not compliant with policy and regulations, the matter will be considered an instance serious non-compliance. The Chair will inform the investigator and the DHSPO via letter and the DHSPO will follow through with reporting to institutional officials and external agencies.

After review, the IRB Chair (or designee) will issue a letter to the prescribing clinician, indicating that the clinician has complied with the internal policy and FDA regulations regarding the emergency or therapeutic use of an investigational drug for a single patient.

- Copies of this letter will be sent by the IRB staff to the Chair of the Pharmacy and Therapeutics Committee and the Director of Pharmacy Services at John Dempsey Hospital.

If required by the IRB Chair, the prescribing clinician must also report the outcome and side effects following the administration of the drug to the IRB Chair within the specified time frame.

Expanded Access Request for Non-Emergency Use for A Single Patient:

The physician should first contact the holder of the IND to confirm that the investigational agent will be made available. If so, approval from the FDA must then be obtained. A written submission should be made to the FDA using FDA Form 3926 for a non-emergency single patient expanded requests.

The submission to the IRB for the non-emergency use of this investigational drug should include the following information which will be reviewed by the convened IRB:

- assurance from the prescribing person that this use is NOT part of a project that is currently awaiting IRB approval;
- assurance that the use of the drug(s) or biologic is primarily to treat a patient with a specific, clinically urgent, condition; and that the patient is not a research subject;
- a brief written statement explaining the rationale for the use of the investigational drug or biologic;
- a copy of the consent form that will be used by the prescribing person to obtain informed consent from the patient or the patient's legally authorized representative. Such consent form to include a description of the clinical protocol (length of administration, dosage, method of evaluation of efficacy, side effects, etc.);
- a formal statement from the manufacturer (or distributor) of the investigational drug , that the prescribing person has received approval for use of the investigational agent (e.g. Letter of Authorization from the sponsor of the IND).
- The completed submission materials that were provided to the FDA.

The physician is responsible for requesting continuing approval from the IRB if the use expands more than one year from the date of the IRB's determination**.**

Expanded Access Request for Intermediate-Size Patient Populations, or Treatment IND (TI) or Treatment Protocol (TP):

The submission to the IRB for the above type of expanded access requests should include the following information which will be reviewed by the convened IRB

- Material that was provided to the FDA to make the determinations required per the expanded access regulations as described above
- The informed consent to be used

The IRB will issue a letter indicating its determination regarding the TI/TP

The physician is responsible for requesting continuing approval from the IRB if the use expands more than one year from the date of the IRB's determination**.**

Related Policies

2009-001 - Reporting Unanticipated Problems to the Institutional Review Board
2009-004 – Required Reporting to Institutional Officials and External Agencies
2011-007.0 – Definitions Applied to Policies
011-008.5 –Informed Consent – Providing and Obtaining

Basis

21 CFR 312, Subpart I
21 CFR 56
Emergency Use of an Investigational Drug or Biologic - Information Sheet:
Guidance for Institutional Review Boards and Clinical Investigators
Individual Patient Expanded Access Applications: Form FDA 3926 Guidance for Industry

Document Attributes

Date Created: 12/21/2016

Replaced Version: **7**/8/2011

Reviewed and Approved By: **Signed by Richard Simon** **Date:** **12/27/2016**
Richard Simon, MD
Director Human Subjects Protection Program

Appendix A to Policy 2011-022.2

FDA Contacts

FDA Contacts Per 21 CFR 312.10(d)(1):

For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 240-402-8010 or 1-800-835-4709, e-mail: *ocod@fda.hhs.gov*. For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail: *druginfo@fda.hhs.gov*. After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail: *emergency.operations@fda.hhs.gov*.

FDA Contacts per web site link

For questions about expanded access for emergency contact the Division of Drug Information at 855-543-3784 or 301-796-3400, or for a specific investigational drug, contact the appropriate review division below.

If DDI and the review division are not available, contact the CDER Emergency Coordinator (CEC) of the Counter-Terrorism and Emergency Coordination Staff (CTECS) at phone: 301-796-9900 or 301-796-2210; fax: 301-431-6356; or e-mail at: cdererops@fda.hhs.gov.

CDER Review Division	Telephone Number	FAX Number
Division of Anti-Viral Products	301-796-1500	301-796-9883
Division of Oncology Products 1	301-796-2330	301-796-9845
Division of Oncology Products 2	301-796-2320	301-796-9849
Division of Hematology Products	301-796-7550	301-796-9849
Division of Reproductive and Urologic Products	301-796-2130	301-796-9897

CDER Review Division	Telephone Number	FAX Number
Division of Medical Imaging Products	301-796-2050	301-796-9848
Division of Gastroenterology and Inborn Errors Products	301-796-2120	301-796-9905
Division of Anesthesia, Analgesia, and Addiction Products	301-796-2280	301-796-9723
Division of Metabolism and Endocrinology Products	301-796-2290	301-796-9712
Division of Pulmonary, Allergy and Rheumatology Products	301-796-2300	301-796-9728
Division of Dermatology and Dental Products	301-796-2110	301-796-9895
Division of Anti-Infective Products	301-796-1400	301-796-9883
Division of Transplant and Ophtalmology Products	301-796-1600	301-796-9881
Division of Cardiovascular and Renal Products	301-796-2270	301-796-9841
Division of Neurology Products	301-796-2250	301-796-9839
Division of Psychiatry Products	301-796-2260	301-796-9838

Contact Information for Emergency Individual Patient INDs

During normal business hours (8 am – 4:30 pm EST weekdays)

For general questions about expanded access for emergency use for investigational drugs, contact CDER's Division of Drug Information (DDI) 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 a specific investigational drug, contact the appropriate review division, if known, or DDI, if not known.

If DDI and the review division are not available, contact the CDER Emergency Coordinator (CEC) of the Counter-Terrorism and Emergency Coordination Staff (CTECS) at phone: 301-796-9900 or 301-796-2210; fax*: 301-431-6356; or e-mail at : cdererops@fda.hhs.gov . * Please call or e-mail the CDER Emergency Coordinator before faxing documents.

After hours (after 4:30 pm EST weekdays and all day on weekends)

All questions about and requests for expanded access for emergency use for drugs, biologics and medical devices should be directed to the FDA Emergency Call Center, telephone: 866-300-4374.