

Guidelines for the Submission of an Expanded Access IND to Permit Diagnosis, Monitoring or Treatment of Intermediate-size Patient Populations with an Investigational Drug or a REMS-restricted, Approved Drug

Guidelines:

1. Applicability: The FDA regulations permit expanded access to investigational drugs (i.e., drugs not currently approved by the FDA for commercial marketing) or REMS-restricted approved drugs (i.e., FDA-approved drugs that are limited in availability as a result of a FDA-assigned Risk Evaluation and Mitigation Strategy) for the diagnosis, monitoring or treatment of a patient population smaller than that which necessitates the submission of a Treatment IND (or a treatment protocol amendment to an existing IND); provided that the following general criteria apply:
 - a. The 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;
 - 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 a sufficient criterion, 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 judgement, 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.
 - 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.
 - b. The potential patient benefit justifies the potential risks of the expanded access use and those potential risks are not unreasonable in the context of the disease or condition to be treated;
 - c. 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;

d. There is enough evidence that the drug is safe at the dose and dosing duration proposed for the expanded access use so as to justify use of the drug in the approximate number of subjects expected to receive the drug under this expanded access; and

e. There is at least preliminary clinical evidence of effectiveness of the drug (e.g., obtained through expanded access use in one or more individual patients), or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

2. A written Expanded Access IND must be submitted for review and approval of the FDA prior to implementing diagnosis, monitoring or treatment with an investigational drug or a REMS-restricted approved drug in the patient population.

a. Diagnosis, monitoring or treatment of the indicated patient population with an investigational drug or a REMS-restricted approved drug may not begin until 30 days following the FDA's receipt of the Expanded Access IND; unless the FDA provides earlier notification that the expanded access may begin or the FDA has authorized Emergency Use of the investigational or REMS-restricted approved drug (see below).

b. Treatment, monitoring or diagnosis with the investigational or REMS-restricted approved drug shall not be initiated if the FDA places a "clinical hold" on the Expanded Access IND.

3. A physician who submits an Expanded Use IND for an intermediate-size patient population and under whose immediate direction an investigational drug is administered or dispensed is considered to be the *sponsor-investigator* of the IND application and is subject to compliance with the responsibilities of *sponsors* and the responsibilities of *investigators* as set forth in subpart D of the IND regulations at 21 CFR Part 312. (Refer to www.o3is.pitt.edu; IND Information and Templates; IND Applications: Sponsor and Investigator Responsibilities.)

□ *Sponsor* responsibilities include, but are not limited to, the submission of Annual Reports and Safety Reports to the IND application and monitoring of the expanded access to ensure compliance with the expanded access protocol and the regulations applicable to the responsibilities of *investigators*.

4. The protocol for expanded access use of the investigational drug or REMS-restricted approved drug in intermediate-size patient populations must also be submitted prospectively (i.e., prior to implementing respective patient diagnosis, monitoring or treatment) for review and approval of the University of Pittsburgh Institutional Review Board (IRB).

- For IRB review/approval of the expanded access use of an investigational drug or REMS-restricted, approved drug contact the IRB Assistant Director for Regulatory Affairs, 412-383-1563.

Application Form for Expanded Access Use – Intermediate-size Patient Population

1. *Name of requesting physician (sponsor-investigator):*
2. *Identity of the investigational drug or REMS-restricted, approved drug for which expanded access use is being sought:*
3. *Describe, below, the patient population to be treated.*
4. *Address, below, the rationale for the intended use of the drug in this patient population, including a list of available therapeutic options that would ordinarily be tried before resorting to this drug or an explanation of why the use of this drug is preferable to the use of available therapeutic options.*
5. *Attach, to this application form, an Expanded Access Protocol that addresses each of the following:*
 - *The criteria for patient selection/exclusion*
 - *The method of administration of the drug, dose and duration of therapy*
 - *A description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks*
6. *Identity of the facility where the drug will be manufactured:*
7. *Address, below, chemistry, manufacturing, and control information adequate to ensure that the drug meets appropriate standards of identity, strength, quality and purity. Alternately, incorporate the statement, "Refer to manufacturer information (see attached cross-reference letter)" and attach a letter from the drug manufacturer that permits the FDA to access the manufacturer's IND or Drug Master File for this CMC information.*
8. *Provide, below, pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for the expanded access use. Alternately, incorporate the statement "Refer to attached manufacturer information" and attach a copy of the current version of the manufacturer's Investigator Brochure for the drug; and/or incorporate the statement "Refer to manufacturer information (see attached cross reference letter)" and attach a letter from the drug manufacturer that permits the FDA to access the manufacturer's IND or NDA for this pharmacology and toxicology information.*
9. *Indicate, below, if the drug is being developed or is not being developed (i.e., whether or not the drug is currently being evaluated in a clinical trial submitted under a separate IND application, or is a REMS-restricted, approved drug).*

- *If the drug is not being actively developed, explain why the drug cannot be developed for the expanded access use and under what circumstances the drug could be developed. (Refer to subscripts 1 and 2)*
- *If the drug is currently being developed and studied as part of a clinical trial, explain why the patients to be treated under this expanded access cannot be enrolled in the clinical trial and under what circumstances a clinical trial for the expanded access use could be conducted in these patients. (Refer to subscript 3)*

¹E.g.; the drug is not being developed because the sponsor is an individual physician (i.e., sponsor-investigator), not a commercial pharmaceutical company; and/or the drug is not being developed because the expanded access disease or condition is so rare that it would be difficult to recruit subjects for a traditional clinical trial.

²E.g., 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.

³E.g., the patients may not be able to participate in the clinical trial because they have a different disease or stage of disease than that being studied or otherwise do not meet the enrollment criteria; because enrollment into the clinical trial is closed; or because the clinical trial site(s) is (are) not geographically accessible.

10. *Additional Items to accompany the submission:*

- *Form FDA 1572, <http://www.o3is.pitt.edu/fda-forms>*
- *CV of Investigator*
- *Informed Consent Document*

Submission Requirements: – Expanded Use IND – Intermediate –size Patient Populations:

1. General requirements:

a. The Expanded Access IND submission to the FDA must include a completed FDA Form 1571 <http://www.o3is.pitt.edu/fda-forms>

- Box 1: Incorporate the name of the requesting physician (i.e., sponsor-investigator)
- Box 2: Self-explanatory
- Box 3: Incorporate the address of the Office for Investigator-Sponsored IND and IDE Support (O3IS) as the address of the sponsor-investigator; i.e.:

Academic department of requesting physician

University of Pittsburgh

Hieber Building, Suite 303

3500 Fifth Avenue

Pittsburgh, PA 15213

- Box 4-6: Self-explanatory
- Box 7: Specify “Expanded Access Use” followed by a brief description of the corresponding disease or condition that will be diagnosed, monitored or treated using the investigational drug or REMS-restricted, approved drug
- Box 8: Check the box corresponding to “Other” and specify “Expanded Access Use”
- Box 9-10: Self-explanatory

- Box 11: Check the box corresponding to “Other” and specify “Expanded Access Use”
- Box 12: Check the box corresponding to “Intermediate Size Patient Population, 21 CFR 312.315”
- Box 13: Check the box corresponding to “Form FDA 1571”
- Box 14: Self-explanatory
- Box 15: Specify the name of the requesting physician (i.e., sponsor-investigator)
- Box 16: Specify the name of the requesting physician (i.e., sponsor-investigator)
- Box 17-19: Self-explanatory
- Box 20: Incorporate the address of the Office for Investigator-Sponsored IND and IDE Support (O3IS) as the address of the sponsor-investigator (see above)
- Box 21-25: Self-explanatory

b. Expanded Access IND submissions and all subsequent related correspondence must be submitted to the FDA through the Office for Investigator-Sponsored IND and IDE Support (O3IS).

- Provide the O3IS with one original plus 3 copies of the Expanded Access IND submission.
- The O3IS shall promptly forward the Expanded Access IND submission and all subsequent correspondence to, as applicable, the FDA or the requesting physician (i.e., sponsor-investigator).

c. The Expanded Access IND submission to the FDA and the Expanded Access Approval request the IRB should include a(n):

- Cover letter requesting review/approval of the expanded access use of the (identified) investigational drug or REMS-restricted, approved drug. The cover letter should be plainly marked “EXPANDED ACCESS SUBMISSION – INTERMEDIATE-SIZE PATIENT POPULATION”
- The cover letter to the FDA should be addressed to:
- For investigational or REMS-restricted, approved biological drug products regulated by the Center for Biologics Evaluation and Research (CBER):

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Building 71, Room G112
Silver Spring, MD 20993-0002
Attn.: Expanded Access Submission

- For all other investigational or REMS-restricted, approved drugs:

Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266
Attn.: Expanded Access Submission