Expanded Access and the Individual Patient IND

Research Wednesdays
April 26, 2017

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Office of Regulatory Affairs and Quality
Office of Regulatory Affairs and Quality

- The office was started in 2006 with the first of Duke’s Clinical Translational Science Awards.

- It was originally part of the Duke Translational Medicine Institute (DTMI) and was formerly known as DTMI Regulatory Affairs.

- In 2016, the office was moved into the School of Medicine under the Associate Dean for Regulatory Oversight & Research Initiatives and renamed the Office of Regulatory Affairs and Quality (ORAQ).
Office of Regulatory Affairs and Quality

- Our goal is to provide the Duke community with the tools, training, and support needed to navigate the complex regulatory pathways that accompany translational research. We aim to do this by providing support in the following areas:
  - Early Regulatory Strategy Development
  - Preclinical Testing and GMP Manufacturing
  - Regulatory Submissions and Maintenance
  - FDA Meetings and Inspections
  - Regulatory Education and Training
  - Outreach and Collaboration
ORAQ Resources

- **New Website:** [http://medschool.duke.edu/ORAQ](http://medschool.duke.edu/ORAQ)
  - Includes new and updated template documents
  - Functionality to register your regulatory applications with ORAQ online
  - Contact information for our staff

- **Educational Seminars:** Best Practices Workshops
  - IND Workshop: June 13\(^{th}\), 2017 1:00pm-4:00pm
  - IDE Workshop: June 14\(^{th}\), 2017 9:00am-12:00pm
  - Trent Semans Center, Great Hall — Register our on website

- **Training Program:** Onsite and Remote Programs Available
  - Overview of premarket regulatory work, including INDs and IDEs
  - Free to participate; Visit our website to register

- **Contact for Questions:** ORAQ@duke.edu
Goal: To understand the purpose and use of expanded access and FDA’s new process for physician requested individual patient INDs
Expanded Access

- **Expanded access**, sometimes called "compassionate use," is the use of an investigational medical product (i.e., one that has not been approved by FDA) outside of a clinical trial.

- Expanded access is different from investigational studies typically conducted under an IND or IDE.
  - The **goal** of expanded access is to facilitate access to investigational therapies for patients with serious or life-threatening diseases or conditions that lack therapeutic alternatives.
  - The objective is not to obtain information on safety or effectiveness of the investigational product.
  - The primary goal is treatment as opposed to research.
Expanded Access

- Wherever possible, the Agency prefers that an investigational drug be used as part of a clinical study.
  - Clinical trials generate data that may lead to the approval of a product and generate wider availability.

- When patient enrollment in a clinical study is not possible, patients may be able to receive the product through expanded access.
  - Patient is not eligible for ongoing clinical trial.
  - There are no ongoing clinical trials.
Expanded Access Regulations for Drug Products

- **21 CFR 312, Subpart I**

- **312.300 – General**
  - **Scope:** This subpart contains the requirements for the use of investigational new drugs when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition.
  - **The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.**
Expanded Access Regulations

312.305 – Requirements for all expanded access use

1) Patient(s) must have **serious** or **immediately life-threatening** disease/condition and no comparable or satisfactory alternative therapy

2) Potential benefit justifies potential risks, and potential risks are not unreasonable in the context of disease/condition

3) Access will not interfere with clinical investigations to support marketing approval of the expanded access use

- **Immediately life-threatening** means that there is a reasonable likelihood that death will occur within a matter of months or that premature death is likely without treatment.

- **Serious disease or condition** means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.
How do I make an expanded access use request?

If you have one or more patients who qualify for expanded access use, you will need to seek the following approvals in order to use the investigational product:

- **Step 1**: Sponsor Approval
- **Step 2**: FDA Approval
- **Step 3**: IRB Approval
How do I make an expanded access use request?

- **Step 1: Sponsor Approval**
  - The company must agree to provide the investigational drug for expanded access use. FDA cannot require a company to provide an investigational drug for expanded access use.
  
  - A company may decide to turn down a request if it is not able or willing to provide access to an investigational drug outside of the clinical trial(s) intended to support marketing approval.
  
  - If an IND exists for the investigational drug, request a Letter of Authorization (LOA) from the sponsor. The LOA permits FDA to refer to information that the sponsor has submitted to FDA.
How do I make an expanded access use request?

**Step 2: FDA Approval**

- Identify the type of expanded access request applicable to your treatment scenario and submit the request to the appropriate FDA review division.

- Treatment may begin 30 days after FDA receives the IND, or earlier if FDA notifies that the use may begin. FDA authorizes over 99% of expanded access requests it receives.

- Be sure to document your IND number, as the sponsor may require this prior to shipping the investigational drug.

[https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm](https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm429610.htm)
How do I make an expanded access use request?

**Step 3: IRB Approval**

- The treating physician must ensure that IRB review is obtained in accordance with FDA’s regulations. This includes obtaining informed consent from the patient.

- Prior IRB review and approval is required for all expanded access use, with the exception of emergency use.
  - **Emergency Use:** Exempt from prior IRB review and approval, provided that the use is reported to the IRB within 5 working days.

- Expanded access protocols are reviewed by the same process as research protocols by the DUHS IRB.
How do I make an expanded access use request?

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Categories of Expanded Access

- Current regulations define three main categories:
  1) Expanded access for **individual patients**, including emergency use (21 CFR 312.310)
  2) Expanded Access for **intermediate-size patient populations** (21 CFR 312.315)
  3) Expanded Access for **large patient populations** under a treatment IND or treatment protocol (21 CFR 312.320)
Expanded Access Submissions

Two types of submissions for each category of access:

1) An expanded access protocol can be submitted as a protocol amendment to an existing IND
   • Preferred method of access when an existing IND is in effect
   • Facilitates earlier detection of safety concerns
   • Less burdensome process for sponsors and FDA

2) New IND submission – expanded access IND
   • Used when there is no IND in effect or when sponsor of existing IND declines to be the sponsor of the access use
   • Submission is separate and distinct from any existing INDs
   • Intended only to make drug available for treatment use
Expanded Access Submissions

- 8 subcategories of access submissions:
  1) Individual patient IND (single patient IND)
  2) Individual patient protocol (single patient protocol)
  3) Individual patient emergency IND
  4) Individual patient emergency protocol
  5) Intermediate-size patient population IND
  6) Intermediate-size patient population protocol
  7) Treatment IND
  8) Treatment protocol
Individual Patient: Emergency Use

- Should only be used when treatment of the patient needs to occur within a very limited number of hours or days.

- Still required to comply with federal regulations:
  - FDA will grant verbal authorization if sponsor agrees to submit written request (IND or protocol) within **15 working days** to the FDA.
  - If prospective IRB review is not possible, use needs to be reported to the IRB within **5 working days** of initiation of treatment.
  - Must comply with requirements for obtaining informed consent.
Intermediate vs. Treatment

- Intermediate-size patient population
  - More than one individual but typically less than 100
  - Used earlier in drug development
  - Used to obtain access to a drug that is not being developed or to gain access to an approved drug that is not available through marketing channels

- Treatment IND/Protocol
  - Large population, typically hundreds to thousands
  - Used later in drug development, usually after the completion of clinical trials while the drug is awaiting marketing approval
  - Can not be used to obtain access to a drug that is not being developed
Submission Content

- Requirements outlined in 21 CFR 312.305(b)
  1) Cover sheet (Form FDA 1571)
  2) Rationale for the intended use of the drug
  3) Criteria for patient selection or, if for an individual patient, a description of the patient’s disease or condition
  4) Method of administration, dose, and duration of treatment
  5) Description of manufacturing facility
  6) Chemistry, manufacturing and controls (CMC) information
  7) Pharmacology and toxicology information
  8) Description of the clinical procedures, lab tests, or other monitoring procedures necessary to evaluate drug effects
## Submission Content

### Expanded Access Use, 21 CFR 312.300

- Individual Patient, Non-Emergency 21 CFR 312.310
- Intermediate Size Patient Population, 21 CFR 312.315
- Individual Patient, Emergency 21 CFR 312.310(d)
- Treatment IND or Protocol, 21 CFR 312.320
Submission Content

- If submitting a new IND, much of the required information can be supplied by **right of reference** to an existing IND.

- IND is in effect, but the sponsor has declined to be the sponsor of the expanded access use.
  - Sponsor may give permission to reference content in the existing IND to satisfy submission requirements
  - Description of the manufacturing facility; Chemistry, manufacturing, and controls information; Pharmacology and toxicology information
  - Burden ≈ expanded access protocol

- Right of reference is granted via a **Letter of Authorization**.
Submission Content

- **Letter of Authorization (LOA)**
  - This is a letter from the sponsor of the existing application (IND) stating that confidential information from their submission can be used in support of the new application (Access IND).
  - The letter is submitted to the existing application and a copy is included with the submission requesting reference.
  - Grants FDA “permission” to reference the named material in support of your IND.
When can treatment begin?

- **Expanded Access Protocol**

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<tr>
<th>Review Timelines</th>
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<tr>
<td>Individual Patient (emergency)</td>
<td>Upon verbal authorization*</td>
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<tr>
<td>Individual Patient (non-emergency)</td>
<td>Once submitted to FDA</td>
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<tr>
<td>Intermediate-size Population</td>
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<tr>
<td>Treatment Protocol</td>
<td>30 days after submission</td>
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- **Expanded Access IND**

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* Written report needs to be sent to FDA within 15 working days of verbal authorization.
Additional Requirements

In addition to submitting the expanded access protocol or IND, additional regulations pertaining to the use of an investigational drug product must be followed:

- Must obtain informed consent (21 CFR 50)
- IRB review and approval must be obtained (21 CFR 56)
- IND safety and annual reporting requirements (21 CFR 312)*
- Must comply with the responsibilities for sponsors, investigators, and sponsor-investigators (21 CFR 312, subpart D)
- Ensure that licensed physicians are qualified to administer the investigational drug for the expanded access use
- An investigator’s brochure must be provided, if one exists
- All access programs are subject to the clinical hold provisions

*Single Patient Access Use: At the conclusion of treatment, the licensed physician or sponsor must provide a written summary of the results, including adverse effects.
An investigator contacts you and asks whether it would be possible to treat a patient with intractable epilepsy with hemp extract. Hemp extract is not an FDA approved drug, but is currently being investigated as a potential therapy in several clinical trials. The investigator tells you that his patient doesn’t qualify for the ongoing clinical study due to age and is interested in pursuing access through FDA’s expanded access program. How would you advise the investigator?
New Process for Physician Requests

Individual Patient Expanded Access Applications: Form FDA 3926

Guidance for Industry

Form FDA 3926

- Physicians requesting individual patient INDs were having difficulty completing Form FDA 1571 and providing required documents since this process was not tailored to these requests.

- **Form FDA 3926** provides a streamlined alternative for submitting an IND under 21 CFR 312.23 for use in cases of individual patient expanded access.
  - Can be used for emergency and non-emergency requests
  - Does not apply to other types of expanded access requests
  - Can not be used for medical devices
**Office of Regulatory Affairs and Quality**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Food and Drug Administration

**Individual Patient Expanded Access**
Investigational New Drug Application (IND)
*(Title 21, Code of Federal Regulations (CFR) Part 312)*

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<thead>
<tr>
<th>1. Patient's Initials</th>
<th>2. Date of Submission (mm/dd/yyyy)</th>
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<th>2a. Initial Submission</th>
<th>2b. Follow-Up Submission</th>
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<tr>
<td>[ ] Selected this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.</td>
<td>Investigational Drug Name</td>
</tr>
<tr>
<td>[ ] Selected this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 1 through 11.</td>
<td>Physician's IND number</td>
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**4. Clinical Information**

**Indication**

Brief Clinical History (Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)

**5. Treatment Information**

Investigational Drug Name

Name of the entity that will supply the drug (generally the manufacturer)

FDA Review Division (if known)

Treatment Plan (Including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)

**6. Letter of Authorization (LOA), if applicable (generally obtained from the manufacturer of the drug)**

[ ] I have attached the LOA. (Attach the LOA if electronic, use normal PDF functions for file attachments.)

Note: If there is no LOA, consult the Form instructions.

**7. Physician's Qualification Statement** (Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.)

**8. Physician Name, Address, and Contact Information**

**Physician Name:**

[ ] Email Address of Physician

Address 1 (Street address, No P.O. boxes)

Address 2 (Apartment, suite, unit, building, floor, etc.)

City

State

Facsimile (FAX) Number of Physician

ZIP Code

Physician's IND number, if known

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**Contents of Submission**

This submission contains the following materials, which are attached to the form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1871 for your submission:

- Initial Written IND Safety Report
- Follow-up to a Written IND Safety Report
- Annual Report
- Summary of Expanded Access Use (treatment completed)
- Change in Treatment Plan
- General Correspondence
- Response to FDA Request for Information
- Response to Clinical Hold

**Request for Authorization to Use Form FDA 2926**

[ ] I request authorization to submit this Form FDA 2926 to comply with FDA's requirements for an individual patient expanded access IND.

**Certification Statement**

I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials. If I receive earlier notification from FDA that treatment may begin, I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, consistent with Federal requirements, and that an Institutional Review Board (IRB) that complies with the Federal IRB requirements will be responsible for initial and continuing review and approval of the treatment use. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all applicable regulatory requirements.

**WARNING:** A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

**Signature of Physician**

To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.

**For FDA Use Only**

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<tr>
<th>Date of FDA Receipt</th>
<th>Is this an emergency individual patient IND?</th>
<th>Is this indication for a rare disease (prevalence &lt; 200,000 in the U.S.)?</th>
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<td></td>
<td>[ ] Yes [ ] No [ ] Yes [ ] No</td>
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This section applies only to requirements of the Paperwork Reduction Act of 1995.

**DO NOT SEND YOUR COMPLETED FORM TO THE FDA STAFF EMAIL ADDRESS BELOW.**

The burden time for this collection of information is estimated to average 45 minutes per response, including the time to review instructions, searching existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

- Department of Health and Human Services
- Food and Drug Administration
- Office of Operations
- Paperwork Reduction Act (PRA) Staff
- PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."
Form FDA 3926

- FDA generally intends to accept Form FDA 3926 to comply with the IND submission requirements.

- **Box 10: Request for Authorization to Use Form FDA 3926**
  - I request authorization to submit this Form FDA 3926 to comply with FDA’s requirements for an individual patient expanded access IND.
    - FDA intends to consider the checking of this box to be a waiver of any additional requirements required by part 312 for an IND submission.
    - Waiver is appropriate because a physician’s noncompliance with any such requirements would not pose a significant and unreasonable risk to the individual patient and compliance with any such requirements is unnecessary for the Agency to evaluate the IND.
Sponsor-Investigator Roles and Responsibilities

- Under individual patient expanded access INDs, the physician who submits the IND is considered the sponsor-investigator.
  - Responsible for complying with the responsibilities for both sponsors and investigators (Subpart D of 21 CFR part 312).
  - Includes submitting IND safety reports, annual reports, summary of expanded access use and maintaining adequate drug disposition records.

- Institutional Requirements:
  - Register the IND with ORAQ
  - Receive sponsor-investigator training
  - Maintain an active IRB approved protocol
    - Emergency Use: If not approved by a convened IRB board, use will be presented and acknowledged as in compliance with FDA regulations
IND Maintenance

Form FDA 3926 may also be used for follow-up submissions, including those required to maintain an effective IND:

- Initial Written IND Safety Report (312.32(c))
- Follow-up to a Written IND Safety Report (312.32(d))
- Annual Report (312.33)
- Summary of Expanded Access Use (treatment completed) (312.310(c)(2))
- Change in Treatment Plan (312.30)
- General Correspondence or Response to FDA Request for Information (312.41)
- Response to Clinical Hold (312.42(e))
Is there support for expanded access INDs?

- Duke University Health System (DUHS) is committed to helping physicians obtain access to medical products to treat patients with serious or life-threatening conditions for which no alternative therapy exists.

- DUHS is collaborating with the School of Medicine to help physicians submit individual patient expanded access INDs.

- SOM Research Infrastructure to be Utilized:
  - ORAQ Staff to assist with obtaining sponsor approval
  - ORAQ Staff to perform IND submission and maintenance
  - Core of Regulatory Coordinators to perform IRB submission
Process Development

- Average of 12-18 individual patient INDs per year at Duke (emergency and non-emergency)

- Primary Departments:
  - Infectious disease
  - Solid organ transplant
  - Oncology

- Identified and met with involved parties in December 2016
  - Faculty, ORAQ, DOCR, IRB, IDS, OCRC, and REDCap Designer to create operational plan
Faculty needs E or S IND → Faculty member will end up on ORAQs website where REDCap link is held → Faculty member fills out REDcap tool and pages ORAQ if they believe it to be an EIND → Email faculty core that IND has been picked up by ORAQ and whether is has been determined to be an E or S IND by ORAQ

Regulatory Coordinator (RC) must accept the task in REDCap to prompt an email notification that will be sent out to the RC core that someone has taken the IND

REDCap sends an email to ORAQ and RC so that they can generate the PRO # in IRB presubmission → ORAQ determines single or EIND

ORAQ works to get sponsor approval

If no contract is needed then OCRC will not receive the email

ORAQ gets sponsor approval and enters into REDCap which sends out email notifications to:

- OCRC
- IDS
- IRB
- Faculty
- RC

FDA approval?

No → Email all parties. IND ends.

Yes → ORAQ enters the approval into REDCap which emails RCs and IDS to begin drug preparation

The RC will work on the IND in the eIRB

RC will enter basic information into the REDCap once IND is completed (*must be done by the first of the month)
Next Steps

- Building and testing the REDCap form
  - In process; Completion anticipated early May

- Educating staff on the workflow, use of the REDCap tool and overall responsibilities for these requests

- Begin educating and advertising the service to the clinical and research communities at Duke
Questions?

Please contact us at ORAQ@duke.edu.

http://medschool.duke.edu/ORAQ

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