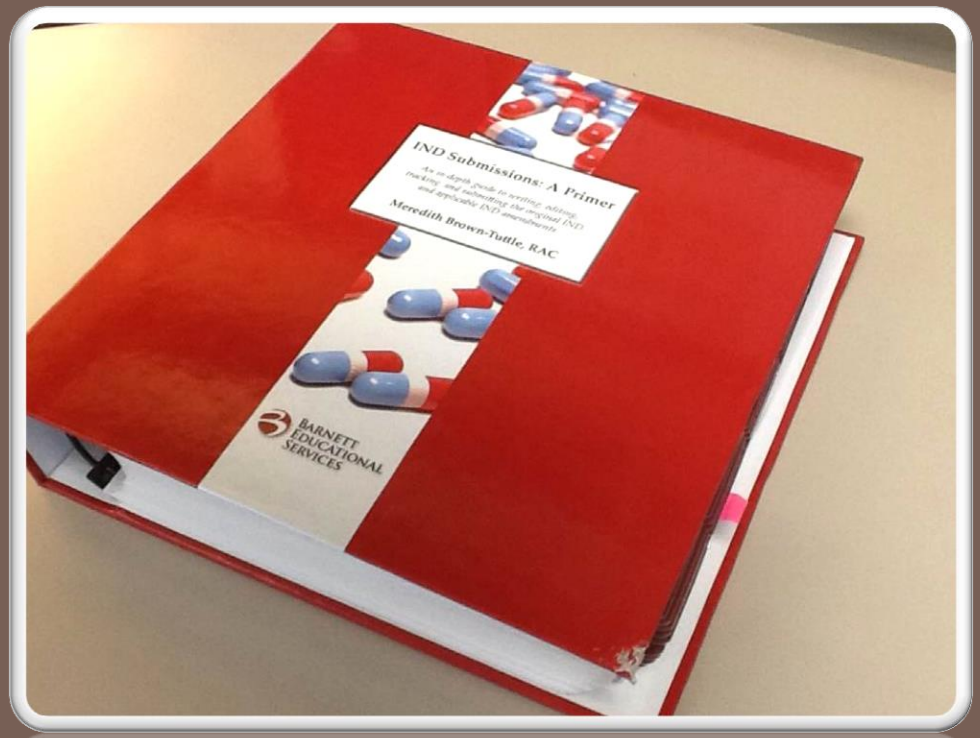


REGULATORY ISSUES: HOW TO APPLY FOR AN IND

Penny Jester and Maaike Everts

Outline

- What is the purpose of an IND?
- What types of INDs are there?
- When do you need one?
- How do you apply for one?
- How do you manage an active IND?

- IDEs are very similar with some minor differences

Purpose of an IND

- Exemption from the law requiring an approved marketing application for drugs to allow clinical testing
- Assess that the proposed clinical protocol is not unnecessarily risky
  - Evaluate preclinical data for safety
  - Evaluate investigators qualifications
  - Evaluate drug purity

What is a New Drug?

- "Any drug (or biologic) that is not generally recognized as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof" (section 201 FD&C Act)

- FD&C Act prohibits shipment of any drug across the state lines without an approved NDA
- Investigational New Drug (IND) application provides an exemption to allow shipment of the drug for clinical testing,.

Permissions needed for clinical trial

- The sponsor must apply for permission to study drugs in humans
  - From FDA for IND – traditional or exploratory
  - From an IRB for either
  - From various other entities at your institution
- "Sponsor"
  - Individual physician
  - Institution
  - Industry

Types of INDs

- Three types of traditional INDs
  - Sponsor-initiated
  - Expanded Access: Treatment IND
  - Emergency use IND

- Relatively new type of IND
  - Exploratory ('phase 0')

When do you need one?

Unapproved Product

- Required for a new drug or biological product to be used in a clinical trial

Approved Product

- Required to study a new aspect of an approved drug
  - Different indication
  - Different route of administration or dose
  - New drug combination
  - Different population

Off-label Use

- Approved products may be used by physicians outside of labeled indications for the practice of medicine
- No IND is needed

When is it not required?

- Generally not required when all these criteria met:
  - No intent to support new use or labeling change
  - No intent to support change in advertising
  - No factor such as route of administration, dosage, or study population significantly increases risk
  - Compliance with FDA informed consent and IRB review requirements
  - No promotion or representation of product as safe or effective treatment for condition under study

IND needed?

- Study the therapeutic effect of a food supplement available OTC on the progress of type I diabetes
- Yes! Therapeutic intent
- Study the effects of a commonly used drug for the treatment of asthma on bone turnover markers
- Yes! May change the label

Not sure?

- Read the guidance:
  - http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf
- Ask the IRB**
- Ask the FDA

So… you have to apply for an IND

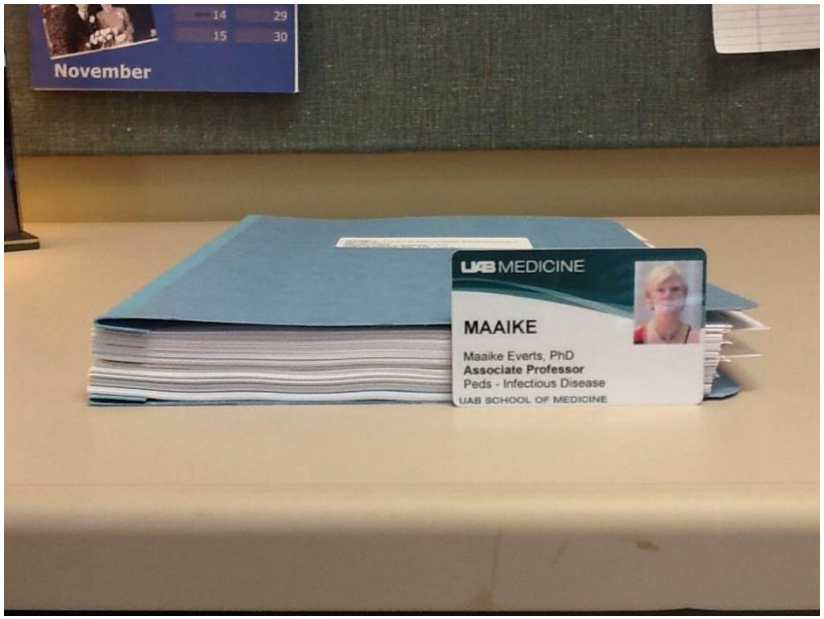
Relax…we're here to help!

How to apply for an IND

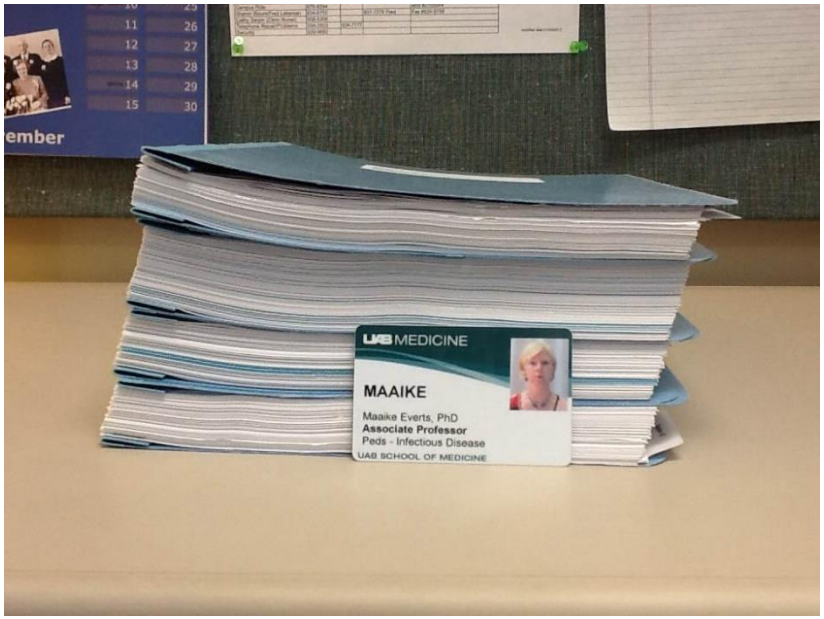
- Forms forms forms!
- Most important ones (will discuss in detail later):
  - 1571
  - 1572
  - 3674
  - 3454
- Clinical protocol should have been finalized
- Informed consent form should be available

Paperwork: in triplicate; fancy binders

Approved product



New product



Pre-IND meeting

- Formal way of communicating with the FDA about your plans
  - Request input on toxicity studies, protocol design, etc
- Not required
- Informal ways of communicating with the FDA are encouraged as well
  - Phone
  - Email
- ***Benefit:*** may move IND through the FDA more quickly

The application itself

- Pre-determined sections with certain types of information; sometimes information repeats

Section 1: **1571**	Section 5: **IB or PI**	Section 9: **Previous human experience**
Section 2: **TOC**	Section 6: **Protocol**	Section 10: **Additional info**
Section 3: **Introductory statement**	Section 7: **CMC**	Section 11: **Biosimilar user fee**
Section 4: **General investigational plan**	Section 8: **Pharmacology/Toxicology**	Section 12: **References**

IND application template

- We created a template to be used for UAB investigators (could be modified for other institutions)
- Contains some 'stock' language (modify as needed)
- Links to forms
- Instructions to forms
- Instructions what information goes where

- Let's go through it!

What happens after submission?

- Receipt of FDA Acknowledgment Letter
  - Arrives 1-2 weeks after FDA receipt of IND submission
  - Assigns IND number, gives date of receipt, reminds sponsor-investigator of obligations under the IND
  - NOT an approval to begin
- May not start until 30 days after IND receipt date
  - Unless earlier notification indicates otherwise
  - Unless 'hold' placed on protocol

Possible FDA Actions

- Request additional information or place on clinical hold
  - Research cannot begin until clinical hold issues are addressed in ways acceptable to FDA
- Conclude project is exempt
  - Research may be conducted without an IND
- Passive Activation
  - Allowing 30 days from filing to pass without comment
  - (confirm FDA non-objection is a good idea anyway)

Common reasons for hold

- Human subject exposure to an unreasonable and significant risk of illness or injury
- Incomplete information to assess the risk to subjects
- Deficient plan or protocol
- Misleading, erroneous, or materially incomplete investigator brochure
- Unqualified clinical investigators

After IND is active, how to manage?

- Annual IND reports
  - How is it going? Primarily safety issues!
- Report (S)AEs
  - Report to the FDA within 15 days of discovery of an event that is *serious, related* and *unexpected*.
- Maintain required documents
  - Updated documents
- Monitoring – to monitor or not!
  - Independent monitoring (QA effort)
  - Data and Safety Monitoring Board

Can you close a study?

- If finished: you may 'inactivate' the study
- If need to stop for some reason: 'withdraw' IND
- If FDA is concerned, study is 'terminated'

- Study CAN be 'reinstated'

Let us help!

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