

REGULATORY ISSUES: HOW TO APPLY FOR AN IND

Maaiké Everts

Outline

2

- 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

3

- Exemption from the law requiring an approved marketing application for drugs to allow clinical testing across state lines
- FDA language:
 - ▣ Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

What does the FDA look for?

4

- Assess that the proposed clinical protocol is not unnecessarily risky
 - ▣ Evaluate preclinical data for safety
 - ▣ Evaluate investigators' qualifications
 - ▣ Evaluate drug purity, stability, etc.

Permissions needed for clinical trial

5

- The sponsor must apply for permission to study drugs in humans
 - ▣ From FDA for IND
 - ▣ From an IRB
 - ▣ From various other entities at your institution (e.g. IBC)
- Sponsor can be:
 - ▣ Individual physician
 - ▣ Institution
 - ▣ Industry

What happens after submission?

6

- 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

7

- Request additional information or place on clinical hold
 - ▣ Research cannot begin until all concerns 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
 - ▣ (Confirming FDA non-objection is a good idea anyway)

Common reasons for hold

8

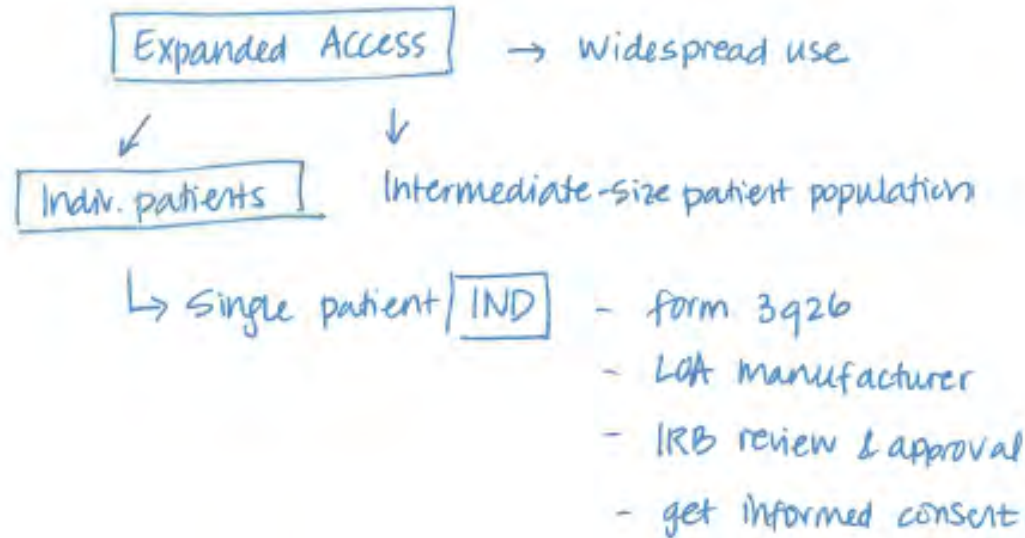
- ❑ Human subject exposure to an unreasonable and significant risk of illness or injury
- ❑ Incomplete information to assess the risk to subjects
- ❑ Deficient plan or protocol
- ❑ Misleading, erroneous, or materially incomplete investigator brochure
- ❑ Unqualified clinical investigators

Types of INDs

9

- Types of traditional INDs
 - ▣ Sponsor-initiated
 - ▣ Expanded Access (emergency or not)
 - Single patient:
 - Single patient IND: 30 day wait
 - Single patient protocol: no waiting period
 - Wide spread use or intermediate size patient population
- Relatively new type of IND
 - ▣ Exploratory ('phase 0')
 - Evaluate natural course of disease
 - Microdosing: less than 100 ug per dose

Expanded Access Options...



→ 30 day wait ; may proceed earlier if FDA gives OK

if emergency : call FDA & they can give authoriz. over the phone

written submission w/in 15 business days

report to IRB w/in 5 working days

- ↳ Single patient **protocol** :
- New protocol to be submitted by sponsor
 - no waiting period
 - protocol must have been received by the FDA though
 - IRB review & approval

if emergency: call FDA to get authoriz.

written submission w/in 15 business days

if no time for IRB approval: report to

IRB w/in 5 working days

When do you need an IND?

11

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

12

- 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?

13

- Generally not required when all these criteria are 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?

14

- Study the therapeutic effect of a food supplement available OTC on the progress of type I diabetes
- Yes! Therapeutic intent
- Study whether the use of fluoxetine (Prozac) enhances the effects of physical rehabilitation on motor function in stroke patients
- No! (Surprise to us!) Meets all exemption criteria... (see previous slide)

Not sure?

15

- 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

16



Relax...we're here to help!

17



How to apply for an IND

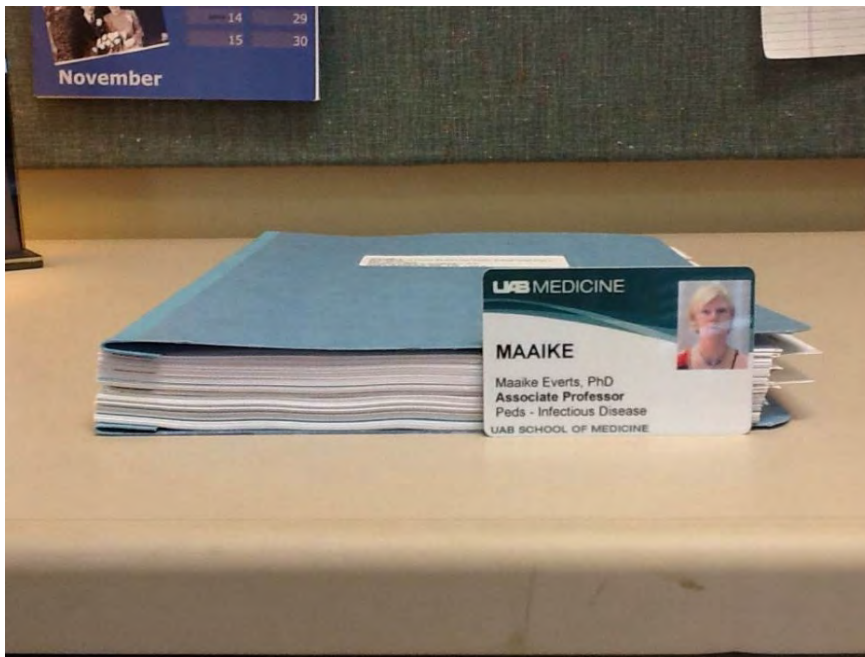
18

- Forms forms forms!
- Most important ones:
 - ▣ 1571: cover form
 - ▣ 1572: statement of investigator
 - ▣ 3674: clinicaltrials.gov registration
- Clinical protocol should have been finalized
- Informed consent form should be available

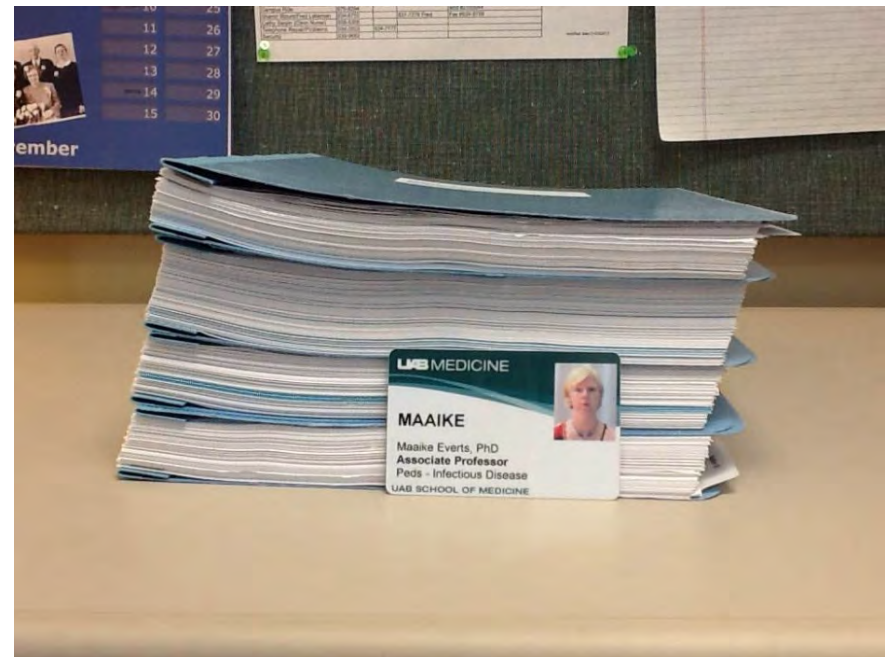
Paperwork: in triplicate; fancy binders

19

Approved product



New product



Pre-IND meeting

20

- 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

21

- 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: Clinical Trials Certificate of Compliance

IND application template

22

- We created a template to be used for UAB investigators
- Contains some 'stock' language
- Links to forms
- Instructions to forms
- Instructions on what information goes where
- We have added 'Section 13: References'

After IND is active, how to manage?

23

- Annual IND reports
 - ▣ How is it going? Primarily safety issues!
 - ▣ (We try to remind you...but it is your responsibility)
- Report (S)AEs
 - ▣ Report to the FDA within 15 days of discovery of an event that is *serious, related* and *unexpected*.
 - ▣ OR based on what was said in the protocol for reporting SAEs (and AEs).
- Maintain required documents
 - ▣ Updated documents

Critical: MONITORING

24

- Per subject monitoring
 - ▣ Independent monitor
- Safety and efficacy monitoring
 - ▣ Data and Safety Monitoring Board

Let us help!

25

- Maaïke Everts: maaike@uab.edu
- Dunia Ritchey: dritchey@peds.uab.edu

