REGULATORY ISSUES: HOW TO APPLY FOR AN IND

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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
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
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
  - Emergency use
  - Treatment (Compassionate use)

- Relatively new type of IND
  - Exploratory (‘phase 0’)
### When do you need one?

<table>
<thead>
<tr>
<th>Unapproved Product</th>
<th>Approved Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for a new drug or biological product to be used in a clinical trial</td>
<td>Required to study a new aspect of an approved drug</td>
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<tr>
<td></td>
<td>□ Different indication</td>
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<tr>
<td></td>
<td>□ Different route of administration or dose</td>
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<td></td>
<td>□ New drug combination</td>
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<td></td>
<td>□ Different population</td>
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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 1 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:
- 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
Pre-determined sections with certain types of information; sometimes information repeats

<table>
<thead>
<tr>
<th>Section 1: <strong>1571</strong></th>
<th>Section 5: <strong>IB or PI</strong></th>
<th>Section 9: <strong>Previous human experience</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 2: <strong>TOC</strong></td>
<td>Section 6: <strong>Protocol</strong></td>
<td>Section 10: <strong>Additional info</strong></td>
</tr>
<tr>
<td>Section 3: <strong>Introductory statement</strong></td>
<td>Section 7: <strong>CMC</strong></td>
<td>Section 11: <strong>Biosimilar user fee</strong></td>
</tr>
<tr>
<td>Section 4: <strong>General investigational plan</strong></td>
<td>Section 8: <strong>Pharmacology/Toxicology</strong></td>
<td>Section 12: <strong>References</strong></td>
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</table>
IND application template

- We created a template to be used for UAB investigators
- Contains some ‘stock’ language
- 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 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
  - (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
Let us help!

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