National Cancer Institute

Navigating the Regulatory Shoals: Transitioning Your Imaging Agent To The Clinic

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CANCER IMAGING PROGRAM

Disclaimers

- Opinions are mine alone
- I do not speak for FDA
- No financial conflicts of interest
- No professional conflicts of interest
- Will discuss investigational drugs

So you have a wonderful new molecular probe…

How will it go?

Smooth Sailing

National Cancer Institute

or…..

Institute

Outline

- Concepts
- Basic regulatory requirements
- Practical details for an IND
- CMC documentation
- Maintenance

From Laboratory to Human Studies

- Screen related molecules *in vitro*
- Select the best ones
- Learn to prepare them consistently
- Perform preliminary *in vivo* pharmacology and toxicology in appropriate animal models
- Chose initial dose for human studies
- What next?

Basic regulatory requirements

- Each clinical study of ANY unapproved drug MUST be approved by:
  - IRB
    - RDRC or
    - FDA: x-IND (exploratory IND) or Regular IND
    - RSO if radioactive
  - [Department]
  - [Cancer Center]
- Focus on IND in this presentation

Basic regulatory requirements

- Requirements do not change if:
  - Some else has an IND, even in your institution
  - You have a letter to another's IND
  - You are doing it for clinical care
  - You are doing it for research
  - You buy the agent from a commercial vendor
- Some examples

Basic regulatory requirements

- IND must be maintained – it is not a “license to operate”. Submit all of these to FDA
  - Annual reports
  - Protocol amendments
  - New protocols
- It does not have to be scary
- Ignorance is no excuse

Overview of the IND

- Exemption from requirement for NDA
- Details needed:
  - Pre-clinical studies
  - Clinical study planned with complete protocol
  - CMC (Chemistry, Manufacturing & Control)
- A living document
  - Annual report required
  - Protocol amendments must be submitted
  - New protocols must be submitted

Examples: F-18 PET Agents

- NCI INDs for FLT, FES, FMISO, NaF
  - Site-specific manufacturing information
  - Letters of Reference to commercial DMFs
- Sponsor multicenter trials
- Provided about 30 Letters of Reference
  - Academic sites
  - Pharmaceutical industry multisite studies
- PET research and therapeutic research

A very simple IND for FLT

1. Talk to your local commercial reps to see if they can supply you
   - The major companies have DMFs at limited sites
   - If not, you will need to make it -- discussed later
2. Get a LOA from the NCI
3. Get the drug brochure from the NCI
4. Write your clinical protocol
5. IND consists of your protocol, the IB, and the LOA
6. All the other sections refer to the LOA

Approach to Regulatory Requirements

- Regulatory path is the same for
  - Small molecules
  - Most biologics
  - Radiolabeled drugs
- Strategy may differ with goal
  - Chose among related compounds
  - Pharmacokinetics, pharmacodynamics
  - Dose escalation

Regulatory Mechanisms

- Operate under another's IND
  - The other entity is fully responsible
  - Filing with FDA required
- RDRC – if drug has been in humans
- File your own IND, with LOA to another IND
  - NCI provided more than 30 to academia/industry
  - Only sections not in original IND needed
- File your own IND, all sections

Types of IND

Three types of traditional INDs:

- An investigator initiated IND
- Emergency use IND (E-IND)
- Treatment IND

And a reasonably new type:

- Exploratory (“phase 0”, x-IND)

What's the difference?

- Traditional
  - Single agent, plans for Phase 3 trials and NDA
  - Extensive pre-clinical data needed to begin
  - Dose escalation, therapeutic evaluation
- Exploratory
  - Multiple agents under one IND, go/no go
  - Microdose, first in man studies
  - No therapeutic intent
  - Biodistribution, pharmacokinetics, safety
  - Less pre-clinical data required
  - Resubmit as Traditional IND if successful

Where to get information

- FDA Guidance on the IND process with multiple links to other documentation:
  - http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm
- RDRC:
  - http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Oncology/ucm093322.htm
- Comprehensive Guidance Page
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - An "how-to" guide from the Biological Development Program at NCI-Frederick with multiple links http://web.ncifcrf.gov/research/bdp/documents/Request.aspx

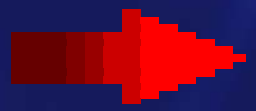
Talk to the FDA!

Nuts and Bolts of an IND

- What data are needed
- What supporting information is needed
- How is the application put together
- What happens when it is submitted

Information Required in INDs

- Pharmacology/toxicology in animals
- Dosimetry for radiopharmaceuticals
- CMC: Chemistry, Manufacturing and Controls – more later
- Previous human exposure
- All may be referenced from existing INDs or the literature
- Clinical Information



Clinical Protocols and Investigator Information

- Detailed protocol for clinical study
- Qualifications of clinical investigators
- Commitments by sponsor
  - To obtain informed consent
  - To obtain review of the study by an institutional review board (IRB)
  - To adhere to the investigational new drug regulations

IND Application

1. Form 1571 (Application)
2. Table of Contents of Application
3. Introductory Statement
4. General Investigational Plan
5. Investigators' Brochure (multi-site)
6. Protocol
   - Study Protocol
   - Investigator Data – Form 1572, CV (must have, do not have to submit)

IND Application

7. Chemistry, Manufacturing, and Control Data
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information.
    - Dosimetry
    - Letter from IND or DMF-holder allowing cross-reference to their files
    - Site/NCI Data and Safety Monitoring Plan
    - Cited literature

Obtaining Investigational PET Drugs

- Buy it from someone with a DMF with LOA
  - [F-18] FLT: Cardinal, IBA, PETNET
  - [F-18] NaF: Cardinal, IBA, PETNET
  - [F-18] FMISO: Cardinal
- Make it yourself – requires:
  - Cyclotron, Radiochemists
  - cGMP/USP<823>
  - Quality control testing
  - Submission of data to FDA

CMC Requirements in INDs

- Manufacture under cGMP conditions
  - Adjust for PET radiopharmaceuticals
  - Adjust for phase of clinical trial
  - USP <823> or 21CFR 212
- File CMC with FDA
  - Within the IND
    - or -
  - By Letter of Reference to a Drug Master File

What goes in a CMC section?

- Manufacturing & testing facilities & management
- Manufacturing details
- Quality control procedures
- Qualification runs and QA data
- Stability data
- Labels
- See examples at:
  - http://imaging.cancer.gov/programsandresources/Cancer-Tracer-Synthesis-Resources
- Proper DMF reference covers all of this

Manufacturing Details

- Cyclotron ID and conditions
- Local facility and equipment
- Management structure and staffing
- Manufacturing SOP documents
  - Generally a detailed batch record is sufficient
  - List of all of the supporting documents
  - NCI example: 144 documents (most generic)

Quality Control Information

- QC Methods
  - Submit your SOPs or write up methods
  - Write up generally where possible
- Specifications – if USP, that is minimum
- Management structure and staffing
- Data on 3 successive passing qualification runs
- Stability data through the expiration time

Practical IND Submission Issues

- Make it easy for multiple reviewers –sections should be self-explanatory
- Include all sections, even if N/A
- Comprehensive Table of Contents and TOC for any section more than a few pages
- Consecutive page numbers for entire IND (can be numbered by section)
- Include copies of all cited literature
- Don’t assume the reviewers are expert in your subject area

What happens next?

- Submit 5-15 copies (ask FDA Division first)
- Wait 30 calendar days before beginning the first study on IND
- The document goes to several reviewers
- FDA reviews the IND first and foremost for risk to subjects – NOT for scientific interest
- FDA may request changes
  - Safety related in protocol
  - Purity/safety related in CMC
- FDA will call/fax with questions

Active IND

- Conduct investigational studies
- Report to FDA
  - any serious or unexpected adverse events
  - any protocol amendments or new protocols
  - any CMC changes
  - Any pre-clinical data suggesting clinical risk
- Annual report to FDA – there's a guidance for that!

Weblinks

- CMC SOPs that you can customize (ignore the specific drug – 95% are for general operations):
  http://imaging.cancer.gov/programsandresources/Cancer-Tracer-Synthesis-Resources
- Guide to Regulatory Submissions – in comprehensible English – orientated to biologicals but very valuable Here under Regulatory Affairs (and much more there):
  http://web.ncifcrf.gov/research/bdp/documents/Request.aspx
- FDA guidances:
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- My email address: jacobsp@mail.nih.gov.

Thanks for your attention

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