Supply of IND Agents to Multi-center trials by Skilled Academic Sites

Paula M. Jacobs, Ph.D.
Associate Director, Division of Cancer Treatment and Diagnosis, NCI
Cancer Imaging Program

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Disclaimers

- No financial conflicts of interest
- Investigational drugs are discussed
- The opinions expressed should not be interpreted as the official position of NCI, NIH, HHS or the Federal Government

Supply issues for multi-center PET trials

- Multi-center trials require that the imaging drugs be the same at all sites
- Short lived radio pharmaceuticals must be prepared locally
- Commercial entities may not be willing to supply
- Assuring consistency across unique academic radiochemistry sites can be challenging
- Throughout here, NCI will be used as the example sponsor but this approach can be used by any sponsor of a multi-site trial

Some Basic Issues

- Investigational drugs require an IND from the FDA to test in humans
- A multicenter trial requires one "sponsor" for the IND
  - Holds the IND, files new protocols to the IND
  - Files annual reports
  - Files adverse event reports
- If you don't understand:
  - An Investigational New Drug (IND) file
  - A drug master file (Hint: the CMC section of an IND)
  - Letters of right of reference
  - This approach is not for you

Uses of DMF & IND

- DMF (Drug Master File)
  - Can manufacture for others with IND or NDA/ANDA by giving a trial sponsor a cross-file letter
  - Responsible for CMC only
- IND (Investigational New Drug Exemption)
  - Can perform one or more clinical trials
  - If submit CMC, can manufacture for own trials
  - If give cross-file letter, can manufacture for IND trials sponsored by others
  - Responsible for CMC and for AE reporting for own clinical trials

What goes in a DMF (or the CMC section of IND)

Chemistry Manufacturing and Controls (CMC) for each and every site that manufactures

- Detailed manufacturing information
- Detailed packaging & labeling information
- Detailed quality control procedures
- Release specifications
- Facility information
- Results from at least 3 batches
- Stability data

What goes in an IND

- Clinical Plan
  - Clinical Protocols
  - Investigator Information
- Chemistry, Manufacturing and Controls
- Pharmacology/toxicology in animals
- Previous human exposure
- Dosimetry for radiopharmaceuticals

All but the clinical aspects can be “imported” from someone else’s IND by a letter of reference

Letter of Right of Reference

- Also called: cross-file letter, letter of authorization (LOA)
- Incorporates the specified sections from one DMF, IND, or NDA into another by reference
- The information authorized is not repeated in the new IND and does not have to be provided to the new applicant
- All the new applicant needs is the letter

The holder of the original IND has no responsibility for the new IND

What does this accomplish?

- Whatever the letter references is legally incorporated in the IND to which it is given without actually copying it into the new IND
- Allows any entity (commercial or non-commercial) to supply drug for any IND with their site specific DMF or IND and an LOA to the trial IND
- Helps independent PIs to get their own IND – no need to repeat toxicity studies, for example
- Reduces FDA review time/effort

How Does This Work?

Interlocking regulatory documents

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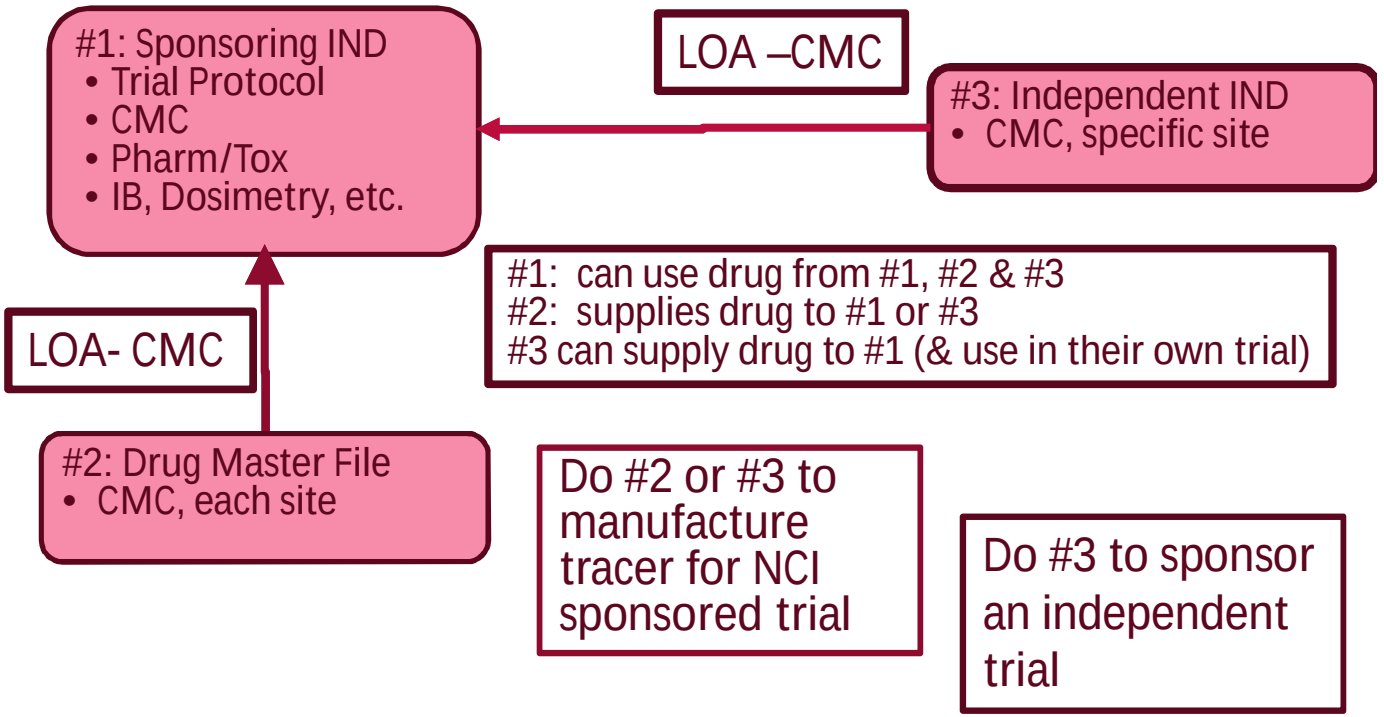
Flow chart


#1: Sponsoring IND
• Trial Protocol
• CMC
• Pharm/Tox
• IB, Dosimetry, etc.
LOA –CMC
#3: Independent IND
• CMC, specific site
#1: can use drug from #1, #2 & #3
#2: supplies drug to #1 or #3
#3 can supply drug to #1 (& use in their own trial)
LOA- CMC
#2: Drug Master File
• CMC, each site
Do #2 or #3 to manufacture tracer for NCI sponsored trial
Do #3 to sponsor an independent trial

ECOG-ACRIN Example

- NCI IND for FLT
  - One MF sites filed in the IND – U Wash
  - One commercial entity with DMF filed & LOA in NCI IND
  - Mixture of academic and commercial acceptable
- Academic manufacturing sites possible
  - Important to assure that drug is consistent across sites
  - Establish process to permit experienced academic radiochemistry/pharmacy sites to supply their own site

Requirements for Multiple Supply Sites

- The CMC for every site for the specific agent must be filed with FDA (DMF or IND)
- The agent must be “equivalent” across sites
- The agent must meet the NCI specifications
- The site must comply with USP<823> or 21CFR212
- The site must be experienced
- NCI is not responsible for site CMC compliance/filings

How can we assure this?

NCI Approach

- Site must have active IND or DMF for the specific drug and supply an LOA to NCI
- IND or DMF must not be on hold
- The drug must meet NCI specifications
- Site experience is assured by:
  - Current NDA or ANDA for approved agent
  - OR – multiple active or recent INDs
  - Inspection records, no warning letters
  - Drug made in inspected facility

Approach (2)

- NCI holds the IND for the trial
  - Makes the regulatory filings for IND and trial
  - Monitors and reports Adverse events
  - Files the IND annual report
- Each manufacturing site:
  - Supplies its site with drug under GMP or USP<823>
  - Maintains its DMF or IND current
  - Notifies entities as required (FDA, NCI, other sites supplied) of MF deviations/failures, etc.

Thank you for your attention

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jacobsp@mail.nih.gov

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