

We will start momentarily at 2pm ET



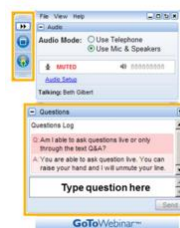
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Thursday, July 31, 2014

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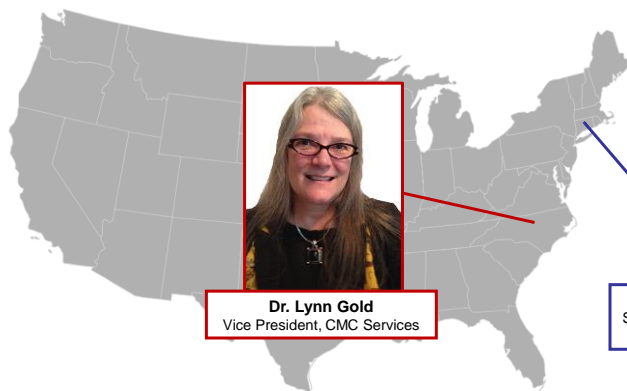
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2014 Drug Discovery Series
Session 5: Tips for Filing IND and Starting your Clinical Trials



Dr. Lynn Gold
Vice President, CMC Services



Dr. John Morrison
Senior Research Investigator,
Bristol-Myers Squibb

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**Tips for Preparation of IND and Start of
Clinical Studies**

Lynn Gold, PhD, AAPS-RS- Camargo Pharmaceutical Services, LLC

John Morrison, PhD, AAPS-DDDI/PPB-Bristol-Myers Squibb

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Overview

- Introduction
- What should happen first?
- IND Preparation
- IND Submission
- Start your Clinical Study!
- IND Updates
- Lessons Learned



Introduction

- Successful internal selection of candidates for development
- Based on target activity/efficacy, physicochemical properties, pharmacokinetics, safety, tolerability and toxicity profile
- Ready for First-in-Man studies
- Time to start planning for success



Audience Trivia Question

When do you prepare an IND?

- When you want to develop a drug.
- When you have synthesized a new drug candidate.
- When you think you have justified a safe starting dose on a small animal.
- When you think you have justified a safe starting dose in man.

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Inventory of tasks to complete prior to IND Submission

- **Drug substance (DS) batch(es) initial synthesis outlined**
- **Preliminary Manufacturing batch record in place**
- Protocol describing the batch size, in-process testing, any additional sampling, the release criteria and the stability testing (or reference to the stability protocol)
- **Prepare DS batch for nonclinical studies**
- **Document and report all results**

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Inventory of tasks to complete prior to IND Submission (cont'd)

- **Drug Product (DP) initial formulation**
- Preliminary testing upon receipt all all components performed and documented
- Protocol for the manufacture of the drug product batch prepared describing the batch size, in-process testing, any additional sampling, the release criteria and the stability testing (or reference to the stability protocol).
- **Prepare DP nonclinical batch**

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Inventory of tasks to complete prior to IND Submission (cont'd)

- Quality Target Product Profile describing the expected target attributes of drug product
- **Nonclinical toxicology draft report**
- **A starting dose for the new drug product has been defined with a reasonable safety margin**
- **Protocol for your First-in-Man study drafted**
- **Investigational Brochure**
- **Informed Consent Forms**

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Inventory of tasks to complete prior to IND Submission (cont'd)

- Manufacture DS for clinical trial materials (CTM)
- Manufacture DP for CTM
- Manufacture Placebo for CTM
- **Certificates of Analysis for CTMs**
- Document the progress



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Questions to prepare for the IND



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Questions to prepare for the IND

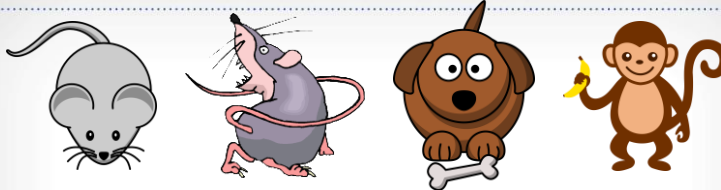
- Do you need a Pre-IND meeting with the FDA?
- How to decide?
- When to prepare for this meeting?
- 21 CFR 312.82 (a)



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Why have a Pre-IND Meeting?



- Are you using the appropriate animal model to show the safety of your product?
- Is the toxicology data generated sufficient to support your First-in-Man study design?
- Any data that needs to be discussed with the Agency prior to the study start?

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Why have a Pre-IND Meeting? (cont'd)

- Are there any Agency concerns about the clinical protocol or FDF specifications you are defining for the Phase 1 study?
- What the road blocks will there be for your development program?
- Good to get to know the group that will be reviewing your submission.
- Often you get insight to division specific issues.

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Audience Trivia Question

How long between the request for a Pre-IND meeting and attendance if a meeting is granted?

- 21 Days
- 30 Days
- 60 Days
- 90 Days
- 120 Days

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Pre-IND Meeting Preparation and Execution

- Request Pre-IND meeting with appropriate division of the FDA including the questions to be discussed.
- Prepare a Pre-IND meeting Package to be submitted about 4 weeks ahead of meeting.
 - Contains information to support the questions
- Attend Pre-IND meeting within ~60 days of Agency acceptance
- Receive Pre-IND Meeting Minutes ~30 days after meeting

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Outcomes of Pre-IND Meeting

- Typically directional, final outcome will always be a review issue
- How well have you identified and justified the inherent risk in your program?
- Is there something on the FDA agenda that was not on yours?
- Understanding of the path to First-in-Man
- Division, indication and drug product dependent

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IND for a First-in-Man Study

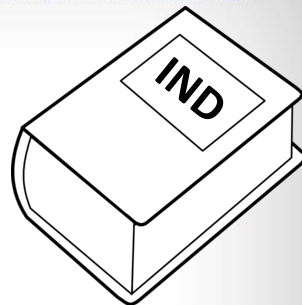


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What is an Investigational New Drug application?

- An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.
- Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.



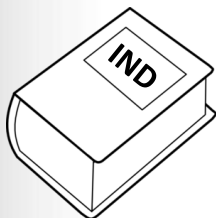
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IND for a FIM Study

- Will the IND be paper or electronic?
- What format will be used?



- Most frequently eCTD format
- Original paper format used less often



- Key attributes of your drug product that will help the agency understand the safety should be highlighted in summaries.

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IND Contents

1

- **Module 1-** Administrative and Prescribing Information

2

- **Module 2-** Overall Summaries for Quality, Nonclinical and Clinical

3

- **Module 3-** DS and DP

4

- **Module 4-** Nonclinical

5

- **Module 5-** Clinical

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IND Module 1-Administrative and Prescribing Information

1

- Cover Letter

- To appropriate division

2

- Reference any key discussions that occurred in the Pre-IND meeting

3

- State any points that are critical to the reviewer's understanding of the contents of the IND

4

- Ask any questions that are outstanding

5

- Point person and contact information

- Help the Agency navigate your application

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IND Module 1 (cont'd)

1

- Table of Contents

2

- Forms

- 1571-Fill out on-line

3

- 1572-Each Investigators

4

- 3674-clinical trials reference

5

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IND Module 1 (cont'd)

1

- Investigator Brochure

- Per 21 CFR 312.23(a)(5)

2

- Guidance for Industry: Good Clinical Practices for Investigator's Brochure

3

- Pre-IND correspondence

4

- Labeling for Investigational Drug Product active or placebo

- 21 CFR 312.6

5

- Caution statement

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Label Example

- Name of Clinical Trial Material
- Clinical Study Number
- Drug Product Batch Number and Expiry Date
- Count per container and Storage Condition
- **Caution: New Drug Limited by Federal (or United States) law to investigational use by a qualified investigator**
- Manufacturer name and address



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IND Module 1 (cont'd)

1

- Environmental Analysis or Claim for exclusion

2

- Plan for assessing Pediatric Safety and Effectiveness

3

- Introductory Statement/General Investigational Plan

4

- Proposed clinical development plan 21 CFR 312.23(a)(3)

5

- Drug Master File Letters of Authorization

- References

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IND Module 2-Summaries

1

- Table of Contents

2

- Introduction

- Overview

3

- Drug Substance Information

- Drug Product Information

4

- Nonclinical Studies

- Clinical Investigations

5

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Module 2 (cont'd)

1

2

3

4

5

- **Quality Overall Summary**
 - **Drug Substance**
 - **General information**
 - **Manufacture**
 - **Characterization**
 - **Control of Drug Substance**
 - **Reference Standards or Material**
 - **Container Closure System**
 - **Stability**

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Module 2 (cont'd)

1

2

3

4

5

- **Quality Overall Summary**
 - **Drug Product**
 - **Description and Composition**
 - **Pharmaceutical Development**
 - **Manufacture**
 - **Control of Excipients**
 - **Control of Drug Substance**
 - **Reference Standards or Material**
 - **Container Closure System**
 - **Stability**

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Module 2 (cont'd)

1

- Appendices

2

- Facilities and Equipment (Biotech)
- Adventitious Agents Safety Evaluation

3

- Novel Excipients
- Regional Information

4

- **Batch records from Critical batches**

5

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Module 2 (cont'd)

1

- Nonclinical Overview

2

- **Overview of the Nonclinical Testing Strategy**

3

- Pharmacology
- Pharmacokinetics

4

- **Toxicology**
- Integrated Overview and Conclusions

5

- **List of Literature Citations**

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Module 2 (cont'd)

1

2

3

4

5

- Clinical Overview
 - **Product Development Rationale**
 - Overview of Biopharmaceutics
 - Overview of Clinical Pharmacology
 - Overview of Efficacy
 - Overview of Safety
 - **Benefits and Risks Conclusions**
 - **References**

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Module 2 (cont'd)

1

2

3

4

5

- Nonclinical Written and Tabulated Summaries
 - **Introduction**
 - Pharmacology Written Summary
 - Pharmacology Tabulated Summary
 - Pharmacokinetics Written Summary
 - Pharmacokinetics Tabulated Summary
 - **Toxicology Written Summary**
 - **Toxicology Tabulated Summary**

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Module 2 (cont'd)

1

2

3

4

5

- Clinical Summary
 - Summary of Biopharmaceutic Studies
 - Summary of Clinical Pharmacology Studies
 - Summary of Clinical Efficacy
 - **Summary of Clinical Safety**
 - **Literature References**
 - **Synopses of Individual Studies**

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Module 3-Quality

1

2

3

4

5

- Often in an early or Phase 1 IND this is the same information as is would be provided in section 2.3.
 - Both are not needed, either provide the Quality Overall Summary in Module 2 or both Section 3.2.S for drug substance and 3.2.P for drug product.

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Module 3 (cont'd)

1

2

3

4

5

- Table of Contents
- Body of data
 - Drug Substance
 - Drug Product
- References

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Module 4-Nonclinical Study Reports

1

2

3

4

5

- Table of Contents
- Study Reports
- Literature Reference

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Module 5-Clinical Study Reports

1

- **Table of Contents**

2

- Tabular Listing of All Clinical Studies

3

- Clinical Study Reports

4

- Literature References

5

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Submission of IND to Agency

- Submit an original and two copies
 - Or submitted electronically
- The Agency has a **30-day** review period
 - They may ask questions during this period
 - They will typically require **timely** responses
- The IND goes into effect 30-days after the FDA receives it **unless**;
 - The FDA notifies the Sponsor that the investigations described in the IND are subject to clinical hold



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Audience Trivia Question

Clinical trial material should be shipped when...

- As soon as it is ready
- The clinical site is ready
- The IND is active
- The Sponsor is ready

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Active IND

- When the IND SN0000 is active
 - Clinical trial material (DP) may be shipped to sites.
 - Human subjects may be dosed with Clinical trial material
- Subsequent submissions to IND SN0000 should be numbered chronologically in sequence
 - Protocol amendments
 - Information amendments
 - **Safety reporting**

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Active IND (cont'd)

- Data Safety Update Report (DSUR or Annual Report)
 - DSUR within 60 days of the anniversary date the IND went into effect
 - Guidance for Industry: E2F Development Safety Update Report August 2011

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Active IND (cont'd)

- Withdrawal of an IND
 - Sponsor may withdraw at anytime, notifying the FDA and all clinical investigations shall be ended, all investigators notified and all stocks of drug returned or disposed of.
 - If for reasons of safety, Sponsor shall promptly notify the FDA, all participating investigators and all IRBs together with the reasons for withdrawal

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Lessons Learned

- Pre-IND Meetings are very important, use every opportunity to meet or communicate with the Agency.
- Impurities related to the drug substance, and drug product are critical.
 - Residual solvents and heavy metals
 - GLP levels compared to GMP levels
- Container closure; particularly for parenteral products

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Lessons Learned (cont'd)

- Pay close attention to the regulatory acceptance of any colors or flavors
 - Iron
 - Tetratazine
 - Non FEMA flavors
- Changes in your product from nonclinical to the first clinical material should be justified and supported for safety
- In vitro methods can be helpful in showing batch similarity



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Conclusions

- An IND is required to ship clinical supplies
- The FDA's wants to understand what the safety issues are for your investigational product and how you are mitigating them
- The Sponsor has the responsibility for providing the necessary information in a clear and usable format
- Engage the agency in a dialog where possible

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Documents and References

- 21 CFR 312 Investigational New Drug Application
 - 21 CFR 312.22 General principles of the IND submission
 - 21 CFR 312.23 IND content and format
- Content and Format of Investigational New Drug Applications (**INDs**) for **Phase 1** Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products. November 1995
- ICH M2, M3 and M4 and M4S are supportive
- <http://www.fda.gov/regulatoryinformation/guidances/>

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