RUTGERS
THE STATE UNIVERSITY
OF NEW JERSEY

BPHE6800P
Regulatory Writing for Submissions and Publications

Lesson: Writing an Investigators Brochure

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Regulatory Basis for the IB – Medical Devices

No IB requirement, however…

- 21 CFR 812.45 requires that the sponsor supply all investigators with copies of the investigational plan and the report of prior investigations of the device

Regulatory Basis for the IB – Drug Products

21 CFR 312.55(a) : Before beginning an investigation, sponsors must give each investigator an IB containing information required by 21 CFR 312.23(a)(5)

- 21CFR312.23(a)(5) has 5 parts
  - (i)-(v) lay out IB requirements

Why do we need an IB?

Contents of an IB

21 CFR 312.23(a)(5)

(i) A brief **description of the drug substance** and the formulation, including the structural formula, if known.

(ii) A summary of the **pharmacological and toxicological effects** of the drug in animals and, to the extent known, in humans.

(iii) A summary of the **pharmacokinetics and biological disposition** of the drug in animals and, if known, in humans.

Contents of an IB

21 CFR 312.23(a)(5)

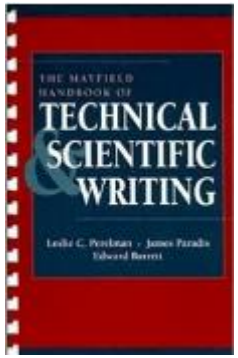
(iv) A summary of information relating to safety and effectiveness in humans obtained from **prior clinical studies**. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of **possible risks and side effects to be anticipated** on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

Investigator's Brochure
It's all about communication!

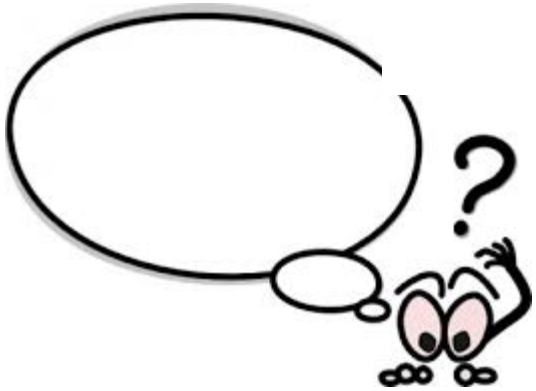
1) *Know your story and your data.*

2) *Know your audience.*
   a) *Investigator*
   b) *Clinical Research Coordinator*
   c) *FDA/IRB/IEC*



3) *Write so you won't be misunderstood.*

Writing an IB



- ✓What should we include in the IB?
- ✓Is there a specific format we should use?

FDA Guidance

- Primary guidance as to what to include in the IB can be found in FDA's *Guidance for Industry ICH E6 Good Clinical Practice: Consolidated Guidance*

- The following material was taken from *Section 7 Investigator's Brochure* of this guidance document

Purpose of the Investigator's Brochure (IB)

- Compilation of clinical and nonclinical data about the investigational product that are relevant to the study of the product in human subjects
- Provides the investigator information to help him/her understand of the rationale for, and their compliance with, key features of the protocol
- Enables investigator to understand and make his/her own assessment of proposed research

The Contents of an IB…

- Simple and Concise
- Objective and Balanced
- Non-promotional and easily understood

Inform the investigator:

- IB should provide an unbiased risk-benefit assessment of the proposed clinical protocol
- A medically qualified person should participate in the editing of the document

Review and Revise

- Review at least annually

- Revise

  …as necessary in compliance with a sponsor's written procedures

  …at each stage of development

  …with the generation of new information

How should an IB be organized?

✓What would you want know if you were an investigator?

Title Page of an IB

- Sponsor's name
- Identity of each Investigational Product
  (research number, chemical or approved generic name, trade name)
- Release date of the IB
- Edition number of the IB
- Date of edition

Confidentiality Statement and Signature Page

- A statement instructing the Investigator and other recipients of the IB to treat it as a confidential document for the sole information and use of the investigator's team and IRB/IEC.

- A Signature Page for acceptance of both the responsibility for confidentiality and for the IB.

Table of Contents (example)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical and Pharmaceutical Properties and Formulations
5. Non-clinical Studies
5.1 Non-clinical Pharmacology
5.2 Pharmacokinetics and Metabolism in Animals
5.3 Toxicology

Table of Contents (2)

6. Effects in Humans
6.1 Pharmacokinetics and Product Metabolism in Humans
6.2 Safety and Efficacy
6.3 Marketing Experience
7. Summary of Data and Guidance for the Investigator

References and/or Appendices (if any)

Summary of the Product

- Brief summary (not exceeding 2 pages)
- Physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, clinical information

Introduction

- Chemical name of the IP
- All active ingredients
- Pharmacological class and expected position
- Rationale for performing the current research
- Anticipated prophylactic, therapeutic or diagnostic indication
- General approach to the current study

Properties and Formulations

- Description of IP (chemical, structural formula)
- Physical, chemical, pharmaceutical properties
- Description of formulation (including excipients)
- Instruction of Storage and handling
- Structural similarities to other known compounds

Non-Clinical Studies -Summary

- Introduction
- Non-clinical pharmacology

  Pharmacokinetics and metabolism in animals
- Toxicology

  Methodology, Results and Discussion of the relevance of these findings to the drug under study, and its possible unfavorable or unintended effects in humans

Non-Clinical Studies- Methods

- Species tested
- Number & sex of animals
- Unit dose
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results

Non-Clinical Studies - Results

- Nature and frequency of pharmacological or toxic effects
- Severity or intensity of pharmacological or toxic effects
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- Dose response

Non-Clinical Pharmacology

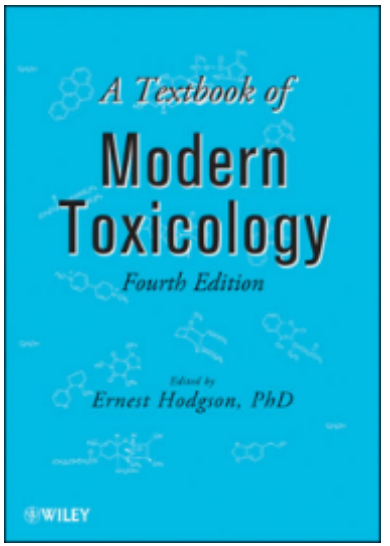
- Pharmacological aspects of the IP
- Significant metabolite
- Assessment of potential therapeutic activity
  - Efficacy models, receptor binding, specificity
- Assessment of safety
  - Special studies to assess pharmacological actions other than the intended therapeutic effects

Pharmacokinetics and Metabolism

- Pharmacokinetics, biological transformation, and disposition in all species
- Absorption, bioavailability (IP, metabolites)
- Relationship to the pharmacological and toxicological findings

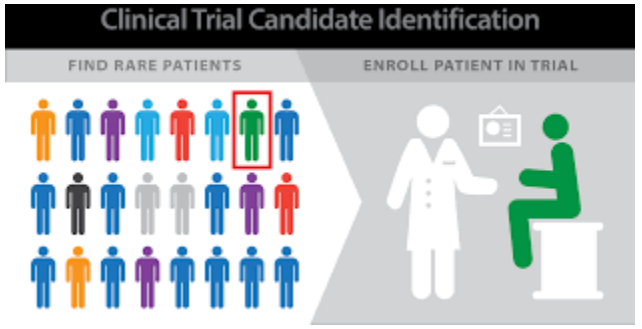
Toxicology

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (irritancy, sensitization)
- Reproductive toxicity
- Genotoxicity



Effects in Humans

- Introduction
- Pharmacokinetics and metabolism
  in humans)
- Safety and efficacy
- Marketing experience (if appropriate)



Introduction to Clinical Effects

- Pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, other pharmacological activities, and marketing experience

Clinical Pharmacokinetics and Metabolism

- Pharmacokinetics
  - Metabolism, absorption, plasma protein binding, distribution, elimination
- Bioavailability
- Population subgroups
  - Gender, age, impaired organ function
- Interaction
  - Product-product interactions; effects of food
- Other pharmacokinetic data

Safety and Efficacy

- Safety
- Pharmacodynamics
- Efficacy
- Dose response
- Tabular summaries of ADRs

Marketing Experience

- Countries (marketed or approved)
- Information from the marketed use (formulations, dosages, routes of administration, adverse product reactions)
- Countries that did not receive approval/registration, or where registration has been withdrawn

Summary of Data and Guidance for the Investigator

- Overall discussion of the nonclinical and clinical data
- Information from various other sources on pertinent aspects of the IP
- Assessment of the implications of the information for future clinical trials

Conclusions

The overall aim of IB is to provide the investigator with a clear understanding of the…

- possible risks
- adverse reactions
- specific tests
- observations and
- precautions he should observe as the investigator undertakes his/her responsibility to manage a clinical trial.

Thank you!!