

United States Department of

Health & Human Services

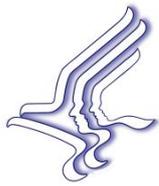
Office of the Assistant Secretary for Preparedness and Response (ASPR)

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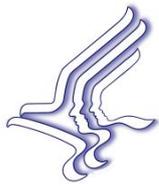
# What FDA Expects in your Submissions: *Biologics & Drugs*

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# FDA Mission

- The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation
- The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health



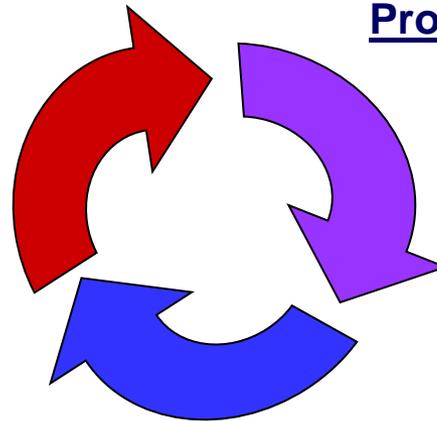
# FDA's Core Business Functions

## Pre-Market Review

*Assessment of safety and effectiveness of new medical technology*

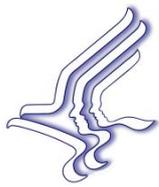
## Product Safety & Compliance

*Inspection of manufacturing facilities and products to assure safety, quality & compliance with FDA regulations*



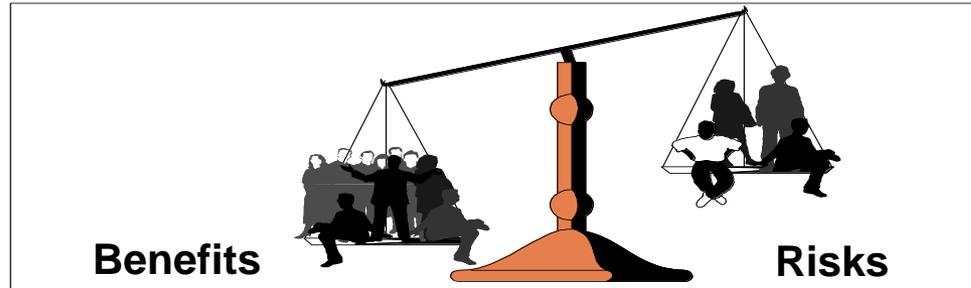
## Consumer & Patient Safety

*Post-marketing surveillance to ensure the safety of consumers & patients who use FDA-regulated products*

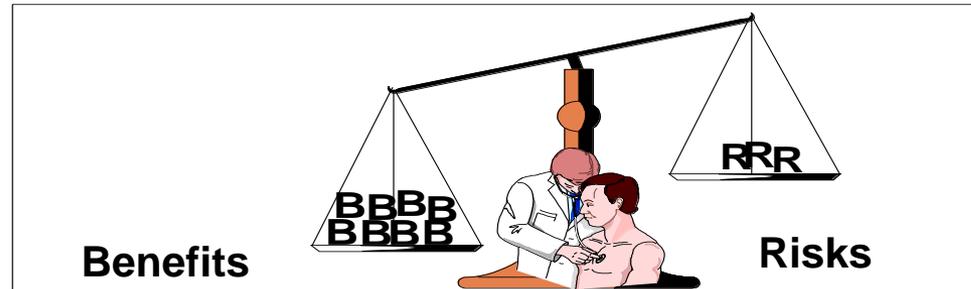


# FDA is One Part of Complex Picture

**FDA**  
Evaluates  
benefits/risks  
for the population

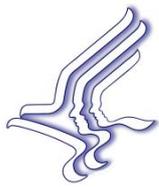


**Healthcare Practitioner**  
Evaluates  
benefits/risks  
for a patient



**Patient**  
Evaluates  
benefits/risks  
in terms of  
personal values





# Drug development

## ➤ **Food, Drug & Cosmetic (FD&C Act §505)**

- No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

## ➤ **Public Health Service (PHS Act §351)**

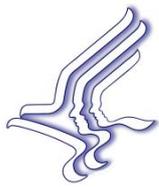
- No person shall introduce or deliver for introduction into interstate commerce any biological product unless a biologics license is in effect for the biological product

## ➤ **Investigational New Drug (IND) Application (21 CFR 312)**

- Required to distribute an investigational drug in interstate commerce

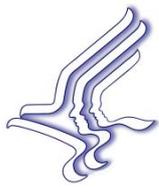
## ➤ **New Drug Application (NDA)/Biologics License Application (BLA) (21 CFR 314 & 600)**

- Adequate and well-controlled studies provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. (21 CFR 314.126)



# Drug development (cont'd)

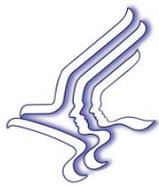
- **Approval of new drugs/biological products when human ethical studies are not feasible or ethical (21 CFR 314 Subpart I & 21 CFR 601 Subpart )**
  - Substantial evidence of the effectiveness of certain new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances
  - Approval based on animal data when adequate and well-controlled efficacy studies in humans cannot be ethically conducted
- **Chemistry, Manufacture, and Controls [21 CFR 312.23(a)(7)]**
  - To assure the proper identification, quality, purity, and strength of the investigational drug
  - Good Manufacturing Practice (21 CFR 210 & 211, 600)
- **Preclinical [21 CFR 312.23(a)(8)]**
  - To assure that it is reasonably safe to conduct the proposed clinical investigations
  - Good Laboratory Practice (21 CFR 58)
- **Clinical [FD&C Act § 505]**
  - To establish efficacy and safety of a drug for use in humans, in a dose range and schedule that provides an acceptable risk:benefit relationship
  - Good Clinical Practice (21 CFR 312, 50, 56)



# Guidance for Industry – PI/CMC

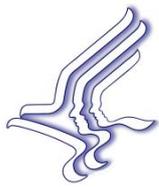


- **Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (1995)**
- **CGMP for Phase 1 Investigational Drugs (2008)**
- **Assay Development for Immunogenicity Testing of Therapeutic Proteins (2009)**
- **ICH Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (1999)**
- **Container Closure Systems for Packaging Human Drugs and Biologics (1999)**
- **Analysis of Expression Construct in Cells Used for Production of rDNA Derived Protein Products (ICH Q5B/1995)**
- **Stability Testing of Biotechnological/Biological Products (ICH Q5C/1995)**
- **Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D/1997)**
- **Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Q6B/1997)**
- **Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (ICH Q5E/2004)**
- **Etc.**



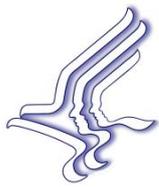
# Guidance on Guidelines

- **FDA regulations interpret US law**
- **FDA Guidance interprets FDA regulations**
- **FDA guidelines take precedence over ICH guidelines**
- **No guideline can cover all possibilities**
  - Use common sense



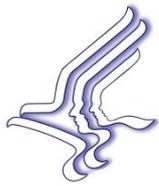
# What must an IND include?

1. **Form FDA 1571**
2. **Table of Contents**
3. **Introductory statement**
4. **General Investigational Plan**
5. **Investigator's Brochure**
6. **Protocol(s)**
7. **CMC**
8. **Pharmacology/toxicology**
9. **Previous human experience**
10. **Additional information , if applicable**
11. **References**



# Regulatory flexibility

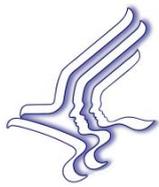
- **Present regulations allow a great deal of flexibility in the amount and depth of various data to be submitted in an IND depending in large part on the phase of investigation and the specific human testing being proposed**
  - For example, the amount of information needed to assure the proper identification, quality, purity, and strength of the investigational drug varies with the phase of the investigation
- **“...FDA's review of phase 1 submissions will focus on assessing the safety of phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.”**
  - 21 CFR 312.22(a)



# Regulatory review goals



- **Seamless transition from IND filing to initiation of clinical study**
- **No unexpected safety issues**
- **Written for the reviewer**



# Grounds for Clinical Hold

21 CFR 312.42(b)

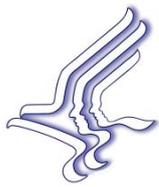


## ➤ Phase I

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
- Clinical investigators are not qualified by reason of their scientific training and experience
- Investigator brochure is misleading, erroneous, or materially incomplete
- The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies

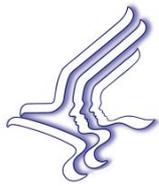
## ➤ Phases II and III

- All of the above plus the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives



# Phase 1 IND

- **Reasons for concern may include, for example**
  - A product made with unknown or impure components
  - A product possessing chemical structures of known or highly likely toxicity
  - A product that cannot remain chemically stable throughout the testing program proposed
  - A product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard
  - A poorly characterized master or working cell bank

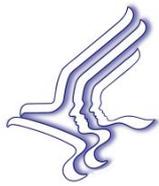


# Introductory Elements

21 CFR 312.23(a)(1-3)



- **Introductory Statement (description of product, formulation, route, broad study objectives, relevant previous use, foreign experience)**
- **General Investigational Plan (rationale, indication, general approach, anticipated studies including number of subjects and possible risks)**

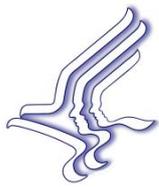


# Investigator's Brochure

21 CFR 312.23(a)(5)



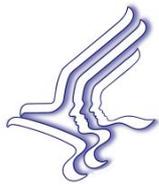
- **Brief product description**
- **Pharmacology/toxicology summaries**
- **Previous human experience**
- **Description of anticipated risk and any special monitoring needs**
- **Updates as appropriate**



# Protocols

## 21 CFR 312.23(a)(6)(a-g)

- Objectives and purpose of the study
- Name and address for each investigator, research facilities, and the IRB
- Qualifications of each investigator
- Criteria for patient selection and exclusion of patients
- Estimate of the number of patients to be studied
- Description of the design of the study
- Description of methods to be used to minimize bias
- Method for determining the dose(s) to be administered, maximum dosage, and duration of individual patient exposure
- Description of the observations and measurements to be made
- Description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk



# Chemistry, Manufacturing, & Controls

21 CFR 312.23(a)(7)

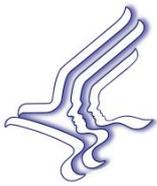


## ➤ Drug substance and drug product

- List of all components
- Quantitative composition
- Name and address of the manufacturer
- Description of the manufacturing and packaging procedure
- Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product
- Stability

## ➤ Placebo

- Composition, manufacture, and control

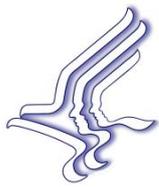


# Pharmacology and Toxicology

21 CFR 312.23(a)(8)



- **Type, duration, and scope of animal and other tests**
- **Describe the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the ADME**
- **An integrated summary of the toxicological effects of the drug in animals and in vitro**
- **A full tabulation of data suitable for detailed review for each study to support safety**
- **A statement that the study was conducted in compliance with GLP**
  - **If the study was not conducted in compliance with GLP, then state so**

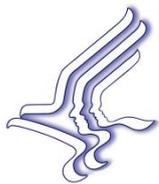


# Investigator's Brochure

## Real life examples



- **Include summaries of all preclinical studies to include your cross reactivity studies, in vitro binding, etc.**
- **Provide data and information on anti-product antibody formation**
  - If studies did not measure/evaluate immunogenicity, then state
- **Clarify that data and information are from products from various companies, are in various stages of development, and from studies which are technologically different (i.e., human vs mouse studies)**
- **Include a section on translation of toxicology findings into human equivalent dose and then justify the dose to be used, including justification of the applied safety factor**
- **Keep in mind the reviewer: “is to be determined” versus “has not been determined”**

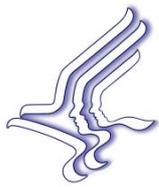


# Chemistry, Manufacturing, & Controls

## Real life examples

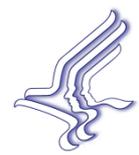


- Provide the amino acid sequence
- Include results and a summary describing methods used for determining general properties, such as peptide mapping, IEF, MS, etc., for characterization
- In order to enable FDA review it is best to provide the information in the sections on cell growth and harvesting, downstream purification, and control of materials in a flow diagram in addition to textual format
- Provide media components for seed train and bioreactor
- Provide justification for each chromatography step
- Raw materials are either compendial (USP, NF, EP) or non-compendial
- Provide information on the cell bank system, to include development of the expression construct, transformation, selection of the clone, production, characterization, and qualification.
- Were the results of DS Lot XXX within specifications?
- Provide a table of manufactured batches that contains manufacturing changes, testing conducted, and results. Were any changes made between the lot used for toxicology studies and the lot(s) that will be used for this clinical study?
- Specifications require justification



# Conclusion

- Remember the FDA's mission
- Provide FDA with the data and information that is required to meet the goals of the submission
- Be mindful of the laws, regulations, and Guidance
- Keep the regulatory reviewer in mind



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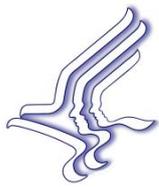
# Thank you!

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Senior Regulatory Advisor

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**Fax: 202-205-8441**



# Interfacing with BARDA



- [www.phe.gov](http://www.phe.gov)
  - Program description, information, news, announcements
- [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)
  - Portal to BARDA
  - Register, request a meeting
  - Tech Watch
- [www.fedbizopps.gov](http://www.fedbizopps.gov)
  - Official announcements and detailed information about all government contract solicitations

