# Early Drug Development: A Regulatory Perspective

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# Outline

- Background
- Drug development process
- Investigational New Drug Applications (INDs)
- Interaction opportunities
- Expedited development/review programs
- Conclusions

# CDER Mission

CDER's mission is to protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients

# CDER Mission

- Promote public health by ensuring the availability of safe and effective drugs
  - Oversight of new drug development and review of drug marketing applications
    - Development-phase consultations with drug innovators
    - Development of regulations and guidance to industry
    - Oversight of the conduct of clinical trials
- Protect public health by promoting the safe use of marketed drugs
- Protect public health by ensuring the quality and integrity of marketed drug products

# Office of Pharmaceutical Quality

**Pharmaceutical quality is our *shared* goal of assuring consistently safe and effective drugs are available to patients and consumers.**

**Pharmaceutical quality is what gives them confidence in their *next* dose.**

**OPQ Mission**

OPQ assures that quality medicines are available to the American public

**ONDP Mission**

Leveraging knowledge and expertise to collaboratively link product performance to the patient and communicating risk-based recommendations effectively to all internal and external stakeholders

**ONDP Vision**

Linking pharmaceutical quality to the patient in a meaningful way

**Motto**

One Quality Voice

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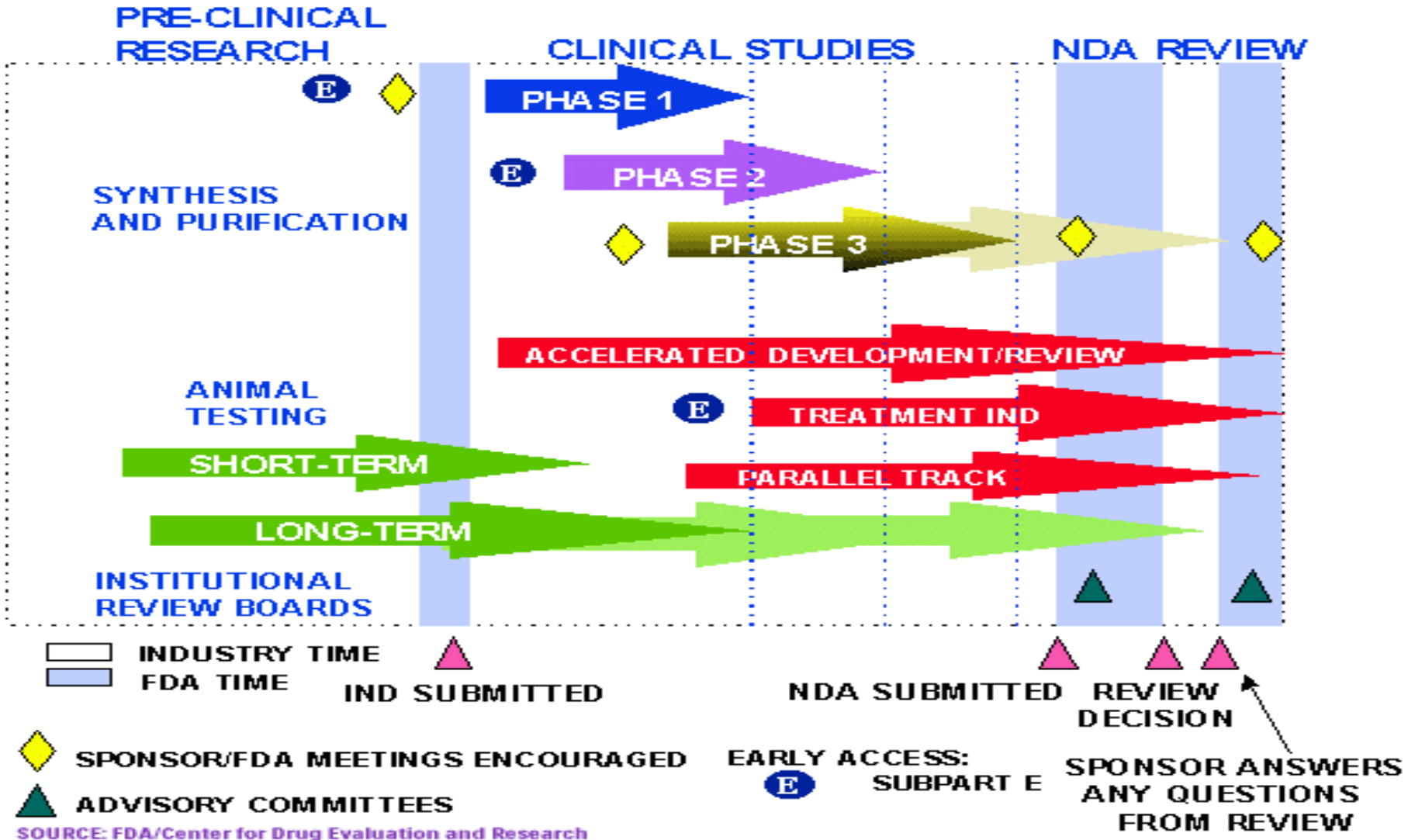
# Drug Discovery Phases



# Drug Discovery Phases

# Investigational New Drug Application (IND)

- "A sponsor shall submit an IND to FDA if the sponsor intends to conduct clinical investigation with an investigational new drug that is subject to section 312.2(a)."
  - There are certain exemptions
- Section 312.2(2) states: "….this part applies to all clinical investigations of products that are subject to section 505 of the FD&&C act or to the licensing provisions of the Public Health Services Act "

# General Principles of IND Submission

- CFR 312.22 (a):
- “FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety”.
  - Phase 1: safety of the phase 1 investigations
  - Phase 2 and 3: Also includes assessment of the scientific quality of the investigation and likelihood that the data will meet standards for supporting marketing approval

# IND Content and Format

- Information needed in the IND (CFR 312.23):
  - Cover Sheet
  - Table of Content
  - Introductory statement and general investigational plan
  - Investigators brochure
  - Protocols
  - Chemistry , Manufacturing and Controls information (CMC)
  - Pharmacology and toxicology information
  - Previous human experience with the investigational drug
  - Additional information (e.g., abuse potential, pediatric study, radioactive drug, etc.)

# CMC Content

- 21CFR 312.23(a)(7)(i)
- "Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of investigation, proposed duration of investigation, dosage form and amount of information otherwise available…"

# Drug Substance

- Description
- Physicochemical and biological characteristics
- Name and address of manufacturer
- General method of preparation
- Analytical procedures and limits to assure identity, strength, quality and purity
- Stability of DS to support its use during toxicological studies and planned clinical studies
- Impurity profile of toxicological and clinical batches

# Drug Product

- Components and composition
- Name and address of the manufacturer
- Description of manufacturing and packaging processes
- Analytical procedures and limits to assure identity, strength, quality and purity
- Stability information to support the product stability during clinical studies duration

# Additional Information

- Description of the composition, manufacture and control of placebo when used
- Information about any comparator being used
- Labeling information
- Claim for categorical exclusion under section 25.31 (e)

# Outcome of Initial Review

- FDA has 30 calendar days to review the initial IND
- Safety is the main consideration at this stage
- Interdisciplinary team reviews the initial IND for their respective sections
- Any additional information needed to make a decision may be requested
- Based on the review
  - IND may be safe to proceed
  - Or may be put on hold, if there are pending safety related concerns

# Major Reasons for Clinical Hold

- Subjects are or would be exposed to an unreasonable and significant risk or illness or injury
- Clinical investigators named not qualified by reason of scientific training and experience
- Investigators brochure misleading, erroneous, or materially incomplete
- IND does not contain sufficient information required under section 312.23

# Examples of CMC Reasons or Clinical Hold

- CMC information to ensure safety of the subjects is not provided or the information provided presents safety concerns
  - Product made with unknown and impure components
  - Synthesis/manufacturing information provided is insufficient to evaluate safety attributes of the material to be used
  - Presence of impurities with known or likely toxicity which have not been adequately evaluated in preclinical safety studies
  - Insufficiently defined impurity profile of clinical material
  - Lack of sterility assurance or endotoxin control for sterile products
  - Product not stable through the clinical study duration or information to make this assessment not provided
  - Poorly characterized master or working cell banks

# Additional Information During Clinical Development

- Protocol amendments (section 312.30)
  - Change in protocol, new protocol, new investigator
- Information amendments (section 312.31)
  - New toxicology, CMC or other technical information
    - Change in dosage form, major formulation change, change in API source, new impurities etc.
- IND safety reports (section 312.32)
- Annual reports (section 312.33)
  - Within 60-days of anniversary date
  - E.g., Summary of studies in progress/completed
  - Summary of significant manufacturing changes, stability data

# Treatment INDs

- Purpose:
  - To facilitate the availability of the promising new drugs to desperately ill patients early in the drug development before marketing approval
- Treatment IND can be submitted for
  - The drug intended to treat serious or immediately life threatening disease
  - There is no comparable or satisfactory alternative drug or therapy available to treat that stage of disease in the intended patient population
  - The drug is under investigation under an IND or all clinical trials have been finished
  - The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence

# Treatment IND/Protocol

- Treatment protocol can be submitted by the IND sponsor
- Treatment IND can be submitted by a licensed practitioner if the IND sponsor does not want to submit a treatment protocol but will give drug under investigation to the practitioner
  - CMC information mentioned before under section 312.23 will be needed
  - However, If IND sponsor agrees to provide investigational drug to the licensed practitioner in support of his/her treatment IND is deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND
- Treatment can start 30-days after receipt of the IND/protocol or earlier notification by FDA

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# Meetings with FDA

*Meetings may be face to face, teleconference, or written response*

*FDA generates official non-binding meeting minutes*

**Type A** Stalled development or dispute

**Type B** Pre-IND, pre-NDA, pre-BLA, Breakthrough/RMAT

**Type B(EOP)** End of phase meeting

**Type C** All other meetings

| Meeting Type | Meeting Scheduling or Written Response Time |
|---|---|
| A | 30 calendar days from receipt of meeting request |
| B | 60 calendar days from receipt of meeting request |
| B(EOP) | 70 calendar days from receipt of meeting request |
| C | 75 calendar days from receipt of meeting request |

# FDASIA (2012)

- Section 901– Fast Track Drug Products
  - Facilitate development and expedite the review of drugs for the treatment of a serious or life-threatening disease or condition that demonstrates the potential to address unmet medical need
- Section 902 –Breakthrough Therapy Drugs
  - Expedite the development and review of a drug for serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
    - Provide timely advice and interactive communication with the sponsor regarding the development of the drug
    - Provide a collaborative cross disciplinary review utilizing senior managers and experienced review staff, as appropriate

# Comparison of FDA's Expedited Programs

| | Breakthrough | Fast Track | Accelerated Approval | Priority Review |
|---|---|---|---|---|
| Qualifying criteria | • Treat serious condition.<br>• Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies | • Treat serious condition.<br>• Non-clinical or clinical data demonstrate the potential to address unmet medical need<br>• OR<br>• Drug designated as Qualified infectious disease product | • Treats serious condition.<br>• Provides meaningful advantage over available therapies<br>• Demonstrates an effect on surrogate end point that is likely to predict clinical benefit | • Application for drug that treats serious condition.<br>• If approved, will provide significant improvement in safety or effectiveness<br>• Drug qualified infectious disease product. |
| When to submit request | With IND or after<br>Ideally no later than EOP2 meeting | With IND or after<br>Ideally no later than the pre-NDA or pre-BLA meeting | Discuss with review division | With original BLA, NDA or efficacy supplement |
| Features | • Intensive guidance on drug development.<br>• Organizational commitment<br>• Rolling review<br>• Other actions to expedite review (e.g. priority review) | • Actions to expedite development and review<br>• Rolling review | • Approval based on effect on surrogate endpoint | Shorter review clock |

# Quality Expectations

- Are safe, efficacious, performs consistently over shelf-life and available
- Quality expectations not based on the approval process (accelerated vs standard)
- Willing to accept inherent potential risk as long as benefit outweighs the inherent risk
- US Prescribing Information has no section to include quality related risk
- Shared responsibility to meet these expectations

# Regulators Challenges for Expedited Development and Assessment

- Accelerated manufacturing development likely to have less information than typically available
  - Challenging to establish/evaluate control strategy
  - Setting product specifications
  - Setting commercially viable expiration period
- Makes it challenging to do a risk-benefit assessment regarding risk of less CMC information vs. patient benefit
- Require innovative risk-mitigation strategies to ensure product quality and reduce quality related product risk to an acceptable level

# Regulators Challenges for Expedited Development and Assessment

- Lack of sufficient data from
  - Commercial manufacturing site
  - Stability data to support long shelf-life
  - Data to bridge clinical and commercial materials
  - Commercial supply/availability considerations
- Procedural/Assessment challenges
  - Increased communication during pre-submission and assessment period
  - Usually have priority status with shortened time line
  - Needs to manage with existing high workload
  - Assessment timing constraints for inspections

# Summary

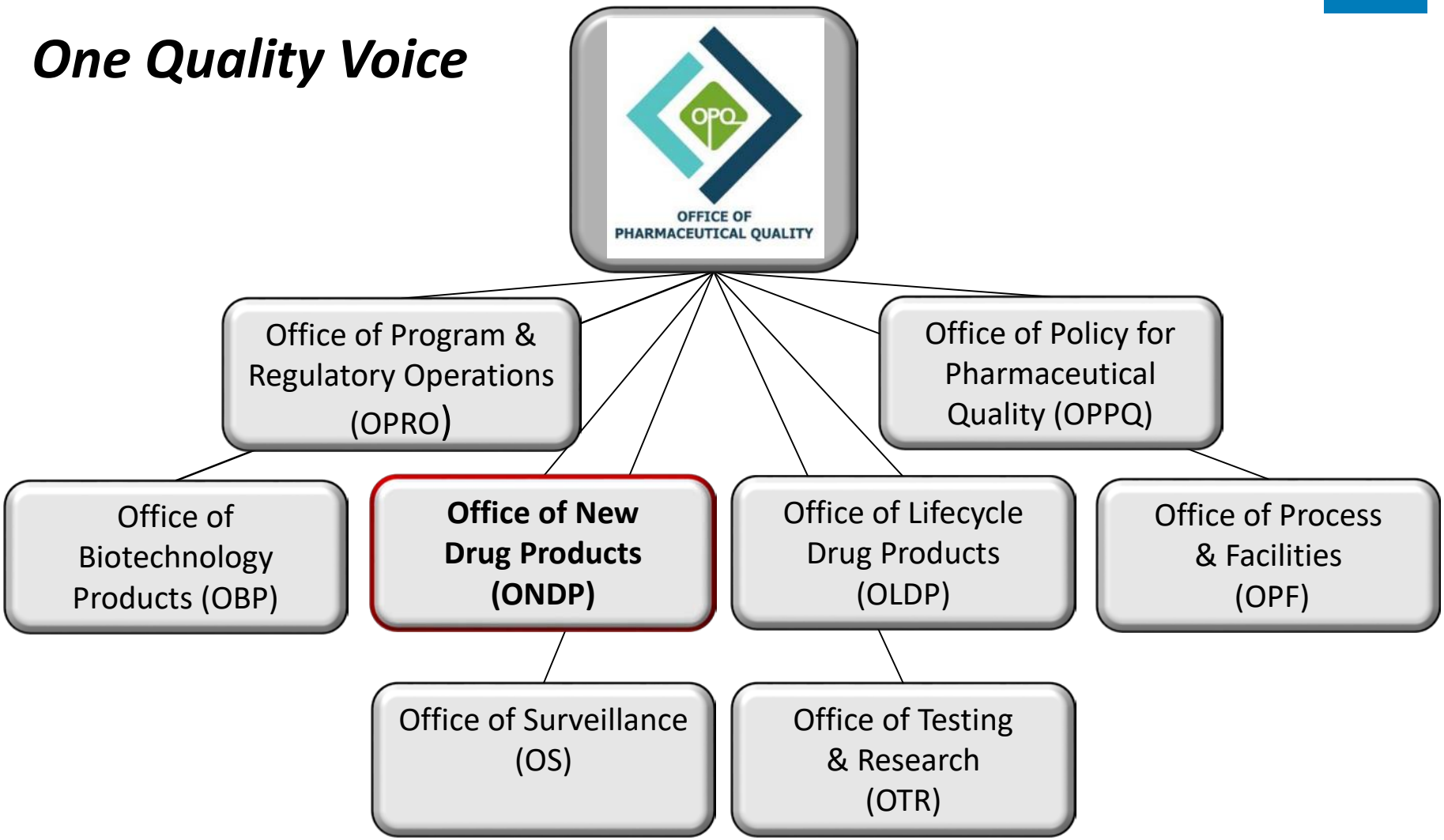
- Most clinical investigations in humans require submission of an IND
- Sufficient CMC information should be provided in an IND to assure identity, quality, purity and strength of the study drug
- The level of CMC information increases as development progresses
- Safety concern is the primary reason for placing an IND on clinical hold based on CMC section in the initial phase 1 study
- Various resources (guidances, meetings) for interaction with FDA are available to sponsors during clinical development
- Expedited pathways are available for developing/getting approval for serious and life-threatening diseases

*Thank you!*

*Questions?*

# Office of Pharmaceutical Quality

***One Quality Voice***

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