The CDER Review Process

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Review Disciplines

- Chemistry
- Epidemiology
- Clinical (Medical or Dental)
- Microbiology
- Pharmaceutics/Clinical Pharmacology
- Pharmacology/Toxicology
- Statistics

Review Teams

- Review Divisions organized by area of medical expertise
- Multidisciplinary teams coordinated by project manager
- Discipline-specific teams
- Primary and secondary review

Role of the Reviewer

- Provide scientific expertise and opinion
- Participate in regulatory decisions

Goal of Drug Development

- Industry Goal
  - To bring new drugs to the market
- FDA Goal
  - To protect the public health by assuring that marketed drugs are safe and effective
  - To advance the public health by helping to speed innovations that make medicines more effective, safer, and more affordable

Orphan Drugs

- For Rare Diseases and Conditions
  - Less than 200,000 persons
  - No expectation of development cost recovery
- Incentives
  - 7 years market exclusivity (vs. 5 years)
  - Tax credit for clinical research
- Designation
  - Administered by Office of Orphan Products Development
  - Does not alter the standard review requirements

Data Needed to Support Approval

- Reasonable assurance of safety
- Substantial evidence of effectiveness
- Adequate directions for use
- Specifications to assure good product quality

The Reviewer's Role

- To ensure that the data submitted is adequate and scientifically sound
- Provide feedback for sponsor
- Provide advice for sponsor about requirements for the next stage of development and approval

“Proactive” Interactions

- Shared goal with industry – to develop safe and effective products as quickly and efficiently as possible
- Interactions to resolve concerns instead of imposing restrictions
- Provide clear and consistent advice (Guidance Web Page)

Written Reviews

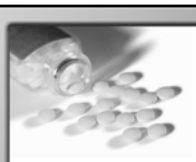
- Document decisions and rationale
- Allow future reviewers to understand the regulatory
- history of the product

Orderly and Logical Progression of Studies

- Laboratory studies first, then animal, then human
- Small studies before large
- Short studies before long
- Low dose before high dose
- Each step builds on preceding experience

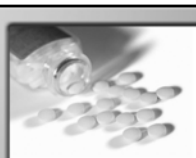
Phases of Clinical Development

- Phase I
  - Pharmacology/pharmacokinetics
  - Basic safety and early concept of efficacy
- Phase II
  - Efficacy/proof of concept
- Phase III
  - Adequate and well-controlled trials to support marketing approval
- Phase IV
  - Post-marketing commitments



CDER Applications

- Investigational New Drug Application (IND)
  - Allows initiation of clinical studies in humans
  - Allows inter-state shipping to clinical trial sites
  - Provides a filing system for serial submissions
- New Drug Application (NDA)
  - Submission of information needed for marketing approval
- Abbreviated New Drug Application (ANDA)
  - Application for approval of a generic drug



IND Exemptions

- An IND may not be needed to study approved products if:
  - No intention to support labeling
  - No intention to change advertising
  - No increased risk
    - » Dose
    - » Route
    - » Patient population

Pre-IND

- Product concept evaluation
  - Does the product concept make sense?
  - Risk vs. benefit (Does this product represent an alternative to or an improvement over currently available therapies?)
- Product development plan
  - Progression from one phase to the next
  - Safety concerns to be addressed
  - Study design issues
  - Endpoints

IND Submission

- Phase I, II, or III studies
- Emphasis on safety concerns
- Determine whether the study is reasonably safe to proceed
- 30-day clock for initial submission
- No review clock for subsequent submissions

Clinical Hold

- An order to delay or suspend an investigation.
  - No new subjects may be recruited and placed on drug.
  - Patients already in the study should be taken off drug (unless discontinuation not in the interest of patient safety).
- Unreasonable risk to human subjects

General Interactions

- Guidance meetings can be held at request of sponsor or FDA to discuss any issue
- Written feedback can be requested by sponsor for amendments to the IND (not always routinely provided)
- Regulatory and procedural advice can be given over the phone or by email

End-of-Phase II

- Reasonable evidence of safety in Phase I trials
- Lowest effective dose determined from dose-ranging studies
- Preliminary efficacy demonstrated
- Sponsor seeks commitments regarding Phase III trials

End-of-Phase II

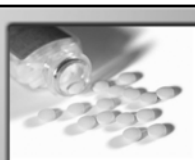
- Study design
  - Appropriate design to show that the drug works
  - Sufficient sample size
  - Study population
  - Comparator products
  - Statistical analysis plan
- Potential claims

Pre-NDA

- Phase III trials almost complete or completed
- Proposals for:
  - Format
  - Content
  - Adequacy of components
    - Clinical: Will trial data support filing of the NDA?
  - Reviewer needs
    - Clinical: Data tabulations and Case Report Forms

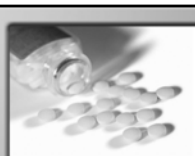
NDA Submission

- 60-day Filing Assessment
  - Is format acceptable?
  - Is necessary information for each review discipline included?
- Site inspections
- Advisory committee meeting if needed
- Labeling review
- Written review
- Approval decision



Post-Approval

- Review adverse event reports
- Annual Reports
- Supplements
- Labeling revisions
- Promotional materials and claims
- Compliance issues
- Product quality issues



ANDA (Generic Drug Application)

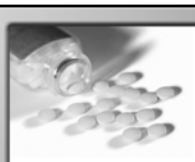
- “Copy” of approved drug
- Safety and efficacy already established for the approved reference drug
- Must contain the same active drug in the same amount and acceptable inactive ingredients
- Must be bioequivalent to the reference drug
- Must have the same labeling as the reference drug

Challenges for Reviewers

- Many ongoing review assignments
- Drugs in all stages of development
- Development isn't always orderly (Phases 1, 2, 3)
- Scant to voluminous prior records
- Multiple goal dates to meet
- No control over date of submission
- Learning regulatory language
- Reviewer turnover

Considerations for Reviews

- Stage of drug's development
- Prior regulatory history
- Prior commitments between the sponsor and the Agency
- Identify what the sponsor is requesting
  - Read between the lines
  - Recall that every study is done for a purpose
  - Request specific pre-meeting questions
- Level of review required depends on knowledge of the product



Regulatory References

- Regulations CFR Title 21
  - 50 Human Subject Protection
  - 54 Financial Disclosure
  - 56 Institutional Review Boards
  - 201 Labeling
  - 312 IND
  - 314 NDA
- Legislation (FD&C Act, PDUFA, FOIA, FACA, PREA, BPCA, and many more)