

The Investigational New Drug (IND) and New Drug Application (NDA) Process

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Public Domain

Relevant Laws

- Federal Food, Drug, and Cosmetic Act
- Public Health Service Act--Part F
Licensing of Biological Products and
Clinical Laboratories

Relevant Regulations

- IND regulations (both drugs and biologics)
21 CFR 312
- NDA (drugs) regulations--21 CFR 314
- Product licensing (biologics)--21 CFR 601
- Protection of human subjects and informed consent regulations--21 CFR 50
- IRB regulations--21 CFR 56

Basis for NDA Approval

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies
- Ability to generate product labeling that
 - Defines an appropriate patient population for treatment with the drug
 - Provides adequate information to enable safe and effective use of the drug

Basis of BLA Approval

- License granted for products that meet standards designed to insure “continued safety, purity, and potency” of the product
- “Potency” interpreted as “efficacy”

42 USC section 262

21 CFR 600.3(s)

The label is the driver

The IND and NDA Process

- Drug Development
 - Preclinical
 - Phases I, II, III
 - Plan with the indication/market in mind
- FDA interactions
 - Communication
 - Meetings
 - Submissions
- All aspects considered simultaneously

Pre-IND Meeting

- Problems with drug substance, drug product, or formulation intended for human use
- Questions regarding the adequacy of preclinical toxicology studies
- PK issues, e.g. related to dosing schedules, known/unidentified metabolites
- Novel dose-escalation scheme is proposed
- Questions regarding clinical monitoring for an anticipated end organ toxicity

Drug Development Timeline



Requirements for a New IND: Chemistry/Manufacturing Data

- Sufficient to assure identification, quality, and strength of the drug
- Impurities, sterility
- Product consistency

Requirements for a New IND: Pharmacology/Toxicology Data

- Acute toxicity data from studies conducted in 2 species
 - Generally, life-threatening toxicity in rodents
 - Study in non-rodents (dog) that confirm dose tolerability
- Histopathology in at least 1 species
- Results sufficient to determine the starting dose for clinical studies

Requirements for a New IND: Pharmacology/Toxicology Data

- Conduct pharmacokinetic and toxicity studies using the *same schedule, duration, formulation, and route* as proposed clinical trial

Requirements for a New IND: Pharmacology/Toxicology Data

- Number and length of studies will vary depending on:
 - Whether you plan a single dose study or a repetitive dose study
 - The schedule of administration (intermittent versus daily x 1 year)
 - Population to be studied: normal volunteers vs. patients with serious and life-threatening disease

Starting Dose for Non-oncology Drugs

- One-tenth the No Observed Adverse Effect Level (NOAEL) in most appropriate species on a mg/m^2 basis
- “Most appropriate” = “most sensitive”
- Increase the safety factor for
 - Steep dose-response curve
 - Severe toxicities or irreversible toxicities
 - Non-monitorable toxicities
 - Toxicities without a prodrome
 - Variable bioavailability; dose, AUC variability
 - Unexplained mortality

Starting Dose for Oncology Drugs

- One-tenth the severely toxic dose to 10% of the rodents (STD_{10}) on a mg/m^2 basis
 - unless $1/10$ STD_{10} causes severe, irreversible toxicity in non-rodents, or
 - the rodent is an inappropriate model, then
- One-sixth the highest non-STD in non-rodents

IND Review

- 30-day review clock
- Clinical hold
 - Safety concerns (known risk, inadequate information, IB misleading, PI not qualified)
 - Design will not allow protocol objectives to be met
- Requires teleconference with sponsor and division director
 - Specific communication about what is required to lift the hold

Phase I Clinical Trials (Non-cancer Drugs)

- Determination of :
 - Safety, toxicity
 - Dose range appropriate for further studies
 - NOT maximal tolerated dose
- Generally conducted in normal volunteers

Phase I Clinical Trials (Anticancer Drugs)

- Determination of :
 - Safety
 - Toxicity
 - Dose Range appropriate for further studies (MTD)
- Generally conducted in cancer patients
- Concerns:
 - Number of patients treated
 - Careful monitoring for treatment toxicities
 - Pharmacology/Pharmacokinetic studies

Phase I Cancer Trials

- Novel dose-escalation schemes
- May use surrogate endpoints as “proof of principle”
 - Not accepted as proof of efficacy

Phase II Clinical Trials (Anticancer Drugs)

- Initial determination of possible efficacy
- Further evaluation of safety
- Further study of appropriate dose range
- Generally conducted in cancer patients with measurable disease
- Concerns:
 - Number of patients treated
 - Efficient determination of potential efficacy
 - Careful monitoring for treatment toxicities

Communications Issues: IND Milestones

- During Phase II:
 - Discuss feasibility of requesting accelerated approval based on a surrogate endpoint (e.g., if initial results suggest that Phase II studies may indicate improved results in a life-threatening disease)
 - If there is agreement that accelerated approval may be a possibility, proposals for post-approval randomized studies may be discussed
 - An advisory committee member usually participates

Communications Issues: IND Milestones

- During Phase II:
 - Address product/formulation issues
 - Scale-up
 - Linking to-be-marketed formulation with clinical trial formulation

End-of-Phase II Meeting

- **Discuss design of proposed randomized trials**
 - Patient eligibility criteria
 - Primary and secondary efficacy endpoints
 - Sample size considerations/accrual concerns
 - Specific safety issues/special populations
- Advisory committee member participates
- Patient advocate participates
- [Determine safety of proceeding to Phase III]
- [Address product/formulation issues]

Some comments about clinical
trial design...

The choice of endpoint will depend on:

- Therapeutic area
 - Oncology versus non-cancer indication
 - Type of cancer
- Patient population
 - Metastatic disease
 - First-line
 - Refractory or no effective therapy
 - Adjuvant
 - Chemoprotection
 - “Chemoprevention”

The choice of endpoint will depend on:

- Traditional approval or accelerated approval
 - Traditional approval: Clinical benefit
 - Accelerated approval: Surrogate endpoint
 - S< disease
 - Better than standard therapy

Clinical benefit vs. Biologic activity

- Full approval requires demonstration of clinical benefit
 - Traditional endpoint, such as survival
 - Surrogate endpoint (RR) plus symptom relief
 - Magnitude of benefit must outweigh the risks
- Accelerated approval: surrogate endpoint
 - “Reasonably likely” to predict benefit
 - Evidence of biologic activity (RR) sufficient
 - Requires subsequent confirmation of benefit

Biologic activity vs. Clinical benefit

- Full approval requires demonstration of clinical benefit
 - Traditional endpoint, such as survival
 - Surrogate endpoint, such as RR, plus symptom relief
 - Magnitude of benefit must outweigh the risks
- Accelerated approval uses a surrogate endpoint
 - Requires subsequent confirmation of benefit
 - If no confirmation, “accelerated withdrawal”

The choice of endpoint will depend on:

- The phase of the clinical trial
 - Related to type of approval
- Type of agent
 - Typical cytotoxic
 - Relatively non-toxic (hormonal; some biologics)
- Consider regulatory precedents

Regulatory Approach to Trial Design

- Superiority or non-inferiority trial
- Number of trials
 - Generally need at least two trials
 - Particularly important with non-inferiority studies
 - “Evidence” guidances
- If accelerated approval, start thinking about the confirmatory study

Trial design: Practical points

- Stratify study appropriately
 - Imbalance may bias results
 - Post-hoc adjusted analyses or subset analyses exploratory only
- Consider effect of prior therapy
 - Androgen or tamoxifen withdrawal
- Use the appropriate comparator
 - Should reflect standard of care
 - Labeled therapy or well-documented in literature
 - Should have documented efficacy

Trial Design: Practical points

- Detailed prospective statistical analysis plan
 - Follow that plan when the study is completed
- Consider Data Safety Monitoring Board
 - Members should not be part of the company
 - Results should be confidential
 - Independently evaluate for safety
 - Independently evaluate for efficacy only if early stopping is a consideration

Efficacy Endpoints: Traditional Approval

- Survival (gold standard)
- Prolongation in time to recurrence or disease-free survival (adjuvant studies)
- Durable complete response
- Palliation (objective response with reduction in tumor-related symptoms)

Efficacy Endpoints: Traditional or accelerated approval?

- Traditional approval for hormonal therapy
 - Response rate
 - Time to progression, with response rate
- Accelerated approval for cytotoxic therapy
 - Response rate

Efficacy Endpoints: Accelerated Approval

- Response rate
 - Tumors
 - Lymphomatous meningitis
 - Hematologic response
 - Cytogenetic response
- [Colonic polyps]

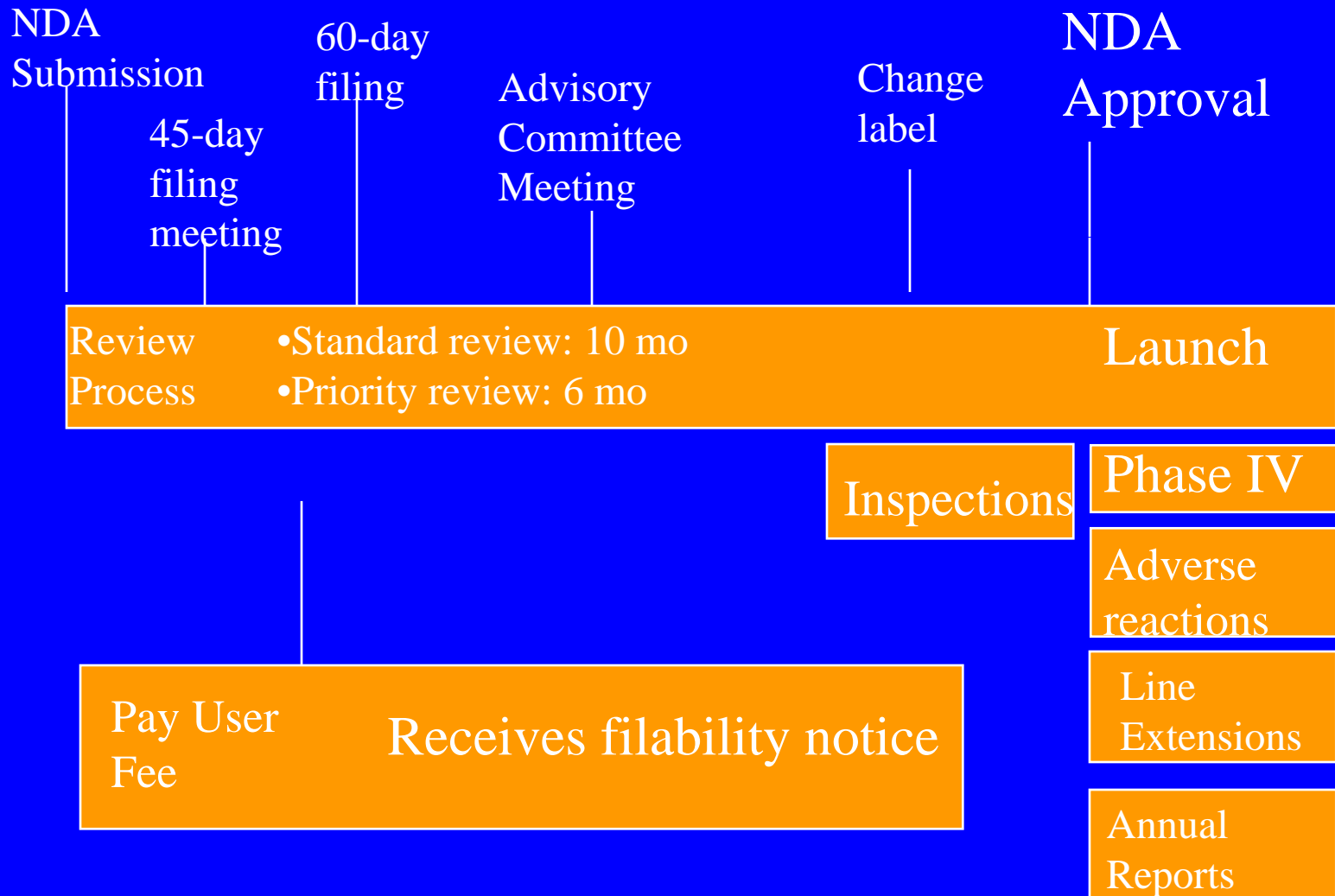
Phase III Clinical Trials (Anticancer Drugs)

- Further characterization of efficacy and safety compared to control
- If the control has known efficacy, studies may be designed to show non-inferiority
- If the control is not known to be effective (or a “no treatment” arm is used), studies are required to show that the new drug is superior

Pre-NDA Meeting

- Brief summary of trial results
- Address any major unresolved problems
- Identify “pivotal” studies for submission
- Discuss (not rewrite) statistical analysis plans
- Outline plans for presentation/formatting of data
- An advisory committee member may participate

Drug Approval Timeline



Filing Meeting (45 days)

- Division must notify applicant whether NDA will be filed within 60 days of its receipt
- If Refuse to File, applicant may request a meeting
- Classification of standard or priority review also completed within 60 days

Classification Requirements

- Priority Classification (6-month clock)
 - Demonstration of increased effectiveness over existing therapy
 - Product provides a therapy where none exists
 - Eliminates or reduces treatment-limiting ADRs
 - Enhanced patient compliance
 - Safety and efficacy in a new sub-population
- Standard Classification (10-month clock)
 - All non-priority applications

Financial Disclosure

- 21 CFR 54: February 2, 1998 and December 31, 1998
- Purpose: to ensure that financial interests of and arrangements with PIs that could affect the reliability of data submitted to FDA in support of product marketing are identified and disclosed by the applicant
- Drugs, biologics, devices

Financial Disclosure

- For NDAs submitted on or after 2/2/99, the applicant must certify that no financial arrangements with the investigator have been made where:
 - compensation is affected by the outcome of the clinical studies
 - Investigator owns a significant equity interest
 - Investigator has a proprietary interest in the tested product
 - Investigator has received significant payments of other sorts
- OR Applicant discloses the nature of the arrangements

Financial Disclosure

- Definition of PI
- Definition of effectiveness study
- Effective date
- The Rule does not include a provision for waivers
- Failure to provide financial disclosure information may constitute a “Refuse to File” issue

NDA Review Process

- Team approach
- Emphasize primary endpoint, prospectively defined statistical plan
- Data quality

NDA Review Process

- M.D. reviews the data to confirm applicant's safety and toxicity analyses
- Statistician evaluates appropriateness of analyses and replicates them
- Analyses may be re-run with a “corrected dataset”
- Application may be discussed at a public Advisory Committee meeting

Phase IV Clinical Trials (Anticancer Drugs)

- Postmarketing studies to further study drug safety and efficacy
- Generally in comparison to other drugs used for the same malignancy
- Conversion from accelerated to full approval

Reinventing the Regulation of Cancer Drugs

President Bill Clinton

Vice President Al Gore

National Performance Review

March 29, 1996

Oncology Initiatives

- Accelerated approval of some cancer therapies
- Expanded access to cancer therapies approved in other countries
- Clarification of policy on INDs for studies of marketed products
- Patient representation on cancer-related advisory committees

Accelerated Approval

- Eleven accelerated approvals for NDAs
 - Dexrazoxane (Zinecard)
 - Docetaxel (Taxotere)
 - Irinotecan (Camptosar)
 - Doxorubicin liposome (Doxil-2 indications)
 - Capecitabine (Xeloda)
 - Cytarabine liposomal injection (Depocyt)
 - Temozolomide (Temodar)
 - Celecoxib (Celebrex)
 - Gemtuzumab (Mylotarg)
 - Imatinib mesylate/STI-571 (Gleevec)
 - Oxaliplatin (Eloxatin)

Accelerated Approval

- Two for efficacy supplements
 - Amifostine (Ethyol)
 - Anastrozole (Arimidex)

Accelerated Approval

- 3 products converted from accelerated approval to full approval
 - Taxotere, with expansion of its indication
 - Irinotecan, with the same indication
 - Capecitabine, with expansion of its indication

Accelerated Approval

- Open to therapeutic areas other than oncology and HIV disease
- Rarely utilized to date

Clarification of Policy on INDs for Studies of Marketed Products

- Submission of an IND to study a marketed drug or biologic product not required when:
 - Product used in generally the same patient population and same manner for which the agent was approved (ie, will not substantially increase patient risk)
 - Study not intended to support approval of the new use or a significant change in labeling or advertising

Fast Track

Fast Track Drug Development

- Facilitate development and expedite review of drugs
 - Intended to treat serious or life-threatening conditions (S or LT) and
 - that demonstrate the potential to address unmet medical needs
- Different from Accelerated Approval
- Includes diagnosis, prevention, and treatment of the disease or of a serious side effect/complication

Fast Track: Criteria for Qualification

- Serious or life-threatening
 - Refers to the combination of the product and the specific indication
 - The condition must be S or LT
 - The product must treat a serious aspect of the condition

Fast Track: Criteria for Qualification

- Potential to address unmet needs
 - No available therapy
 - Superior to available therapy
 - Provides a benefit comparable to available therapy, but with less toxicity/different toxicity/better compliance
 - Affects a serious aspect of a disease that is not treated by available therapy

Fast Track

- Refers to the overall development plan
- Close collaboration with the Agency
- Regular schedule of meetings
- SoPA

Fast Track

May seek

- Traditional approval
 - Accelerated approval
 - Based on a clinical endpoint or a surrogate endpoint reasonably likely to predict clinical benefit
 - Post-marketing studies required to verify benefit
- OR

Fast Track: Benefits

- Allows submission of portions of an NDA prior to receipt of the complete application
 - Must consist of a complete section
 - Must include a schedule for submission
 - Pay user fees
 - Review clock starts when the complete application has been submitted
- Other programs (meetings) open to any sponsor

Fast Track

- Sponsor requests designation as early as the time of IND submission
- FDA review within 60 days
- Designation may be withdrawn if the product no longer meets the qualifications

Fast track is not the same as Priority Review

- Standards for P
 - Significant improvement in safety or effectiveness of treatment, diagnosis, or prevention of a disease
 - Refers to designation of a completed NDA
- Fast track drugs will generally meet criteria for P review
- Non-Fast Track drugs may also warrant P review

Fast track is not the same as Treatment (Compassionate) Use

- Treatment Use
 - Drug provided to patients with S or LT illnesses while the NDA is prepared/reviewed
 - Describes availability at the end of the drug development timeline
- Fast Track drugs often good candidates for Treatment Use
- Non-Fast Track drugs may qualify also

Fast track overlaps with Accelerated Approval

- Accelerated approval
 - Same criteria to describe S or LT for AA, FT
 - AA refers to the use of a surrogate endpoint as the basis of approval
- Fast track drugs may seek traditional or accelerated approval
- Non-Fast track drugs may also seek accelerated approval

Experience

- **CDER** **CDER** **CBER**

- 164 requests

Granted **32** **20** **52**
 – 109 granted 42 denied 13 open

Denied **12** **7** **19**
 – Approximately 30 indications

Open **7** **3** **10**
 – All ODEs represented

- **CBER**

Total **51** **30** **81**
 – 83 requests - 48 granted; 33 denied; 2 pending
 – Approximately 20 indications

(as of 6/30/02 and 3/31/02 respectively)

Experience

- A sponsor may submit more than one request for different indications for a single product
- Fast track designation for one indication for a product applies to that indication only
 - It does not imply that requests for other indications will be granted

Selected Indications

CDER

Coronary syndrome
CVA
ALS
Malignancies
Acute pancreatitis
Platelet adhesion
HIV
SLE
ARDS
Acromegaly
Huntington's chorea
Gaucher's disease
Diabetic vascular disease

CBER

Advanced RA
Malignancies
Fabry's Disease
Critical limb ischemia
Muscular Dystrophy
Hepatic failure
Crohn's Disease
HIV
SLE
Multiple Sclerosis

Fast Track Approvals

- CDER: 10 drugs with FT designation approved (6/30/02)
 - HIV disease, non-small cell lung cancer, APL, refractory aspergillosis, CML, hereditary tyrosinemia
- CDER: 8 FT products approved (8/31/02)
 - RA, breast cancer, CLL, HIV, NHL, osteopetrosis, *s. pneumoniae*

“Available Therapy”

Draft guidance, February 2002

- Cited for treatment INDs, Subpart E, Accelerated Approval, Pediatric Rule, Fast Track, priority review standards
- Definition:
 - “Should be interpreted in almost all cases as therapy that is reflected in the approved labeling”
 - “In unusual cases, a treatment...not labeled for use but is supported by compelling literature evidence...can be considered available therapy.”

Special Protocol Assessment

- FDA will review special protocols, defined as carcinogenicity, stability, and pivotal Phase III trials within 45 days (90% compliance by FY 2002)
- If FDA approves the protocol, FDA will not change its mind unless public health concerns unrecognized at the time of the agreement emerge

Summary

- Efficient drug development “works backward”--start with the label and construct plan
- Work closely with FDA

FDA Website

- <http://www.fda.gov> (access to all pages)
- <http://www.fda.gov/cder> (drugs)
- <http://www.fda.gov/cber> (biologics)