Overview of the Regulatory Approval Process:
Development of New Drugs and Devices from Discovery to Market

with thanks to
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Sweeney Regulatory Consulting

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Development of New Drugs and Devices from Discovery to Market

- Types of Drugs and Devices
- FDA Regulations Affecting Each Stage
- Phases of Product Development

FDA Regulations – Code of Federal Regulations, Title 21

- Part 11 – Electronic records and Signatures
- Part 58 – Good Laboratory Practices - nonclinical
- Part 50 – Protection of Human Subjects – clinical trials
- Part 54 – Financial Disclosure
- Part 56 – Institutional Review Boards – clinical trials
- Part 312 – Investigational New Drug Application (CBER CDER)
- Part 314 – New Drug Application (CDER)
- Part 601 – Biologics License Application (CBER)
- Part 812 – Investigational Device Exemption (CDRH)
- Part 807 – Subpart E – PreMarket Notification 510(k) CDRH
- Part 814 – PreMarket Approval Application – Devices (CDRH)

Guidance Documents (may be general or product specific)

Guidance Documents @

- www.fda.gov/cder/guidance/index.htm
- www.fda.gov/cder/regulatory/default.htm
- www.fda.gov/cber/guidelines.htm
- www.fda.gov/cder/about/smallbiz/default.htm
- www.fda.gov/cdrh/index.html (topics index)
- Comprehensive List of FDA Guidance Documents
  www.fda.gov/opacom/morechoices/industry/guidedc.htm
**Definition of a Drug**

FD&C Act, Chapter II, Definitions, Sec 201:
- Recognized in the U.S. Pharmacopeia (USP), National Formulary (NF) (current revision is 25/20), or Homeopathic Pharmacopeia of the United States AND
- Intended use for diagnosis, cure, mitigation, treatment or prevention of disease in man or animal AND
- Intended to affect the structure or function of the body AND
- Intended for use as a component of any article specified
- Not a food, dietary ingredient or dietary supplement.

**Definition of a Biological Product**

Public Health Service Act Sec. 262(i) & (j):
- Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product....

21 CFR 600.3
- Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries to man.

**Definition: Biotechnology Derived Therapeutic (BDT, biotech drug, etc.)**

21 CFR 601.2, “specified categories of products”:
- Therapeutic synthetic peptide of 40 or fewer amino acids.
- Therapeutic DNA plasmid products.
- Monoclonal antibodies for in vivo use.
- Therapeutic recombinant DNA-derived product.

(exempt from certain biologics regulations – Does not require an ELA or samples to be submitted to CBER for lot release)

**CBER’s own words ...**

- Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms).
- Most biologics are complex mixtures that are not easily identified or characterized, and many biologics are manufactured using biotechnology.
- Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available.
Beginning October 4, 2004, all therapeutic biologic submissions (EXCLUDING 21 CFR 600.80 postmarketing adverse experience reports; advertising and promotional labeling; and 21 CFR 600.14 biological product deviation reports) should be sent to:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Types of Drugs & Market Submissions

- **New Drug Application (NDA)**
  - Classical Chemical Drugs: small molecules – Center for Drug Evaluation and Research (CDER)

- **Biological License Application (BLA)**
  - Biotechnology Derived Therapeutics: complex, large molecules – Center for Biologics Evaluation and Research (CBER)

### Drug Development and Approval Process Steps

1. Discovery
2. NonClinical Animal Testing
4. Investigational New Drug Application (IND)
5. Clinical Trials [Phase 1, 2, 3, (4)]
6. New Drug or Biologics License Application (NDA or BLA)
7. Market Approval
8. Phase 4 (with PDUFA3)

[http://www.fda.gov/cder/about/smallbiz/newdrug.htm](http://www.fda.gov/cder/about/smallbiz/newdrug.htm)
Non-Clinical Research
(in vitro or in vivo studies in animals)

- Early Feasibility Studies - what works.
- Pharmacology – where does it go
  - pharmacokinetics (pk) [effect of body on drug]
  - pharmacodynamics (pd) [effect of drug on body]
- Efficacy Studies – how well does it work and what does it do in the body.
- Dose Ranging Studies – how much does it take to work.
- Safety Studies – what adverse effects does it produce (21CFR58)
- Biocompatibility Studies - for devices

Subject-Related Guidances of Interest

CDER Handbook @ www.fda.gov/cder/handbook

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
  www.fda.gov/cder/guidance/clin2.pdf
- INDs for Phase 2 and 3 Studies of Drugs
- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro
- Investigational Device Exemptions Manual
  www.fda.gov/cdrh/devadvice/ide/index.shtml

Filing the Investigational New Drug Application (IND) - §312

- Introductory Statement and General Investigational Plan
- Investigators Brochure
- Clinical Protocol
- Chemistry, Manufacturing and Control Information
- Pharmacology & Toxicology Information in Animals
- Previous Human Experience
- Requires a 30 day wait period prior to start
Clinical Development for Drugs

- **Phase 1** – safety studies in ~20 to 80 normal subjects, pharmacokinetics and pharmacology data help design Phase 2
- **Phase 2** – efficacy and safety in ~few hundred subjects who have the indicated disease
- **Phase 3** – expanded to determine benefits-risks in a particular disease (sub)population in several hundred to thousands of patients
- **Phase 4** – post-marketing surveillance

Drug Product and Process Development

- Drug Substance – active ingredient
- Drug Product – Final drug formulation and packaging – how will it be given and in what dose
- Product Specifications
- Processing controls and adequate yields
- Stability - how to store, in what, for how long

Additional Animal Studies

- Long Term – chronic studies
  - Carcinogenicity
  - Mutagenicity
  - Teratogenicity

Drug Market Application: NDA, BLA or Common Technical Document

- 21 CFR 314 and ICH M4*
- Summary
- Nonclinical Pharmacology and Toxicology
- Chemistry, Manufacturing and Control
- Human Pharmacokinetics and Bioavailability / Bioequivalence

Market Application: NDA, BLA or CTD – 2

- Clinical Data
- Statistics
- Samples and Labeling
- Case Report Forms and Tabulations
- Patents
- Establishment Description

Definition of a Device

FD&C Act, Chapter II Definitions:
- An Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or similar including component, part, accessory AND
- Recognized in NF or USP,
- Intended use for diagnosis, cure, mitigation, treatment or prevention of disease in man or animal OR
- Intended to affect the structure or function of the body AND
- which does not achieve primary intended purpose through chemical action within/on the body AND is not dependent on being metabolized.

Types of Devices & Market Submissions

- Class I, II, or III
- 510(k) – Typically Class I or II or Device that is substantially equivalent to existing (predicate) FDA approved device.
- Pre-Market Approval (PMA) - Class III or device for which there is no predicate.
- Or if seeking new indication for an existing device, 510(k) or PMA.

in vitro diagnostic (IVD)

A medical test that analyzes body samples, such as blood, urine, stool, or saliva, for specific components or analytes.

www.fda.gov/cdrh/oivd/consumer-glossary.html

in vi·tro (n vtr) adv. & adj.
In an artificial environment outside the living organism.
[New Latin in vitr : Latin in, in + Latin vitr, ablative of vitrum, glass]
Significant Risk Devices

- Potential for serious risk to the health, safety, or welfare of a subject.
  - implants
  - devices that support or sustain human life
  - devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health.

- Examples include
  - sutures
  - cardiac pacemakers
  - hydrocephalus shunts
  - orthopedic implants

- Guidance on distinguishing between significant risk and nonsignificant risks studies are outlined in the document

- www.fda.gov/oc/ohrt/irbs/devices.html

Part 812

File the Investigational Device Exemption (IDE) for Significant Risk Devices

- Report of Prior Investigations
- Investigational Plan
- Manufacturing Information
- Investigator Information
- IRB Information
- Sales Information
- Labeling
- Informed Consent Materials
- Environmental Impact Assessment
- Other Information

www.fda.gov/cdrh/devadvice/ide/approval.shtml

Premarket Notification – 510(k)

21 CFR 807, Subpart E

- Submitter’s information
- Device name
- Predicate device
- Device description
- Statement of Intended Use
- Technological Characteristics compared to predicate
- 510(k) summary (nonclinical, clinical studies)

Pre-Clinical Studies

Type of testing depends upon product/use
  - electromagnetic compatibility
  - radio frequency interference
  - electrical leakage
  - power output
  - material strength, flexibility, durability, etc.
  - sterility
  - reliability
Clinical Studies
3 stages: feasibility, pilot, pivotal

- Feasibility test; proof of concept:
  - 3-5 subjects
  - one site
  - usually investigator-sponsored

- Pilot test protocol
  - 10-30 subjects
  - one or two sites
  - “test drives” protocol and operator’s manual

- Pivotal Study
  - consult guidance document, if any (may be on type of product or disease/clinical condition)
  - number of subjects varies
    - experiential study
    - confirmatory study
    - statistically significant
  - multiple sites (at least 3)
  - duration depends on length of human exposure to

Guidance Document

- Manufacturer’s responsibility to determine what is required for individual products
  - i.e., electrical → search guidance documents
    - Safety of Electrically Powered Products: Letter To Medical Device and Electronic Product Manufacturers

Pre-Market Approval Application (PMA) 21 CFR 814

- Applicant name and address
- Table of Contents
- Summary (Indications for Use, Device description, Alternative practices and procedures, Marketing History, Nonclinical and clinical abstracts, and Conclusions).
- Complete Description of the device (functional properties & operation, manufacturing and control methods)

Pre-Market Approval Application – 2

- Performance Standards
- Technical Section (Nonclinical and Clinical studies)
- Bibliography
- Samples
- Labeling
- Environmental Assessment
- Financial Disclosure
- Other Information
**Medical Device Program**

**CDRH: Types and Numbers of Submissions**

<table>
<thead>
<tr>
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* The majority of PMAs and 510(k) applications are subject to fees. Exceptions include small business and pediatric applications.

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**Final FDA Review and Approval**

- 1 year time clock for standard non-life-threatening disease drugs
- 6 month time clock priority review for accelerated or fast track drugs
- 6 month review for PMA
- ~90 days for 510(k) / shorter for Third Party review (92 day average in 2004)
- Advisory Committee Panels – optional
- Final Labeling Negotiations
- Inspection of Clinical Sites
- Inspection of Manufacturing Sites

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**CDER Review Times**

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*Beginning in 2004, these figures include new BLAs for therapeutic biologic products transferred from CBER to CDER effective 10/1/2003.

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**CBER Review Times**

**CBER Approval Times for Priority and Standard BLAs, and Device Applications**

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*Beginning in 2004, these figures include new BLAs for therapeutic biologic products transferred from CBER to CDER effective 10/1/2003.
Post Marketing – It ain’t over yet!

- Possible commitments to perform additional clinical studies; PDUFA3, MDUFMA
- Annual Establishment Registration and Product listing
- Adverse Events Reporting System / MEDwatch
- Device Tracking
- Establishment Inspections