Overview of the Regulatory Approval Process:

Development of New Drugs and Devices from Discovery to Market

with thanks to
Dee Sweeney, RAC
Sweeney Regulatory Consulting

10-April-2006

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.

... CBER → CDER

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

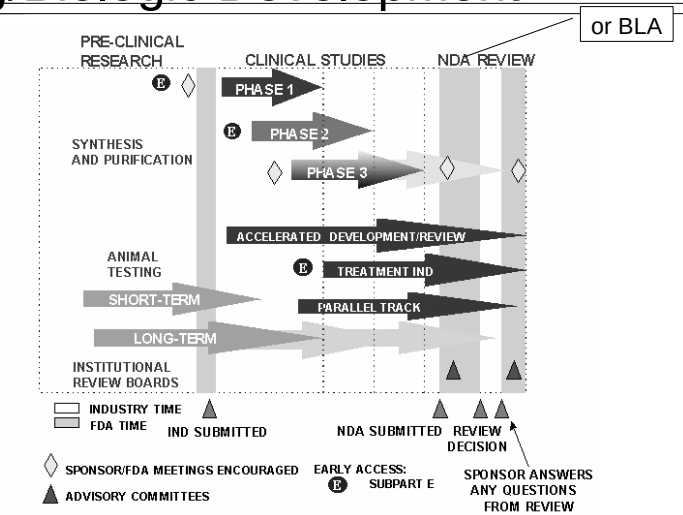
- *New Drug Application* (NDA)
  - Classical Chemical Drugs: small molecules – *Center for Drug Evaluation and Research (CDER)*
- *Biological License Application (BLA)*
  - Biotechnology Derived Therapeutics: complex, large molecules – *Center for Biologics Evaluation and Research (CBER)*

Drug Development and Approval Process Steps

1. Discovery
2. NonClinical Animal Testing
3. Product & Process Development – Chemistry, Manufacturing and Control (CMC)
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

Drug/Biologic Development



Spiffy interactive charts ...

- Overall drug development
- IND Review
- NDA Review
- Generic Drug Review

www.fda.gov/cder/handbook

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

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

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

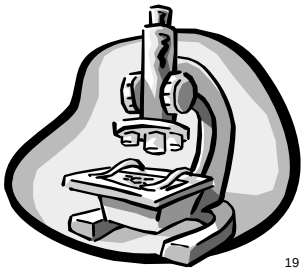
- **Phase 1** – safety studies in ~20 to 80 normal subjects, pharmacokinetics and pharmacology data help design Phase 2
- **Phase 2** – efficacy and safety in ~few hundred subjects who have the indicated disease
- **Phase 3** – expanded to determine benefits-risks in a particular disease (sub)population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

* International Commission on Harmonisation -- www.ich.org

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

TYPE OF SUBMISSION	FY1999	FY2000	FY2001	FY2002	FY2003	ESTIMATED FY2004
Original PMA*	64	67	71	48	54	50
PMA Supplement*	552	545	641	645	669	619
Original IDE	**304**	**311**	**284**	**312**	**242**	**310**
IDE Amendment	**275**	**240**	**206**	**252**	**216**	**240**
IDE Supplement	**4,127**	**4,388**	**4,811**	**4,724**	**4,425**	**4,388**
510(k) – 10% with clinical data*	4,458	4,202	4,248	4,320	4,247	3,533
Original HDE	**12**	**11**	**5**	**5**	**10**	**9**
HDE Supplements	**4**	**10**	**16**	**16**	**29**	**29**
Total	9,792	9,774	10,281	10,321	9,872	9,178

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

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

CDER Review Times

Calendar Year	Priority Review		Standard Review	
	Number Approved	Median Total Approval Time (months)	Number Approved	Median Total Approval Time (months)
1995	10	7.9	19	17.8
1996	18	9.6	35	15.1
1997	9	6.7	30	15.0
1998	16	6.2	14	13.4
1999	19	6.9	16	16.3
2000	9	6.0	18	19.9
2001	7	6.0	17	19.0
2002	7	16.3	10	15.9
2003	9	6.7	12	23.1
2004*	21	6.0	15	24.7

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

CBER Review Times

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

	BLAs						PMAs		510ks	
Calendar Year	Priority Review		Standard Review		Blood Banking					
	Number Approved	Median Total Approval Time (months)	Number Approved	Median Total Approval Time (months)	Number Approved	Median Total Approval Time (months)	Number Approved	Median Total Approval Time (months)	Number Approved	Median Total Approval Time (months)
1995	2	5037	16	34.42	11	10.13	0	--	51	6.7
1996	3	11.87	24	39.63	10	10.18	3	11.7	31	5.0
1997	7	8.94	22	22.07	8	10.99	0	--	46	11.1
1998	8	6.91	13	23.42	6	11.94	0	--	52	15.1
1999	3	13.87	4	24.18	3	8.32	2	24.7	44	7.0
2000	1	8.52	9	28.67	2	16.80	0	--	22	3.3
2001	2	13.18	8	23.74	5	16.63	3	10.5	25	5.5
2002	6	14.69	10	19.91	4	10.61	2	19.9	42	6.2
2003	5	22.18	11	30.00	6	8.66	3	8.5	47	2.3
2004*	0	--	2	19.77	2	12.91	1	5.9	62	2.5

*Beginning in 2004, these figures exclude 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