FDA Guidance, Clinical Pharmacology, and “Regulatory Science”

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- **CDDS** ([http://cdds.ucsf.edu](http://cdds.ucsf.edu))

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Why FDA?

What does FDA* do, When & How?

Clinical Pharmacology at FDA*

Regulatory Science
Initiatives to Improve Drug Development & Regulation

* Focus: CDER, CBER
A Horse Called “Jim”
“Patent Medicines” in Early 20th Century

- Based on testimonials of “miracle cures”
- Most were ineffective, many were dangerous
- main ingredient: *alcohol*
Examples of Snake Oil in Early 20th Century

Peter’s Specific Blood Purifier
for all ailments: arsenic, opium, and insect parts

Curforhedake Brane-Fude
“a most wonderful, certain and harmless relief”
“no ... poisonous ingredients of any kind”
acetanilid - killed numerous people and was addictive

Microbe Killer
cure all disease: 99% water, hydrochloric acid, red wine
"There is no Sore it will Not Heal, No Pain it will not Subdue."

50%-70% alcohol, camphor, ammonia, chloroform, sassafras, cloves, turpentine
Patent Medicine

All Medicines sold
without a prescription

Children and Adults die after taking cough syrup
1906 Pure Food and Drug Act

Precipitated by Upton Sinclair’s novel The Jungle

- Prohibited **adulterated** or **misbranded** foods or drugs in interstate commerce
- **Regulated** product **labeling** rather than requiring approval
- **Labels could not be false or misleading**
The “Elixer of Sulfanilamide” Incident

In 1937, a chemist at the Massengill Company used diethylene glycol (antifreeze) to prepare a new anti-bacterial sulfa drug in syrup form to improve taste

- Diethylene glycol is sweet but deadly
- More than 100 people died from the compounds most of them children
- Most prescribed by doctors
- Company fined $300
- Chemist responsible committed suicide

Public outrage led to passage of 1938 Food Drug & Cosmetic Act
1938 Food Drug & Cosmetic Act

- Established basic structure of today’s law
  - Authority to block new drugs if FDA concluded that additional safety testing needed (premarket notification)
  - **Prohibition of false therapeutic** claims
  - Allowed FDA to require **some drugs to be available by prescription only**
  - Increased FDA’s powers for **factory inspections**
Thalidomide

A sedative often given to pregnant women in late 50’s and early 60’s, caused thousands of babies born with limb defects in Europe and elsewhere

- FDA declined to approve it for U.S
- Thousands of doses send to U.S. physicians as experimental drug, resulting in 17 known U.S. cases of limb defects
1962 Kefauver-Harris Amendments

- Adopted in response to public concern about thalidomide
  - Stricter controls over investigational drugs
  - **Required drugs to be effective as well as safe**
  - **Effectiveness was to be determined by adequate and well controlled studies**
- Required reevaluation of all drugs introduced since 1938 for efficacy (*DESI Process*)
- **Requirement for good manufacturing procedures (GMPs)**
- **First requirements for post-marketing surveillance**
FD&C Acts and Selected Amendments

- Pure Food & Drug Act (1906)
- Biologics Control Act (1902)
- "Jim" & Diphtheria in St. Louis (1901)
- "Jungle" & "Death's Laboratory (1906)
- Sulfonamide (1938)
- Food, Drug & Cosmetics Act (1938)
- Thalidomide (1962)
- Kefauver Efficacy Amendment (1962)


UCSF-CDDS 2010
**What does FDA do:**
provision of standards & guidance

- **Standards**
  - chemistry and manufacturing controls (CMC)
  - preclinical animal toxicology requirements
  - ethics of human clinical trials
  - documentary requirements for INDs, & NDAs

- **Clinical trials**
  - safety
  - effectiveness
  - trial design
How does FDA provide guidance?

- **Written guidances**
  - Regulations, guidelines (incl. ICH), guidances
  - Literature publications
  - Regulatory letters

- **Face-to-face & telephonic meetings**
  - Pre-IND, EoP2a, *EoP2 Clinical Pharmacology*, pre-NDA, others as-needed

- **FDA Advisory Committee meetings**

- **Podium presentations**
How many guidances and are they binding?

**GUIDANCES**
- > 500 guidances (final/draft, FDA/ICH)

**Guidance documents:**
- Cannot legally bind FDA or the public
- Recognizes value of consistency & predictability
- Because companies want assurance
- So staff will apply statute & regulations consistently

www.fda.gov/cder/guidance.htm
Some Clinical Pharmacology Guidances

- Drug Metabolism/Drug Interaction Studies
- PK in renal & hepatic dysfunction
- Pediatric PK Studies, pregnancy, lactation
- Population PK
- Exposure-Response (PKPD)
- Exploratory IND Studies
When does FDA engage?

Figure 7: Industry-FDA Interactions During Drug Development

- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development
  - Phase 1
  - Phase 2
  - Phase 3
- FDA Filing/Approval & Launch Preparation

- Industry-FDA Interactions During Development
  - Pre-IND Meeting
  - End of Phase 2a Meeting
  - Initial IND Submissions
  - End of Phase 2 Meeting
  - Market Application Submission
  - Ongoing Submission
  - Pre-BLA or NDA Meeting

- IND Review Phase
- Application Review Phase

UCSF-CDDS 2013
FDA Clinical Pharmacology “Question-based Review Template*

- Exposure-response for safety & efficacy?
- Drug-drug interaction questions
  - CYP substrate, inhibitor, inducer?
    - Genetic influences?
    - Transporters?
    - PD drug interactions?
- Active metabolites, protein binding?
- PKPD modeling?

*Question Based Review
Extracted from FDA MAPP 4000.4 (4/27/04)
Clinical Pharmacology @ FDA
Impact Of Modeling & Simulation on Regulatory Decision Making *
C. Garnett, J. Gobburu

PM Reviews of 198 IND/NDA/BLA (‘00-’08)
- Trial designs, QT, EOP2a
- popPK, E-R, Peds (38)
- Impacted >60% APP, labeling
- Evidence of effectiveness (9) & APP unstudied doses (21)

Research & Policy
- TQT design & E-R analyses
- Disease models (2+5)

M&S in FDA Today

- Concentrated (but metastasizing) in Offices of Clinical Pharmacology & Biometrics, Division of Pharmacometrics
- ISoP/FDA Modeling & Simulation for Medical Products Workshop, September 26, 2013
- PBPK analyses reported in 33 INDs/NDAs during 2008-2012
  - 18 PBPK analyses undertaken by FDA staff
- Example internal projects & working group
  - Disease model for cognitive function in Alzheimer’s Disease
  - Interdisciplinary Review Team for QT
Recent Amendments
FD&C Act

FDAMA, FDAAAA, FDASIA
FDA Modernization Act of 1997 - “FDAMA”

- Sec. 111. **Pediatric** studies of drugs
  - PK bridging studies

- Sec. 115a. Clinical investigations
  - support of *one* adequate and well-controlled clinical investigation by “**confirmatory evidence**” comprising PK or PK/PD
FDAMA, Sec. 115a
Clinical investigations

“If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence .... are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence.”
COMMENTARY

Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval

Carl C. Peck, MD, Donald B. Rubin, PhD, and Lewis B. Sheiner, MD  Washington, DC, Cambridge, Mass, and San Francisco, Calif
New Formulations and Doses of Already Approved Drugs

- Where **blood levels ... are not very different**, it may be possible to conclude ... is effective on the basis of **pharmacokinetic data alone**.

- Even **if blood levels are quite different**, if there is a well-understood relationship between **blood concentration and response**, ..., it may be possible to conclude ... is effective on the basis of **pharmacokinetic data without** an additional clinical efficacy trial.

Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products", May 1998
FDA Amendments Act of 2007 – “FDAAA” Emphasis on Safety

- Motivated by prominent market W/D’s due to unexpected lack of safety
- New Authorities
  - Public listing of all clinical trials & results
  - Post-approval trials and surveillance
  - Safety labeling
  - REMS (Risk Evaluation & Mitigation Strategy)
  - Pre-approval of Direct to Consumer Ads
  - Penalties
  - Advisory Committees
    - Risk Communication
FDASIA*

Expansion of the accelerated approval process
- Epidemiological, pathophysiological, pharmacologic, biomarkers as evidence of clinical benefit
- Expanded definition of surrogate endpoints

New pathway for “breakthrough therapies”
- Drug “is intended, for a serious or life-threatening disease
- Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
“Breakthrough Therapies”

**Designation activity**
- 40 applications
  - 10 granted
  - 12 denied
  - 18 pending

**Approvals**
- Ivacaftor (Kalydeco, cystic fibrosis, Vertex)
- Tofacitinib (Xeljanz, rheumatoid arthritis DMARD, Pfizer)
Precedent Initiatives to Improve Drug Development and Regulation

- **1995. CDDS Collaboration on Drug Development Improvement** (CDDI, Georgetown University & FDA)
  - to improve substantially the development of biopharmaceuticals

- **1999. New Safe Medicines Faster Initiative** (EUFEPS)
  - Optimize the drug development process by removing bottlenecks

- **2003. Critical Path Initiative** (FDA)
  - “toolkits” for better product development, safety…

- **2007. Innovative New Medicines** (IMI, EC)
  - to speed up the development of better and safer medicines for patients.
FDA “Regulatory Science” Initiative (2010)

Science & Research
- Home
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- Science and Research Special Topics
- Advancing Regulatory Science

Advancing Regulatory Science
Strategic Plan for Regulatory Science
ARS Collaborations
ARS News and Upcoming Events
ARS Past News and Events
Centers of Excellence in Regulatory Science and Innovation (CERSI)

Resources for You
- Driving Biomedical Innovation: initiatives for improving products for patients
- Advancing Regulatory Science for Public Health
- Critical Path Report on Key Achievements in 2009 (PDF - 381KB)
- The Critical Path Report – 2008 (PDF - 316KB)
- Critical Path Opportunities for Generic Drugs
- Critical Path Opportunities List - March 2006 (PDF - 485KB)
- March 2004 - Challenge and Opportunity on the Critical Path to New Medical Products (PDF - 1MB)

Strategic Plan for Regulatory Science
FDA has developed a strategic plan for regulatory science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

View the strategic plan

Advancing Regulatory Science for Public Health
This document outlines a broad vision for advancing regulatory science and unleashing its potential to improve public health.

View speech by FDA Commissioner Margaret A. Hamburg, M.D., 50 National Press Club, Oct. 6, 2010
“Regulatory Science”
FDA’s Definition

“Regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.” ¹

¹Advancing Regulatory Science for Public Health – A Framework for FDA’s Regulatory Science Initiative, October 2010
FDA’s Regulatory Science Priorities

- Modernizing *Toxicology*
- Crafting New Tools for *Personalized Medicine*
- Supporting New & Improved *Manufacturing Technologies*
- Readiness to *Evaluate Innovative Technologies*
- Expanding FDA’s Information Technology Infrastructure
- Implementing Prevention-focused Food Safety
- Speeding Development of *Medical Countermeasures*
- Developing Communications Strategies to help FDA Adapt to new Information Sharing Technologies
NIH & FDA

- 2-24-10 NIH and FDA Announce Collaborative Initiative to Fast-track Innovations to the Public: *Joint NIH-FDA Leadership Council*" for Translational + Regulatory Science

- 2-26-10 NIH Grants: Advancing Regulatory Science through Novel Research and Science-Based Technologies (U01):
  “…study applicability of novel technologies … towards the development and regulatory review of medical products …“

- 7-15-11 FDA Collaborating Centers of Excellence in Regulatory Science and Innovation
Training in Drug Development & Regulation

- European Course in Pharmaceutical Medicine (ECPM) – 1991 to present
- Drug Development & Regulatory Science (CDDS, ACDRS)
American Course on Drug Development & Regulatory Science (ACDRS)

- Conceived 2006, launched 2007 - UCSF
- Evolved from (ECPM), CDDS @ Georgetown University, FDA staff college
- Emphases –
  - Principles
  - Quantitative/learn – confirm approach to improving drug development process and efficiency
  - Best practices integration of principles of efficient medical product development and regulatory science
  - Highly experienced, currently active drug development scientists, regulators, selected academics
  - Participants committed to a career in DD&RS
IMI Education and Training Projects

EMTRAIN
European Medicines Research Training Network

Eu2P
EUROPEAN PROGRAMME IN PHARMACOVIGILANCE AND PHARMAECONOMICS

PharmaTrain
MASTERING MEDICINES DEVELOPMENT

EUPATI
European Patients Academy on Therapeutic Innovation

SafeSciMET
European Modular Education and Training Programme in Safety Sciences for Medicines

imi.europa.eu
San Francisco
EMA

- Workshop on Modeling in Pediatric Drugs
- Role of M&S in Drug Development & Regulation: EFPIA/EMA M&S Workshop, 2011*
- Concept paper on Extrapolation of Safety & Effectiveness, 2012
- Draft Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty, 2013

Some Final Observations

- FDA regulation is science-based
  - Advances innovation
  - Facilitates needed drugs for patients
- FDA clinical guidances are increasingly based on *principles of clinical pharmacology*
- Social value: “guidance” versus “regulation”
- FDA guidance
  - national “treasure” versus “national nuisance”
  - a bargain!
End of Presentation