FDA Guidance, Clinical Pharmacology, and “Regulatory Science”

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Affiliations

- **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

- Curforshedake 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, Js. Pain it will not Subdue.

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

Patent Medicine

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
**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

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**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**

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**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

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**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

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**When does FDA engage?**

Figure 7: Industry - FDA Interactions During Drug Development

- Basic Research
- Preclinical Testing
- Clinical Development
- FDA Review Phase
- Application Review Phase

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**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?

*Extracted from FDA MAPP 4000.4 (4/27/04)*
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, FDAAA, 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.”
CLINICAL
PHARMACOLOGY
&
THERAPEUTICS
VOLUME 75, NUMBER 6
JUNE 2008

COMMENTARY

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

Carl G. Feck, MD, Donald B. Rubin, PhD, and Lewis B. Sherer, MD - Washington, DC, Cambridge, MA, 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.


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.

Peck 2012
**FDA “Regulatory Science” Initiative (2010)**

**Science & Research**

- **Science and Research Support**
  - Advancing Regulatory Science

**Advancing Regulatory Science**

- Developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

**Regulatory Science**

"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

**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

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

**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

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**Training in Drug Development & Regulation**

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

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**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
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