Principles of Clinical Pharmacology
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FDA Guidance, Clinical Pharmacology, and “Regulatory Science”

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Acknowledgements & Affiliations

- Contributors to ideas presented today
  - All of our colleagues in FDA & IMI/PharmaTrain

- Disclosures
  - CDDS (http://cdds.ucsf.edu)
  - NDA Partners LLC (www.ndapartners.com)
Why FDA?

What does FDA* do, When & How?

Clinical Pharmacology at FDA*

FDAMA, FDAAA, FDASIA

Initiatives to Improve Drug Development & Regulation

* Focus: CDER, CBER
Why FDA?

- FD&C Act: history and its supporters
  - resulted from public safety events or public health challenges
      - Safety
      - Effectiveness
      - Individualization
      - Access
      - Guidance, transparency, speed & efficiency
  - a uniquely American phenomenon
    - Investment in FDA
    - Media, Politicization, and Transparency
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
  - (Statute, Congressional Reports)

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

- **FDA Advisory Committee meetings**

- **Podium presentations**

Website - www.fda.gov
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](http://www.fda.gov/cder/guidance.htm)
Some Clinical Pharmacology Guidances

- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies *In Vitro* (97); *In Vivo* (99, 06)
- Pharmacokinetics in Patients w/renal (10) & hepatic dysfunction (03)
- Pediatric Pharmacokinetic Studies for Drugs (98), pregnancy (04), lactation (05)
- Population Pharmacokinetics (99)
- Exposure-Response (03)
- Exploratory IND Studies (05)
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
- IND Review Phase
- Application Review Phase

- Industry - FDA Interactions During Development
  - Pre-IND Meeting
  - Initial IND Submissions
  - End of Phase 2 Meeting
  - Market Application Submission
  - Ongoing Submission
  - Pre-BLA or NDA Meeting
FDA “Question-based Review Template” *

• Exposure-response for safety & efficacy?

• Drug-drug interaction questions
  - CYP substrate, inhibitor, inducer?
  - Genetic influences?
  - P-glycoprotein substrate and/or an inhibitor?
  - Other metabolic/transporter pathways?
  - Pharmacodynamic drug interactions?
  - Active metabolites, protein binding?
  - PKPD modeling?

• Question Based Review
• Extracted from FDA MAPP 4000.4 (4/27/04)
When does FDA engage?
End of Phase 2a Meetings

- **Purpose**: ↓ Late phase clinical trial (2b, 3) unnecessary failure
- **Format**: non-binding scientific interchange.
- **Deliverables**: 
  - Modeling (relevant phase 1/2a data) & simulation of next trial design employing
    - Mechanistic or empirical drug-disease model (“Placebo effect”) 
    - Rates for dropout and non-compliance 
  - Recommendation on sponsors trial design + alternative including patient selection, dosage regimen,… 
  - Answers to other questions from the clinical and clinical pharmacology development plan
- **Time-course**: ~ 6 weeks
- **Key sponsor & FDA participants**: physician, biostatistician, clinical pharmacology (pharmacometrics), project management

Adapted from R. Powell, FDA
**U.S. FDA Perspective:**
*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)

*Chapter 3, Clinical Trial Simulations: Applications & Trends, Kimko, Peck Eds. Springer, 2011*
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.”
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
FDA Safety and Innovation Act of 2012 – “FDASIA”

- User fees for generic drugs and biosimilars
- Risk-benefit framework for the drug approval
  - “… pertaining to health information technology, including mobile medical applications, that promotes innovation, protects patient safety, and avoids regulatory duplication.”
  - Incentives for antibiotic development
- Improved COI rules for Advisory Committees
- Clarification of the least burdensome standards for medical devices
  - Modification of the de novo application process; and
  - Acceleration of the appeals process for medical devices.
FDASIA*

■ Expansion of the accelerated approval process
  - Epidemiological, pathophysiological, pharmacologic, biomarkers as evidence of clinical benefit
  - Promote fast track and accelerated approval processes
  - Encourage development of surrogate and clinical endpoints

■ New pathway for “breakthrough therapies”
  - “a drug product that “is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and [for which] preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.”
  - Expedite development and review of the application for approval via meetings, and guidance to minimize “the number of patients exposed to a potentially less efficacious treatment.”
Fact Sheet: Breakthrough Therapies

The Food and Drug Administration Safety and Innovation Act (FDASIA) includes a provision that allows sponsors to request that their drug be designated as a Breakthrough Therapy. FDA is in the process of developing guidance related to this designation. Until guidance is developed, requests for Breakthrough Therapy designation should follow the criteria outlined below. A request for Breakthrough Therapy designation should be submitted concurrently with, or as an amendment to an Investigational New Drug Application (IND) with a cover letter, a completed form 1571, and the following information:

Breakthrough therapy designation requests should contain the following information (in most cases, this information could be captured in approximately 10 to 20 pages):

- If the breakthrough therapy designation request is submitted to the sponsor’s IND as an amendment, the cover letter should indicate the submission as a REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION in bold, uppercase letters. If the request is submitted with an initial IND, the cover letter should indicate the submission as both an INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION and REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION in bold, uppercase letters.

Frequently Asked Questions: Breakthrough Therapies

1) How many requests for breakthrough therapy (BT) designation have been received by the Food and Drug Administration (FDA) (Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)) since the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012?

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<tr>
<td>Combined Quarterly Total Denied</td>
<td>0</td>
<td>3</td>
<td>9</td>
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Percent where action was taken within 60 days of receipt of the request: 100% (100% 100%)

Note: Table last updated March 31, 2013, and includes requests received but pending a decision at the time of update. Designation will be noted in the quarter in which action was taken, even if the request was received in a previous quarter. This table will be updated quarterly.
“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

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)

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., D.D.S.
National Press Club, Oct. 6, 2010

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“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 Advancing 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 PHARMAEPIEMIOLOGY

PharmaTrain
MASTERING MEDICINES DEVELOPMENT
Pharmaceutical Medicine Training Programmes

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

imi.europa.eu
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