FDA, Clinical Pharmacology, Regulatory Science &

a *Di*sp*u*tl*e Idea

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Today

*FDA*: Why, What, How, When?

*Rise & Roles of Clinical Pharmacology at FDA*

a Pro*fe*live Question

&

a Di*su*tl*e Idea

*Focus: CDER

Patent Medicine 1900

Children and Adults die after taking cough syrup arsenic, opium, insect parts, acetanilid, hydrochloric acid, red wine
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
  - 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

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**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 determined by adequate & well controlled studies
  - Required Good Manufacturing Procedures (GMPs)
  - First requirements for post-marketing surveillance

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**What does FDA do?**

- **Standards**
  - CMC
  - animal pharm/tox
  - Ethics & safety of human clinical trials
  - INDs, & NDAs
- **Guidance**
  - Regulations, guidelines, guidances
- **Review** – INDs, NDAs, pharmacovigilance
- **Enforcement** – drug quality, safety
How does FDA provide guidance?

- **Written guidances**
  - Regulations, guidelines (incl. ICH),
  - guidances (>500), not binding
  - Literature publications

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

- **FDA Advisory Committee meetings**

- **Podium presentations**

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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

- **Clinical Development**
  - Pre-IND Meeting
  - Initial IND Submission
  - End of Phase 3 Meeting
  - End of Phase 2 Meeting
  - End of Phase 1 Meeting
  - Exploratory IND Meeting

- **Regulatory**
  - Pre-Clinical or IND Meeting
  - IND Review Phase
  - Application Review Phase

- **Development**
  - Pre-IND Meeting
  - IND Submission
  - Phase 1 Meeting
  - Phase 2 Meeting
  - Phase 3 Meeting

- **Approval**
  - Pre-Approval Meeting
  - Approval Meeting Phase
Evolution of Quantitative Clinical Pharmacology

FDA Clinical Pharmacology “Question-based Review Template”
- Exposure-response for safety & efficacy?
- Drug-drug interaction questions
  - CYP substrate, inhibitor, inducer?
  - Genetic influences?
  - Transporters?
- Active metabolites, protein binding?
- PKPD modeling?

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

- Metastasizing beyond 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
- Disease models (Obesity, Parkinson’s & Alzheimer’s Diseases, Lung Cancer)
- Interdisciplinary Review Team for QT

A Proractive Question

Is it time to rethink how to affirm evidence of effectiveness?

1962 Amendment of FD&C Act required "substantial evidence" of effectiveness

“Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or as represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

2+ independent, confirmatory clinical trials
**Adequate & Well-controlled Evidence**

- Empirical comparisons with a Control
  - Historical, placebo, another treatment, dose comparison
- Control of biases
  - Protocol & pre-specifications:
    - Randomization
    - Blinding
    - Frequentist test of the null hypothesis
      - Type I & Type II error acceptance criteria, Multiplicity penalties
- Replication

35-50 yr later:
What is the problem with frequentist statistical inference for confirmation of effectiveness?

- 2-trial requirement was devised 1960’s
  - Limited knowledge of disease mechanisms, biopharmaceutics, clinical pharmacology, & trial methodology relied upon empirical approaches
- Patients, developers, investors disadvantaged by slow, costly development
- HIV & cancer advocacy pressured for change in 80’s & 90’s
- By 1990’s, mechanistic understandings and quantitative clinical pharmacology permitted reduced reliance on empiricism

Congressional Hearings leading to the FDA Modernization Act of 1997 (FDAMA)

"Modernizing effectiveness testing in drug development"

- May 2, 1996: Subcommittee on Health and Environment of the House Committee on Commerce
- Feb 21, 1996: Senate Labor and Human Resources Committee
- Feb 21, 1996: Subcommittee on Health and Environment of the House Committee on Commerce
“the science and practice of drug development … evolved significantly in the past 35 years
- implications for the amount and type of data needed to support effectiveness
- Modern clinical trial design often utilizes
  - multiple investigators, multiple study sites, randomization, large enrollment numbers, statistical power, controls, clinical endpoints and other mechanisms that can demonstrate the reproducibility

1 House Commerce Committee, 10/7/97, and Committee of Conference on Disagreeing votes of the two Houses, 11/9/97

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.”

1 House Commerce Committee, 10/7/97, and Committee of Conference on Disagreeing votes of the two Houses, 11/9/97

FDAMA, Sec. 115a

“confirmatory evidence” = “scientifically sound data from any investigation in the NDA that provides substantiation as to the safety and effectiveness of the new drug”

confirmatory evidence = “consisting of earlier clinical trials, pharmacokinetic data, or other appropriate scientific studies”
New Formulations and Doses of Already Approved Drugs

- Where blood levels are not very different, it may be possible to conclude that a drug 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 that a drug is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial.

Attributes of an Adequate Single Trial

- Large multicenter study
  - Consistency
  - Multiple studies in a single study
  - Multiple endpoints involving different events

- Statistically very persuasive finding
  - $P < (0.05 \times 0.05)$ e.g. $< 0.0025$
    - Implied in 1998 Evidence Guidance
    - Achieves > 90% certainty of overall rejection of $H_0$
SUCCESS !?

Single Trial or M&S Approvals

- 505(b1) Approvals (1998 – 2011)*
  - 30/394 = 7.6% – One in Thirteen
    - cancer, hereditary diseases, orphan products
    - 53% open label
    - n = 23 – 18,624 subjects
    - Controls 1:1:1 -> historical : active : placebo
    - Several trials @ p < 0.001

  - 9/198 PMsub ~ 5% provided evidence
    of effectiveness
  - 21/198 ~ 10% supported approval of unstudied doses

Single Trial 505(b1) Approvals

1998-2011*

- Xeloda
- Priftin
- Thymoglobulin
- Temodar
- Cabocidas
- Xigris
- Olafin
- Aralast
- Crosseal
- Fabrazyme
- Aldurazyme
- Aliminta
- Iplex
- Vectibix
- Tyseda
- Torisel
- Tasigna
- Araclyst
- Banzel Oral
- Firmagon
- Almitor
- Effient
- Folotyn
- Carbaglu
- Asclera
- Jevtana
- Pradaxa
- Zytilga
- Brilinta
- Erwinaze


** Garnett C, Goburru J: see References
AdDisruptive Idea

Combine
Bayesian Inference
with
Frequentist Inference
for confirmation of effectiveness

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What is meant by “Frequentist”

■ “Frequentist” stats = inference solely on newly observed data, independent prior data
  □ Frequentists claim fewer assumptions and are critical Bayesian “prior”
  □ Frequentist stats dominate medical product testing, inference, and decisions

What is meant by “Bayesian”

■ “Bayesian statistics is an approach for learning from evidence as it accumulates”*

■ “Bayesian” is a statistical analysis approach for drawing conclusions about a (clinical trial) Hypothesis from observed trial Data, that formally takes account pre-trial Probability of the Hypothesis. (Peck’s definition)

* CDRH Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials
Bayes Theorem (in plain words)

\[ P(H|D) = \frac{P(D|H) \cdot P(H)}{P(D)} \]

1. **Probability of the Hypothesis, updated by trial Data**
2. **Probability of trial Data according the Hypothesis**
3. **Pre-trial Probability of the Hypothesis “PRIOR”**
4. **Probability of the trial Data From all causes**

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Bayes Theorem applied to the Single Clinical Trial Paradigm

- **Substitute frequentist inference:**
  - 90% certainty via frequentist inference of a single trial + “confirmatory evidence”
    - \( p < 0.0025 \)

- **With Bayesian inference:**
  - if “prior” probability of success of a confirmatory trial is 80%,
    - *single trial* \( p < 0.02 \) value, achieves 95%
    - *Type 1 rejection certainty ... NOT < 0.0025 !*

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Examples of Bayesian Stats in Clinical Development & Regulatory Review

- **Bayesian patient PK forecasting** = popPK (prior) + pt data *(1970’s !)*
  - FDA: released mal-manufactured seizure drug @ Bayesian PK of small trial cf in-house popPK data

- **Recent Bayesian clinical trials:**
  - Pravigard (pravastatin + ASA) >> pravastatin or ASA
  - Factor VIII: safety in hemophiliacs
  - Adaptive Randomization: chemoRx Combo’s in AML
DIA Bayesian Scientific Working Group: Use & Challenges Bayesian Methods*

- FDA: CDRH (Devices) >>> CDER/CBER (drugs & biologics)
- Pharma Industry: Phase 1/2 >> Non-clinical
- FDA & Pharma: variable knowledge & receptivity
  - Insufficient knowledge, unclear regulatory receptivity, internal barriers


Points to Consider

- Confirming effectiveness is evolving
  - Due to ups causal knowledge & methodological advances
  - Inefficient, poorly informative, empirical, frequentist inference methods are no longer justifiable
  - Clinical pharmacological & pharmacostatistical learning and Bayesian inference methods can replace frequentist approaches
  - A fallout may be redirection of saved resources to pre-approval safety investigations

References

2. Applications for FDA approval to market a new drug, adequate and well controlled studies, 21 C.F.R. Sec. 214.106.
4. Park CC. Modernizing effectiveness testing in drug development: hearings before the Senate Labor and Human Resources Committee. (Feb 21, 1996).
5. Park CC. Clinical drug development may now be accomplished in less than two years: will FDA and the pharmaceutical industry be ready? Hearings before the Subcommittee on Health and Environment of the House Committee on Commerce, 104th Cong., 2nd Sess. (April 22, 1997).
Some Final Thoughts about FDA

- FDA regulation is science-based
  - Advances innovation
  - Facilitates needed drugs for patients
- FDA clinical guidances are increasingly based on principles of clinical pharmacology
- Benefit of “guidance” versus “regulation”
- FDA guidance
  - National “treasure” versus “national nuisance”
  - A bargain!

End of Presentation