Role of FDA in Guiding Drug Development

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Why FDA?

What comprises FDA guidance?

How does FDA guide drug development?

When does FDA get involved?

Some noteworthy developments at FDA
**Why FDA?**

- FD&C Act: history and its supporters
  - resulted from public safety events or public health challenges
  - a uniquely American phenomenon
    - Investment in FDA
    - Media, Politicization, and Transparency

- Evolution of Drug Regulation (R. Temple)
  
  SAFETY → EFFECTIVENESS → INDIVIDUALIZATION
  .... → PERSONALIZATION → SAFETY → ???

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**What comprises FDA 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 guide drug development?**

- 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

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)

FDA “Question-based Review Template”

- Drug-drug interaction questions
  - In vitro metabolism & transporter studies ?
  - CYP substrate, inhibitor, inducer ?
  - Pharmacogenetic influences ?
  - P-glycoprotein substrate and/or an inhibitor ?
  - Other metabolic/transporter pathways ?
  - Co-administered of active ingredient ?
  - Altered exposure and/or exposure-responses
  - Pharmacodynamic drug interactions ?
  - Active metabolites, protein binding ?
  - PKPD modeling ?
When does FDA get involved?

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

FDA – some note-worthy developments

Efficacy
- Pediatric labeling and FDAMA Section 115a
- Animal Rule & Medical Countermeasure Development

Safety
- PDUFA renewal 2007 – FDAAA

Clinical Pharmacology & Pharmacometrics @ FDA
- Model-based Drug Development (05) (PBPK – 09)

Regulatory & Pharmaceutical Biostatistics
- Fixed trial designs, LOCF, BOCF OUT?
- Bayesian inference, simulations, MMRM IN?
Pediatric Labeling & 1997 FDAMA

- RCT's & Biostatistic
- Chemistry
- Toxicology
- Quantitative Pharmacology, Modeling & Simulation

Pediatric Initiatives in US and Europe

- US
  - Pediatric Exclusivity - 1997
  - Pediatric Research Equity Act - 1998
  - Best Pharmaceuticals for Children Act - 2002
- Europe
  - Better Medicines for Children - 2007
    - Pediatric Investigations Plans (PIPs)
    - Pediatric Marketing Use Authorization (PUMAs)

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
Pediatric Labeling Regulations

“FDA may approve a drug for pediatric use based on ... studies in adults, with other information supporting pediatric use. Additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population. Additional information, such as data on pharmacodynamic studies...”

(21 CFR 201.56)

Mapping S&E Adult Dosage to Children

- Principle - Pediatric effectiveness / safety are inferred via mapping D-E-R from adults to pediatrics
  - Requires
    - Adult Dose-Exposure-Response relationship (PK & ER)
    - Pediatric Dose-Exposure relationship (PK)
    - Confirmatory clinical trial if substantiation is required

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.”
FDAMA, Sec. 115a
CONGRESSIONAL COMMITTEE REPORTS

“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”

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

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 73 NUMBER 6 JUNE 2001

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


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
**Enbrel (etanercept)**

*More Convenient Dosage Regimen Needed*

- Recombinant human TNF receptor blocker
- 1st Approved Adult RA Dosage: 25 mg SC 2x/wk
- PK modeling predicted less frequent dosing:
  - T1/2 ~ 3-5 days
  - 2x dose @ 2x dosing interval
- Proposed: 50 mg SC 1x/week

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**Adult vs Juvenile RA**

**Enbrel PK, 1X & 2X/wk**

- Example - Enbrel (etanercept)
  - Adult RA approved 1998 - 2x/wk dosing
    - 3 RCT's
  - Juvenile RA approved 1999 - 2x/wk dosing
    - Population PK + randomized withdrawal clinical trial
  - Adult RA 1/wk dosing approved 2003
    - Population PK + safety RCT
  - Juvenile RA 1/wk dosing approved 2003
    - Population PK + simulation
  - Adult ankylosing spondylitis, psoriatic arthritis also approved 2003 - M&S only
**“Animal Rule”**

- Alternate FDA approval pathway for CBRN NCM’s when confirmation of human efficacy not ethical or feasible
- Requirements:
  - Reasonably well-understood pathophysiological mechanism of the toxicity of the substance (agent) and its prevention/reduction by the test product
  - Effect is demonstrated in more than one animal species expected to react with a response predictive of human


**SAFETY & 2007 FDAAA**

- 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

**Clinical Pharmacology @ FDA**
Of about a total of 244 NDAs, 42 included a pharmacometrics component. Pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs.

Of 14 reviews that were pivotal to approval decisions, 6 reduced the burden of conducting additional trials.

PM analyses were ranked as important in regulatory decision making in over 85% of the 31 NDAs.

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)

FDA Vision
Pharmacometrics 2020
- Train 500 pharmacometricians
- 100% M&S-based clinical trial designs
- Data analysis & standards for 15 indications
- Publish 250 case studies
Regulatory Biostatistics

- Adaptive Trial Designs – FDA Guidance
- Bayesian Inference, Augmentation Designs & Simulations
- Missing values
  - Recommendation 9: last observation carried forward (LOCF) and baseline observation carried forward (BOCF) ... their underlying assumptions are unrealistic.
  - Recommendation 10: LOCF and BOCF should not be used as the primary approach to the treatment of missing data unless the assumptions ... are scientifically justified.
- FDA critique of LOCF

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