Clinical Pharmacology and The Turning Tide of Drug Regulation

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ASCPT Annual Meeting
Indianapolis, IN
March 8, 2013
Disclaimer

“The fact that we live at the bottom of a deep gravity well, on the surface of a gas covered planet going around a nuclear fireball 90 million miles away and think this to be normal is obviously some indication of how skewed our perspective tends to be.”

— Douglas Adams, The Salmon of Doubt: Hitchhiking the Galaxy One Last Time

The views and opinions expressed in the following slides are mine. Clinical pharmacology is discussed in one context (regulatory evaluation) and, as such, the content is relatively limited in scope.
Outline

• Clinical Pharmacology and the Regulatory Paradox
• Divining the Future of Clinical Pharmacology from its Past
• Accelerating Drug Development Through Clinical Pharmacology: From Inception to Regulatory Action
• The Role of Clinical Pharmacology in Reducing Uncertainty
• Epilogue
The R&D Efficiency Problem: Eroom’s Law

Scannell et al. 2012 [PMID 22378269] | *adjusted for inflation
1° Causes of Eroom’s Law
Problem Statements

• “…regulatory agencies are entirely risk-averse and, as a result, are suppressing remarkable innovation and even frugal opportunities to change medicine.”*

• FDA progressiveness as “irrational exuberance” (see Nissen JAMA 2011) or of questionable public health value (see Moore and Furberg 2012)

• On one hand, reliance on past regulatory decisions creates predictability welcome by drug developers who hope to minimize regulatory uncertainty through interactions with FDA (see Milne 2012)

• On the other hand, there is a continued call for case-by-case regulatory flexibility in FDA’s evidentiary requirements and approach to risk/benefit assessment

* Topol in The Creative Destruction of Medicine
Drug Regulation: Progressive or Regressive?

Medical Innovation: How the U.S. Can Retain Its Lead - Andrew von Eschenbach (WSJ Feb 2012)

In a world where science is advancing at an exponential pace, the FDA must be capable of ensuring that its reviewers know just as much about advances in emerging sciences as the creators of the products they regulate...

The FDA should approve drugs based on safety and leave efficacy testing for post-market studies.

But 1962 wasn’t so long ago...
The Regulatory Paradox and Clinical Pharmacology

• An inherent, but reconcilable, tension between aversion to uncertainty and willingness to accept unknowns about a drug prior to its approval

• Finding the right balance may mean the difference between fostering and stifling innovation

• Clinical pharmacology brings needed clinical, quantitative, and pharmaco-biologic insights to the drug development and regulatory review processes

• Bridges mechanistic reasoning of basic science and provisional empiricism needed in the regulatory evaluation of new therapies
Divining the Future of Clinical Pharmacology from its Past

“Life can only be understood backwards; but it must be lived forwards.”
— Søren Kierkegaard

“What's past is prologue.”
— William Shakespeare, The Tempest
Evolution of Clinical Pharmacology at FDA

- **Now**
  Mechanistic safety; PBPK; Pediatric pharmacology; Pharmacogenomics

- **‘00s**
  Advanced pharmacometrics (D/R, E/R, disease modeling, trial simulation)

- **Late ‘90s**
  Early modeling (IVIVC, PK-PD); Gender effects; Organ impairment

- **Mid ‘90s**
  Dosage forms; Metabolism

- **Early ‘90s**
  BA/BE

- **1980s**
  BA/BE

Evolution of Clinical Pharmacology at FDA
Looking Back – Looking Forward

Evidence Generation

‘62 Amendments

Multisource Data Evaluation
Evolution of Clinical Pharmacology at FDA

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- 1980s: BA/BE
Evolution of Clinical Pharmacology at FDA

1980s: BA/BE

Early ‘90s: Dosage forms; Metabolism

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Late ‘90s: Advanced pharmacometrics (D/R, E/R, disease modeling, trial simulation)

‘00s: Mechanistic safety; PBPK; Pediatric pharmacology; Pharmacogenomics

Now: Evidence generation (e.g., trial design); Individualized therapy; Systems pharmacology; Quality systems/KM
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• Clinical Pharmacology and the Regulatory Paradox
• Divining the Future of Clinical Pharmacology from its Past
• **Accelerating Drug Development Through Clinical Pharmacology: From Inception to Regulatory Action**
• The Role of Clinical Pharmacology in Reducing Uncertainty
• Epilogue
A Sampling of Public Ideas for FDA Reform

[The] pace of new therapeutic development has not kept up with the explosion in scientific knowledge...this situation poses an increasing challenge for ensuring the creation of innovative therapies for patients...There was broad recognition among these stakeholders that there are a wide range of issues that must be solved, only a minority of which are at the FDA. - PCAST

- Progressive drug approval
- “Weight-of-evidence” standard
- “Reasonable likelihood of patient benefit” standard
“Adaptive Licensing”: Balancing Evidence and Access

Accelerated approval (surrogates) | Fast track (“rolling” submissions)
Priority review (6 mo review clock) | Priority review vouchers | PSA

Eichler 2012 [PMID: 22336591]
FDA Flexibility in Approvals: 2011-2012

- **Review Clock**
  - Standard: 57%
  - Priority: 43%

- **Designation**
  - Fast Track: 41%
  - Standard: 59%

- **Approval Mechanism**
  - Standard: 91%
  - Accelerated: 9%
Early Interaction is a Major Correlate of Clinical Development Times

Leveraging clinical pharmacology information will be particularly critical in such areas as "breakthrough" therapy, targeted therapy, and rare disease drug development, where drug development programs will need to be mechanistically-informed by design, and where regulators must deliberate non-conventional mechanisms for evidence generation.

Data courtesy K. Sinicrope, L. Bauer, and A. Pariser, Rare Diseases Program, CDER Office of New Drugs
Breakthrough Therapy

• Drug (alone or in combination)
  – intended to treat a serious or life-threatening disease or condition
  – 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

• A sponsor may request “breakthrough therapy” designation at any time during drug development (under an IND). FDA must then promptly decide 1) whether the product meets the definition of a breakthrough therapy, and 2) what steps should be taken to “expedite the development and review of the application for approval”
Breakthrough Therapy

- FDA will take an “all hands on deck” approach to enhance communication with the drug’s developer (on relevant issues of trial design, evidence generation, product quality, diagnostic development, etc.) to expeditiously complete drug development.

20 requests
9 reviewed
11 under review

5 granted
4 not granted
Breakthrough Therapy

1. What can be considered “clinically significant endpoints”?
2. What constitutes “preliminary clinical evidence” of the drug’s potential to offer substantial advantages over available treatment options?
3. How can these data be best generated?

Because designation is contingent upon preliminary clinical evidence of substantive drug effects, these data will likely be generated in “phase” 1 and 2 trials.
Impact on Drug Evaluation
Targeted Therapy Defined
(for our purposes)

Drug whose mechanism of action (and hopefully benefit) is through modulation of biological processes through interaction with a specific molecular target.

OR

Drug proposed to have a treatment effect in a subset of patients based on empirical clinical evidence, experimental evidence, pharmacological evidence or rationale, or biological reasoning (we’ll get to all of this).

OR

Drug for which knowledge of patient “status” can inform any of a number of individualized treatment decisions (dosing, choice of therapy, monitoring).
Personalized Medicine: Potential and Reality

LATE DEVELOPMENT FAILURES

- Financial and/or commercial: 21%
- Safety (including risk-benefit): 7%
- Not disclosed: 6%
- Efficacy:
  - Versus placebo: 32%
  - As add-on therapy: 29%
  - Versus active control: 5%

ROLE IN INDUSTRY

PMs comprise 12-50% of current company pipelines; <10% of projects are “stratified”

Advancing Regulatory Science at FDA

Regulatory Science
Science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products

Vision
FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community.
1. Modernize toxicology to enhance product safety

2. Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes (clinical trial designs/methodologies, leveraging clinical trial data, biomarker qualification, “virtual patient”)

3. Support new approaches to improve product manufacturing/quality

4. Ensure FDA readiness to evaluate innovative emerging technologies

5. Harness diverse data through information sciences to improve health outcomes

6. Implement a new prevention-focused food safety system

7. Facilitate development of MCM to protect against threats to health

8. Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products
<table>
<thead>
<tr>
<th>Driver</th>
<th>Current State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology</td>
<td>Getting cheaper, robust, leading to enhanced understanding of disease/drug response variability.</td>
</tr>
<tr>
<td>Health IT</td>
<td>EMRs implemented in major healthcare systems. Informatics solutions for data extraction in place. Biomarker data integrated to identify markers of response and ADRs.</td>
</tr>
<tr>
<td>Regulation</td>
<td>Guidances spanning the early through late development spectrum. Clarity around IVD pathway developing. Increasing number of markers (e.g., PGx) in drug labels.</td>
</tr>
<tr>
<td>Payers</td>
<td>Adoption of ‘NICE’ approach drives more scrutiny of value. Reimbursement of IVDs. Restricted formularies.</td>
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<tr>
<td>Advocacy groups (e.g., PMC, FOCR)</td>
<td>Incubators for developmental approaches and regulatory considerations for targeted therapies.</td>
</tr>
<tr>
<td>Pharma</td>
<td>Multiple approvals with IVDs (oncology and non-oncology). “Stratified medicine” as part of planning.</td>
</tr>
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Review Activity in the PM Space - 2012

Composition of NDA/BLA Reviews

- Oncology
- Cardiorenal
- Neurology
- Antiviral
- Pulmonary
- Psychiatry
- Other

- Organ Dysfunction
- In vivo DDI
- In vitro DDI
- Pharmacometrics
- Transporters
- Genomics
- Immunogenicity
- Safety
- PBPK

2007 vs 2012
## Advice Across All Stages of Clinical Drug Development

<table>
<thead>
<tr>
<th>Phase</th>
<th>Pre-IND</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21%</td>
<td>14%</td>
<td>22%</td>
<td>29%</td>
<td>14%</td>
</tr>
</tbody>
</table>

![Pie chart showing distribution of advice across stages](chart.png)

- **Allocation**: 2% of advice
- **Assay Development**: 15% of advice
- **Biospecimen**: 15% of advice
- **Data Analysis**: 9% of advice
- **Endpoints/PD**: 24% of advice
- **Patient Selection**: 31% of advice
- **Treatment**: 4% of advice

CY 2012 INDs
<table>
<thead>
<tr>
<th>Drug Development Program Feature</th>
<th>Review/Policy Issue</th>
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<tbody>
<tr>
<td>Predictive enrichment (based on baseline enrichment factor measurement)</td>
<td>Need for enrolling patients without enrichment factor for safety and/or efficacy assessment</td>
</tr>
<tr>
<td>Enroll only biomarker (+) patients (high prevalence)</td>
<td>Question of need for Dx as part of indication if prevalence of diagnostic “positivity” is very high (e.g., &gt;90%)</td>
</tr>
<tr>
<td>Enroll only biomarker (+) patients (“positive” comprised of several rare mutations with putative functional similarity)</td>
<td>Ability to adequately assess efficacy in each rare mutation group; how to appropriately label</td>
</tr>
<tr>
<td>Predictive enrichment (PD responder-run in)</td>
<td>Appropriateness of the PD endpoint</td>
</tr>
<tr>
<td>Primary efficacy assessment in biomarker-defined subset (continuous or ordinal variable)</td>
<td>Pre-specification of diagnostic cut-off; post-hoc refinement of cut-off</td>
</tr>
<tr>
<td>Exclude genetic subgroup from first-in-human studies because of safety concerns (e.g., PMs)</td>
<td>Need for assessment of excluded subgroup later in development/post-approval; appropriate dosing and labeling; need for Dx</td>
</tr>
<tr>
<td>Variable drug exposure in subgroups (e.g., genetic)</td>
<td>Strategy for dose optimization during development (e.g., exploratory assessment vs. pre-emptive dose reductions)</td>
</tr>
<tr>
<td>In vitro diagnostic needed</td>
<td>Analytical issues; cross-center coordination</td>
</tr>
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Patient Subset Effects – Targeted Therapy Approaches

Multimodal PK

High Variability

Race Effects
Experience-Based Guidances

• Guidance for Industry: Clinical Pharmacogenomics – Premarketing Evaluation in Early Phase Clinical Studies

• Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices

• Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
Clinical Pharmacology Issues in Enrichment Designs

- What factors support appropriateness of studying only marker (+) patients?
- What factors determine what kind/amount of data you need in marker (-)?
- What patient factors or extrinsic considerations will be important in designing trials that minimize response heterogeneity (either treatment or placebo)?
- What factors should be considered in the design of trials that employ predictive (vis-à-vis prognostic) enrichment strategies?
Characteristics in Support of Targeted Drug Development

<table>
<thead>
<tr>
<th><strong>Biomarker</strong></th>
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<tbody>
<tr>
<td>Biomarker is the major pathophysiological driver of the disease to be studied</td>
</tr>
<tr>
<td>Limited or adverse paradoxical activity of the drug is seen in a subgroup</td>
</tr>
<tr>
<td>identified through in vitro or animal models (e.g., cell lines or animals</td>
</tr>
<tr>
<td>without the biomarker)</td>
</tr>
<tr>
<td>The biomarker is the known molecular targeted of therapy</td>
</tr>
<tr>
<td>Preliminary evidence of harm from early phase clinical studies in patients</td>
</tr>
<tr>
<td>without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of lack of activity from early phase clinical studies</td>
</tr>
<tr>
<td>in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of modest benefit in an unselected population, but</td>
</tr>
<tr>
<td>the drug exhibits significant toxicity</td>
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Adaptability is Important

SCREENING TRIAL
Investigational drugs and biomarkers → Achieve surrogate end point predictive of clinical outcome → Promising drug candidate and associated biomarker

CONFIRMATORY TRIAL
Promising drug candidate and associated biomarker → Replicate surrogate end point → Achieve clinical outcome (regulatory standard for FDA approval)

FDA APPROVAL
Accelerated drug approval, Approval of biomarker, Full drug approval
The Role of Clinical Pharmacology in Reducing Uncertainty

“I took a test in Existentialism. I left all the answers blank and got 100.”

— Woody Allen
Outline

• Clinical Pharmacology and the Regulatory Paradox
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• Accelerating Drug Development Through Clinical Pharmacology: From Inception to Regulatory Action
• The Role of Clinical Pharmacology in Reducing Uncertainty
  – Model-informed Drug Development and Evaluation
  – Evaluation of Proposed Biosimilars
  – Antibiotic Drug Development
• Epilogue
Model-Based Drug Development Today

**Chemistry models**
- Dosing
- TK/evaluation
- PBPK
- Human PK/PD Prediction

**Exposure models**
- DDI
- PK/PD
- Dose escalation
- Dose ranging
- Biomarkers
  - Study endpoints
  - Disease progression

**Biology Models**
- Statistical/empirical

Most modeling in regulatory review is currently exposure-based and done using sponsor data, supplemented as needed with basic information on disease processes, drug properties, and patient populations.
Integrated View of Modeling in Drug Review

Preclinical | IND | Clinical | NDA | Post-Approval
---|---|---|---|---

**Chemistry models**
- SAR safety alerts
- ADME prediction

**Exposure models**
- Dosing
- TK/evaluation
- PBPK
- Human PK/PD Prediction
- DDI
- PK/PD
- Dose escalation
- Dose ranging

**Mechanistic Models**
- Knowledge integration
- Toxicity prediction
- Risk evaluation
- Risk translation
- Drug-disease interactions
- Drug-patient interactions

- Study endpoints
- Disease progression
- Biomarkers

- Signal confirmation (6 mo. safety review)
- PK/PD Bridging
- Pediatrics
- Elderly
- Dosage forms

- Efficacy/Safety
- Toxicity
- Outcome drug
- Outcome placebo

(Courtesy of T. Colatsky)
Needs – The Foreseeable Future

• Efficient mechanisms to engage with drug developers early and in real-time (i.e., during the “learn” phase of the “learn-confirm” paradigm) to discuss the role of modeling in the development of a given novel therapeutic

• Knowledge management systems to leverage modeling in ways that inform regulatory guidance development

• Best practices for community vetting of [mechanistic] models for a variety of uses (including regulatory)
  – Decision making
  – Labeling
### Biosimilars
- Biosimilarity, not *de novo* demonstration of safety and effectiveness
- Chemical and pharmacologic comparisons
- “Assay sensitivity”
- Based on CPT knowledge, most appropriate readout, most relevant doses or [drug], most sensitive population
- Indication extrapolation
- Extensive consideration of CP

### Antibiotics
- Microcosmic/ongoing innovation
- Large, empirical NI trials to evaluate efficacy in MDR generally not feasible
- New methods to assess antibiotic efficacy (mechanistic extrapolation; IVIVC and modeling; PK/PD extrapolation; animal models)
- CDER Antibiotic Drug Development Task Force
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The Regulatory Paradox Revisited

• Artifact of a drug development paradigm that did not lend itself to thorough exploration of the disease-drug-patient interface (absence of appropriate scientific evaluative techniques)

• This is changing: “fail” fast by design; “win” (sometimes fast) by design?

• Greater industry-academia-regulatory interactions will be required to better define channels (and practices) for timely application of clinical pharmacology advances.

• Increased scientific traction in areas of drug target pharmacology (understood as systems), molecular signaling, and physiological drug access may not be translating

• Scientific, non-regulatory interactions with FDA for discussions of rapidly evolving areas could be effective in ensuring contemporary clinical pharmacology thinking is incorporated into drug development, regulation, and use
A Holistic (Pharmaco-biologic) View

- Communicate
- Quantify value
  - Empirically
  - Modeled
- Characterize/Account for Variability
  - PK
  - PD
- Characterize Effects
  - Systems approaches
- Define Disease
  - Model Disease
  - Subset Pathologies
  - Subset Patients
Key Initiatives - 2013

“Action expresses priorities.”
— Mahatma Gandhi

1. Identification
   • Catalogue of guidances

2. Certification
   • Justification for revision

3. Revision
   • Work plan and delivery
Take Away Points

• Clinical pharmacology is a critical translational science that can bridge empiricism and mechanistic reasoning needed in drug development and evaluation.

• From a regulatory standpoint, a refocus on evidence generation methods and multisource data integration/evaluation is critical.

• Clinical pharmacology considerations will be paramount in areas of like breakthrough therapy, targeted therapy, rare disease drug, biosimilar, and antibiotic development.

• Quantitative methods remain important in reducing regulatory uncertainty, and renewed dialogue is needed.

• OCP at FDA is committed to key initiatives that will help realize a holistic approach to therapeutic product development, regulation, and use.
Acknowledgments

• FDA Office of Clinical Pharmacology
  – Effort and content

• FDA Office of Translational Sciences
  – Scientific support and leadership

• Dr. Janet Woodcock
  – Concepts (forthcoming in CPT)