Enabling Next Generation Pharmaceutical Safety Assessment: An Evolution

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GlaxoSmithKline

Opinions expressed are those of the author rather than the employer
Key components

- Motive
- Opportunity
- Strategy
- Partnership
There are good reasons for us to be interested in novel ways of working!

**KEY FACTS 2015**

**RESEARCH AND DEVELOPMENT (R&D)**
- Average time to develop a drug = **more than 10 years**
- Percentage of drugs entering clinical trials resulting in an approved medicine = **less than 12%**

**DEVELOPMENT COSTS**
- Average cost to develop a drug (including the cost of failures):²
  - 2000s–early 2010s = $2.6 billion
  - 1990s–early 2000s = $1.0 billion
  - 1980s = $413 million
  - 1970s = $179 million

**R&D SPENDING**

<table>
<thead>
<tr>
<th>Year</th>
<th>PhRMA members³</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>$51.2 billion (est.)</td>
</tr>
<tr>
<td>2013</td>
<td>$51.6 billion</td>
</tr>
<tr>
<td>2012</td>
<td>$49.6 billion</td>
</tr>
<tr>
<td>2011</td>
<td>$48.6 billion</td>
</tr>
<tr>
<td>2010</td>
<td>$50.7 billion</td>
</tr>
<tr>
<td>2009</td>
<td>$46.4 billion</td>
</tr>
<tr>
<td>2008</td>
<td>$47.4 billion</td>
</tr>
<tr>
<td>2007</td>
<td>$47.9 billion</td>
</tr>
<tr>
<td>2006</td>
<td>$43.0 billion</td>
</tr>
<tr>
<td>2005</td>
<td>$39.9 billion</td>
</tr>
<tr>
<td>2000</td>
<td>$26.0 billion</td>
</tr>
<tr>
<td>1990</td>
<td>$8.4 billion</td>
</tr>
<tr>
<td>1980</td>
<td>$2.0 billion</td>
</tr>
</tbody>
</table>

**SALES**
- Generic share of prescriptions filled:⁴
  - 2000 = 49%
  - 2013 = 88%
An analysis of the attrition of drug candidates from four major pharmaceutical companies

Michael J. Waring¹, John Arrowsmith², Andrew R. Leach³, Paul D. Leeson³,⁴, Sam Mandrell², Robert M. Owen⁵, Garry Pairenqueau¹, William D. Pennie⁶,⁷, Stephen D. Pickett³, Jibo Wang⁸, Owen Wallace⁸,⁹ and Alex Weir²

Table 1 | Populations of the primary cause of failure categories for terminated compounds*

<table>
<thead>
<tr>
<th>Termination reason</th>
<th>Overall</th>
<th>Period</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2000–2005</td>
<td>2006–2010</td>
</tr>
<tr>
<td>Clinical safety</td>
<td>68 (11%)</td>
<td>48 (13%)</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Commercial</td>
<td>40 (7%)</td>
<td>23 (6%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>55 (9%)</td>
<td>45 (11%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Formulation</td>
<td>9 (1%)</td>
<td>4 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Non-clinical toxicology</td>
<td>240 (40%)</td>
<td>144 (40%)</td>
<td>96 (40%)</td>
</tr>
<tr>
<td>Patent issue</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Pharmacokinetics or bioavailability</td>
<td>29 (5%)</td>
<td>19 (5%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Rationalization of company portfolio</td>
<td>124 (21%)</td>
<td>46 (13%)</td>
<td>78 (32%)</td>
</tr>
<tr>
<td>Regulatory</td>
<td>2 (0.3%)</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Scientific</td>
<td>33 (5%)</td>
<td>28 (8%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Technical</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>605</td>
<td>362</td>
<td>243</td>
</tr>
</tbody>
</table>

*Table entries for each column indicate the total number and the percentage in parentheses.
Lots of new opportunity!

Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization

Jane P.F. Bai and Darrell R. Abernethy

ASSOCIATE EDITOR: ERIC L. BARKER

Computational Methods in Drug Discovery

Gregory Sliwoski, Sandeepkumar Kothiwal, Jens Meiler, and Edward W. Lowe, Jr.

Meiler Laboratory, Center for Structure Biology, Vanderbilt University, Nashville, Tennessee
Leveraging the opportunity

- Alignment on the gaps and the opportunities best suited to fill those gaps
- Clearly defined context of use for alternative test systems
- Sense of what it takes to build confidence in a different approach
  - biological relevance, data, experience
- Willingness to accept managed risk
- Freedom to operate
- Collaboration with shared goals
Strategic Context of Use

Capabilities

Bioinformatics
Phenotypic assays
Activity assays
Animal studies
Patient studies

Human tissue
Binding assays
-omics

Target ID & validation
Hit/lead discovery
Lead optimisation
Candidate selection
Preclinical safety
Clinical assessment

#compounds
1000’s
100’s
10’s
1-3

Freedom to operate
Regulated expectations

Liability characterization at molecular design - opportunity for non-animal platforms
Challenges of applying a novel modeling strategy early in discovery

- Sufficient biological complexity with adequate throughput
- Accounting for the biology not in the platform (novel platforms, though less reductionist, will be reductionist)
- Defining what you’re measuring against
- Accounting for dose/exposure extrapolation
- Interpreting more mechanistic endpoints
- Considering rapid changes in scope of drug modalities (small molecules, Ab therapies, oligonucleotides, cell/gene therapy)
- Designing a different intellectual framework
- Impacts on cost and time
- Building a reason to believe!
We know where to start

• IQ Dru Safe Attrition of Pharmaceuticals during Preclinical Development
  – 282 compounds
  – 16 pharma contributors
  – contemporary data

• Primary target organs
  – CV, liver, kidney, GI, CNS, testes
  – ~70% of preclinical safety attrition
  – We don’t have to replicate the 15K data points in a 28d rat study
Design-Test-Implement- IQ/NCATS/FDA partnership as a model

IQ Microphysiological Systems Working Group
Organotypic Standards- Cardiovascular
Berridge, B. R., IQ MPS Working Group, HESI Cardiac Safety Technical Committee

Introduction

- The cardiovascular system is dynamic and integrated with significant adaptive function, intra-system interdependencies and non-CV influences.
- It is an important source of drug safety liabilities for which in vivo mammalian systems have been important for identifying and characterizing.
- The myocardium, heart valves, and intra- and extra-cardiac arteries are primary targets of both structural and functional toxicity.
- Contemporary assessments of CV safety include assessment of cardiac rhythm and contractility, systemic blood pressure, heart rates and morphology of the heart and blood vessels.
- An appropriately robust, human-relevant MPS system could provide near term opportunities for early screening as well as a means to differentiate species-specific effects.
- MPS systems are likely to be more mechanistically informative.

Cardiovascular response to toxic injury, endpoints and test compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Classification</th>
<th>Endpoint</th>
<th>Systemic/Local</th>
<th>Intra-cardiac</th>
<th>Test method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds</td>
<td>Safety</td>
<td>Toxicity</td>
<td>Response Phenotype</td>
<td>Response Phenotype</td>
<td>Response Phenotype</td>
</tr>
<tr>
<td>Compounds</td>
<td>Toxicology</td>
<td>Cardiovascular</td>
<td>Response Phenotype</td>
<td>Response Phenotype</td>
<td>Response Phenotype</td>
</tr>
<tr>
<td>Compounds</td>
<td>Pharmacology</td>
<td>Cardiovascular</td>
<td>Response Phenotype</td>
<td>Response Phenotype</td>
<td>Response Phenotype</td>
</tr>
</tbody>
</table>

What does cardiovascular toxicity look like?

- Important physiological features of the CV system
  - Integrated system with significant interdependence, reserve capacity and dynamic function.
  - Significant biological integration at the system (heart and blood vessels), tissue (cardiomyocytes and capillaries) and cellular (cardiomyocyte ion channel) levels.
  - High energy requirements, substrates = fatty acids + glucose, oxygen, high number of mitochondria.
  - Relative lack of regenerative capacity in the myocardium.
  - Functional changes manifest in changes in fluid dynamics. Changes in fluid dynamics can induce structural changes.

- MPS systems express drug transporters and they can be mediators of toxicity but not always completely characterized.

Relating in vitro to in vivo endpoints

- Relate the platform to a specific component of the integrated system
- Demonstrate relevant in vivo morphologic and functional attributes
- Test known positive and negative compounds for specific outcomes
- Representing a spectrum of mechanisms relevant in vivo doses
- With predefined success criteria
- Know how to respond to the data - e.g.
- Stop development
- Needs further characterization
- Validates animal data

Contextualizing other capabilities

- Be able to represent appropriate content of use, throughout, value proposition, weaknesses

Building Confidence

- Demonstrate relevant in vivo morphologic and functional attributes
- Test known positive and negative compounds for specific outcomes
- Representing a spectrum of mechanisms relevant in vivo doses
- With predefined success criteria
- Know how to respond to the data - e.g.
- Stop development
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Contact Information

brian.s.berridge@ash.com
Roadmap

Define critical target organs of tox and AOPs

Define critical DMPK organs, processes and endpoints

Define biological and analytical standards for these target organs/processes

Evolution of Application

Pre-animal Safety Screens

Comparative application with in vivo safety studies

Virtual second safety species

Seek ready now solutions

Seek ready soon solutions

Co-develop and/or test those solutions

Embed/industrialize

PPP Incubator
The ultimate value proposition

• Improved predictive validity of early preclinical models = lower attrition
  – DMPK + safety in the first instance
  – Parallel application of the principles of this approach to specific disease areas improves efficacy modeling in the second

• Decreased cycle time by bringing the best lead forward the first time (avoids iterative assessment of multiple leads pre-CS)

• Enables early risk:benefit integration
• Decreases animal use
• Lowers development costs
• Efforts in innovation more efficient and impactful in the near term
**Alternatives Development Strategy Impact**

**Opportunistic Strategy (current)**

- **Salient features**
  - Representative of current ‘crowd-sourced’ innovation
  - Adoption and confidence in alternative platforms will steadily increase with development out-pacing adoption
  - Animal use will be impacted as confidence grows

- **Pros**
  - Slow gradual change in behaviour
  - No change in investment
  - Animal use will decline as confidence increases
  - Clinical predictivity could increase
  - Unrestricted innovation
  - Regulatory acceptance not needed

- **Cons**
  - Investment not optimally leveraged; lots of wasted resource
  - Progress slow
  - Improvements in clinical predictivity and decreases in animal use minimal over the short term (5-10 yrs.)
  - Additive assessments

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**Graph details**

- **Y-axis**: # animals/assays
- **X-axis**: Time/years
- **Lines**:
  - Red: Rodents
  - Green: Non-Rodents
  - Purple: Alternatives
Alternatives Development Strategy Impact

**Salient features**
- Defined by a bold aspirational goal - i.e. single species safety package
- Alternatives development defined by the prioritized scope of in vivo assessments
- Rate of animal use impact increases with time

**Pros**
- Deliberate innovation defined by current standards
- Significant alignment and complementarity of investment
- Significant decrease in animal studies - particularly for non-rodents
- Clinical predictivity could/should increase

**Cons**
- Significant global coordination
- Regulatory acceptance required for full impact
- Structured development and qualification process
- Innovation directed

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**Holistic Strategy (Single species)**

<table>
<thead>
<tr>
<th>Time/years</th>
<th># animals/assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>10, 8, 6</td>
</tr>
<tr>
<td>4</td>
<td>8, 6, 4</td>
</tr>
<tr>
<td>6</td>
<td>6, 4, 2</td>
</tr>
<tr>
<td>8</td>
<td>4, 2, 0</td>
</tr>
<tr>
<td>10</td>
<td>2, 0</td>
</tr>
</tbody>
</table>

- **Rodents**
- **Non-Rodents**
- **Alternatives**

Incentive-driven