Successes, Threats, Challenges and Opportunities of Early Discovery Safety Pharmacology: Learning from the past.

Jean-Pierre Valentin, PhD

Global Head Safety Pharmacology, Safety Assessment UK, AstraZeneca R&D, Alderley Park, Macclesfield, SK10 4TG, Cheshire, United Kingdom

E-mail: jean-pierre.valentin@astrazeneca.com
Challenges

Annual New Molecular Entity (NME) & New Biologic Entity (NBE) Approvals vs. R&D Expenditures in 2009 Dollars

Report to the US President on “propelling innovation in drug discovery, development and evaluation”. US President’s Council of Advisors on Science and Technology (PCAST). September 25th 2012
## Impact of adverse effects of drugs by organ function throughout the pharmaceutical life cycle

The various toxicity domains have been ranked first by contribution to products withdrawn from sale, then by attrition during clinical development. Note general agreement between pairs of equivalent studies. BM = bone marrow.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Preclinical</th>
<th>‘Nonclinical’</th>
<th>Phase I AZ</th>
<th>Phase I</th>
<th>Phase I-III</th>
<th>Phase I-III</th>
<th>Phase III/Marketing</th>
<th>Post-Approval</th>
<th>Post-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information:</td>
<td>Causes of attrition</td>
<td>Causes of attrition</td>
<td>Dose-limiting ADRs</td>
<td>Serious ADRs</td>
<td>Causes of attrition</td>
<td>Causes of attrition</td>
<td>ADRs on label</td>
<td>Serious ADRs</td>
<td>Withdrawal from sale</td>
</tr>
<tr>
<td>Sample size:</td>
<td>156 CDs stopped</td>
<td>88 CDs stopped</td>
<td>14 CDs with dose-limiting ADRs</td>
<td>1,015 subjects</td>
<td>63 CDs stopped</td>
<td>82 CDs stopped</td>
<td>1,138 drugs</td>
<td>21,298 patients</td>
<td>47 drugs</td>
</tr>
</tbody>
</table>

**Cardiovascular:**
- 24% stopped
- 27% stopped
- 7% 1,015 subjects
- 9% 63 CDs stopped
- 35% 82 CDs stopped
- 21% 1,138 drugs
- 36% 21,298 patients
- 15% 47 drugs
- 45% Withdrawal from sale

**Hepatotoxicity:**
- 15% stopped
- 8% stopped
- 0% 1,015 subjects
- 7% 63 CDs stopped
- 29% 82 CDs stopped
- 21% 1,138 drugs
- 13% 21,298 patients
- 0% 47 drugs
- 32% Withdrawal from sale

**Haematology/BM:**
- 3% stopped
- 7% stopped
- 0% 1,015 subjects
- 2% 63 CDs stopped
- 3% 82 CDs stopped
- 4% 1,138 drugs
- 16% 21,298 patients
- 10% 47 drugs
- 9% Withdrawal from sale

**Nervous system:**
- 12% stopped
- 14% stopped
- 71% 1,015 subjects
- 28% 63 CDs stopped
- 2% 82 CDs stopped
- 21% 1,138 drugs
- 67% 21,298 patients
- 39% 47 drugs
- 2% Withdrawal from sale

**Immunotox; photosensitivity:**
- 7% stopped
- 7% stopped
- 0% 1,015 subjects
- 16% 63 CDs stopped
- 10% 82 CDs stopped
- 11% 1,138 drugs
- 25% 21,298 patients
- 34% 47 drugs
- 2% Withdrawal from sale

**Gastrointestinal:**
- 5% stopped
- 3% stopped
- 36% 1,015 subjects
- 23% 63 CDs stopped
- 2% 82 CDs stopped
- 5% 1,138 drugs
- 67% 21,298 patients
- 14% 47 drugs
- 2% Withdrawal from sale

**Reprotox:**
- 9% stopped
- 13% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 5% 82 CDs stopped
- 1% 1,138 drugs
- 10% 21,298 patients
- 0% 47 drugs
- 2% Withdrawal from sale

**Musculoskeletal:**
- 8% stopped
- 4% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 5% 82 CDs stopped
- 1% 1,138 drugs
- 28% 21,298 patients
- 3% 47 drugs
- 2% Withdrawal from sale

**Respiratory:**
- 1% stopped
- 2% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 2% 82 CDs stopped
- 0% 1,138 drugs
- 32% 21,298 patients
- 8% 47 drugs
- 2% Withdrawal from sale

**Renal:**
- 6% stopped
- 2% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 5% 82 CDs stopped
- 9% 1,138 drugs
- 19% 21,298 patients
- 2% 47 drugs
- 0% Withdrawal from sale

**Genetic tox:**
- 5% stopped
- 5% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 0% 82 CDs stopped
- 0% 1,138 drugs
- 0% 21,298 patients
- 0% 47 drugs
- 0% Withdrawal from sale

**Carcinogenicity:**
- 0% stopped
- 3% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 3% 82 CDs stopped
- 0% 1,138 drugs
- 1% 21,298 patients
- 0% 47 drugs
- 0% Withdrawal from sale

**Other:**
- 4% stopped
- 0% stopped
- 0% 1,015 subjects
- 0% 63 CDs stopped
- 2% 82 CDs stopped
- 4% 1,138 drugs
- 16% 21,298 patients
- 2% 47 drugs
- 2% Withdrawal from sale
## Challenges

### Impact of adverse effects on drug development in 2010

<table>
<thead>
<tr>
<th>Impact</th>
<th>Trial halted/ delayed/ development stopped</th>
<th>Delays to approval (requests for further data etc.)</th>
<th>Non-approval</th>
<th>Publications on adverse effects</th>
<th>Prescribing restrictions / labelling (etc.)</th>
<th>Litigation (patients)</th>
<th>Withdrawal from sale</th>
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</thead>
<tbody>
<tr>
<td>Number of therapies affected:</td>
<td>18</td>
<td>20</td>
<td>12</td>
<td>46</td>
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<td>Cardiovascular:</td>
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<td>Carcinogenicity:</td>
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<td>*Metabolic/ Endocrine:</td>
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<td>*Drug-drug interactions:</td>
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<td>*Exacerbation of the disease:</td>
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<td>Other/ Not specified:</td>
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</tbody>
</table>

Organ functions listed in same order as previous slide; ‘Genetic tox’ dropped (zero throughout); *new categories. Data from ‘DIA Daily Alert’ throughout 2010: predominantly covers North American and European regulatory territories and markets. ‘Therapy’ = combination of a drug with a disease.
<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>Therapeutic target</th>
<th>Functional adverse effect</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 Oct</td>
<td>Qnexa</td>
<td>Obesity</td>
<td>Tachycardia [and embryotox]</td>
<td>Non-approval (US)</td>
</tr>
<tr>
<td>22 Oct</td>
<td>Saquinavir-ritonavir (in combination)</td>
<td>HIV</td>
<td>QT prolongation → TdP</td>
<td>Labelling (US)</td>
</tr>
<tr>
<td>21 Oct</td>
<td>GnRH agonists</td>
<td>Prostate cancer</td>
<td>Metabolic syndrome → MI; stroke</td>
<td>Labelling (US)</td>
</tr>
<tr>
<td>20 Oct</td>
<td>Bydureon</td>
<td>Type II diabetes</td>
<td>QT risk</td>
<td>FDA requested TQT study (after reviewing NDA)</td>
</tr>
<tr>
<td>12 Oct</td>
<td>Adusuve Staccato (inhilation)</td>
<td>Agitation during schizophrenia/bipolar disorder</td>
<td>Respiratory (reduced FEV)</td>
<td>Non-approval (US)</td>
</tr>
<tr>
<td>11 Oct</td>
<td>Meridia (sibutramine)</td>
<td>Obesity</td>
<td>Increased risk of heart attack &amp; stroke</td>
<td>Withdrawn from market (US)</td>
</tr>
<tr>
<td>11 Oct</td>
<td>Fibanserin</td>
<td>Female hypoactive sexual desire disorder</td>
<td>Depression, anxiety, fatigue</td>
<td>Development abandoned</td>
</tr>
<tr>
<td>24 Sep</td>
<td>Avandia</td>
<td>Type II diabetes</td>
<td>Increased risk of heart attack &amp; stroke</td>
<td>Withdrawn from market (EU); restricted use (US)</td>
</tr>
<tr>
<td>17 Sep</td>
<td>Lorcaserin (Lorgess)</td>
<td>Obesity</td>
<td>Increased risk of heart attack &amp; stroke</td>
<td>Non-approval (US)</td>
</tr>
<tr>
<td>16 Sep</td>
<td>Valganciclovir (Valcyte)</td>
<td>Paediatric transplantation</td>
<td>Abdominal pain, vomiting, diarrhoea, tremor, seizure.</td>
<td>Labelling (US)</td>
</tr>
<tr>
<td>13 Sep</td>
<td>Taspoglutide</td>
<td>Type II diabetes</td>
<td>Nausea and vomiting</td>
<td>Suspension of Phase III trial</td>
</tr>
<tr>
<td>02 Sep</td>
<td>Tigecycline</td>
<td>Infection</td>
<td>Death</td>
<td>Physicians advised to consider alternatives (US)</td>
</tr>
</tbody>
</table>

**Challenges**

Impact of **functional** adverse effects on drug development – over a 2 months period!

- Functional AEs should be predictable from primary, secondary or safety pharmacology.....
Challenges
Can we track & predict functional & structural adverse effects?

Mechanism of action of drugs result from activity at primary, secondary targets or non-specific interactions.
Challenges

Dx Safety Pharmacology: What can we do about it?

• **Target Related Safety**
  - Review of target biology to identify potential toxicological issues due to primary pharmacology
    • Hypothesis-based experiments to confirm/refute potential issues
    • Toxicological data support or reject target validity

• **Chemistry Related Safety**
  - Early identification of potential toxicology associated with chemical series
    • Proprietary in silico tool to identify potential chemical related toxicities
    • Hypothesis-based experiments to confirm/refute potential issues
    • Toxicology data support or reject chemical series
    • Toxicology data used to influence chemical design

• **Patient & Disease Safety Context**
  - Seeks to understand the impact of a patient profile and disease-relevant phenotype on a toxicity outcome and vice versa

• **Translational Safety**
  - Understand the translatability of non-clinical safety assays and models to volunteers, patients in the disease context and back translation
Challenges & Opportunities

The past (?)
Extent of SP involvement

The present (?)
Extent of SP involvement

The challenge

Success ?

- SP issues identified;
- NO SP issues

Target Identification → First Administration to Man → Drug Launch

DISCOVERY

Drug Launch
First Administration to Man
Target Identification

R&D | Innovative Medicines | Global Safety Assessment
Successes
Impact of Safety Pharmacology data

**In silico** prediction:
- Pathway mapping
- Structure Activity Relationship

Confidence in the target

Problem solving

Predicting clinical outcome

Influencing Phase I design

Clinical biomarker

Contributing to clinical plan

Supporting Toxicology studies

Drug interactions

Resumption of clinical trial

Influencing chemistry
Successes

**in silico prediction**

- Molecular modelling for hERG prediction

- Virtual screening of many compounds - avoids wasting resources making compounds highly likely to be potent hERG blockers

Successes
Influencing chemistry

- Screen-out hERG activity (□) or find chemical starting points with low hERG liability (□) for project X

- Delivery of Candidate Drugs with reduced hERG liability

Graphs showing the sequence of synthesis for hERG and Primary Target with IC\textsubscript{50} (μM) and Ki (μM) values.
• Early anti-histamines caused side-effects such as dry mouth
  – Due to antagonist activity at muscarinic receptors
• Second-generation compounds have lost muscarinic activity
  – No cholinergic side-effects
• AZD1234 does not have muscarinic activity
  – Unlikely to cause dry mouth in the clinic
  – Improved patient compliance
Successes
Problem solving

- Screening out liability identified in CD – cardiac Na channel (NaV1.5) in project Y

- Improved cardiac safety profile of back-up series

**Compound Y - Slowed action potential upstroke in vivo**
Successes
Problem solving & influencing Phase I design

• Effects of ‘Compound X’ on dark-adapted ERG in the rat

Molecular target of Compound X was known to be located in the retina. Potential for adverse effect on retinal function. ERG study undertaken to assess any functional effects, their reversibility and to evaluate the retinal cell types involved.

**a-wave:** photoreceptors and possibly retinal pigment epithelium (RPE).

**b-wave:** Müller cells and bipolar cells.

Note the loss of b-wave between the low and intermediate dose levels; a-wave largely unaffected.

This revealed the functional deficit was either on transmission between photoreceptors and bipolar cells, or on the bipolar cells.

Tolerance developed during repeat-dosing.

Effect was reversible after cessation of dosing.

• Outcome enabled progression into clinical development with ERG monitoring.
Use of a knock-out mouse strain for the receptor of interest, to determine whether there was any change in baseline gastric emptying (marginal in this case), or in the inhibitory effect of atropine (no-effect).

Method used for assessing gastric emptying was residual weight of stomach contents 15 min after a charcoal meal.

This was an enabling study ahead of testing the ligand interacting with the receptor of interest.

Redfern et al. Poster 79 (this meeting).

- Provided confidence in the target for project progression
Use of a knock-out mouse strain for the receptor of interest, to determine whether there was any change in excitability of hippocampal slices or in the seizurogenic response to a ligand at the receptor.

Population Spike (PS) area (the area above and below the 0 mV line) was determined.

The compound caused an increase in excitability of the slice preparations, indicated by an increase in PS area.

This was clearly not mediated by its primary target.

Redfern et al. Poster 79 (this meeting).

**Successes**

**Confidence in the target**

- **Target-related seizurogenic potential**

- **Provided confidence in the target for project progression**
Successes
Problem solving, CD selection

- Off target pharmacology related side effects

Issue: Poor tolerability in rats with lead compound (↓ body weight, ↓ Faecal pellet count, stomach distension)

Hypothesis: Poor selectivity against IGF/IR in vitro translates to modulation of glucose homeostasis & inhibition of gastric emptying in vivo

Proven

Impact on project:
- Single dose studies allowed rapid explanation for poor tolerability of leads
- Compounds de-selected from shortlist
- Project drives against IGF/IR activity
- Current lead compound ‘2748 has 30 fold↑ IGF selectivity & improved in vivo tolerance

<table>
<thead>
<tr>
<th>Compound</th>
<th>IGF cell (uM)</th>
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<tr>
<td>'0729</td>
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<td>'8357</td>
<td>0.16</td>
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<tr>
<td>'0484</td>
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<tr>
<td>'2748</td>
<td>3.30</td>
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Successes
Influencing Phase I design & predicting outcome

- Negative inotropic effect: translation to the clinic

**Issue:** Negative inotropic effect seen in all preclinical models. Influence Phase I monitoring & biomarkers (troponin, left ventricular function).

**Impact:** Cardiac AEs observed clinically. Unacceptable risk / benefit profile. Compound discontinued from development.
Opportunities

• Societal & Economical drivers
  – Patients
  – Payers
  – Develop & implement cost effective, timely & efficient approaches
  – Collaborations, consortia, co-operations
  – Scientific societies

• New targets & new approaches to treat diseases
  – Develop & refine strategies to assess the safety of:
    • Agents that act at novel molecular sites
      – Cell membrane, intracellular, intra-nuclear
    • New therapeutic modalities
      – Gene therapy, Biopharmaceuticals products, Combinations
Opportunities

- **Science & Technology**
  - Scientific development: to improve our ability to detect, predict and eliminate human safety liabilities
    - PK / PD relationship
    - Predictive value of pre-clinical assays to humans
    - Predicting safety in pathophysiological conditions
    - Human stems cells

Opportunities

- **Science & Technology**
  - Leveraging legacy safety studies; Sharing pre-competitive data
  - Focus on areas of high impact and/or high incidence?
    - Cardiovascular & nervous systems, Gastrointestinal system
  - To identify and incorporate new technologies
    - *In silico* approaches: to predict drug effects on molecular entities, cardiac action potential
    - *In vitro* assays & screens: e.g., optical action potential measurement, “Human on a chip”, stem cells
    - *In vivo* models: e.g., non-invasive telemetry system, Zebrafish larvae based assays, Non-invasive clinical modalities (e.g., Imaging)
Challenges & Opportunities

- Science & Technology

- Number of compounds tested per year

- Year

- Purkinje fibre action potential - MANUAL (2000-2005)
- hERG assay - MANUAL (2000-2003)*
- Dog telemetry QT/CV (1999-)
- Non-invasive telemetry: repeat-dose QT/CV (2003-)
- In silico hERG (2003-)
- IonWorks™ hERG (2003-)
- Optical action potential (2006-)

*NB Manual hERG assay retained for GLP regulatory studies
Challenges & Opportunities

• Regulatory Requirements
  – Influence & implement new, stringent regulatory requirements
    • Increasing number and scope reflecting increasing regulatory concerns
    • Dialogue between key opinion leaders from Industry, CROs, Academia and Regulatory agencies
  • Animal usage 3Rs: Reduction, Refinement, Replacement
Challenges & Opportunities

- **Training, Education, Communication**
  - Attract, train and certify investigators in integrative approaches to physiology, pharmacology & toxicology
  - Training & education
  - Funding for training & education
  - Publications, Webinars, Social Media....
Acknowledgement

• Safety Pharmacology Departments in AstraZeneca, in particular all the Team Leaders / Head of Departments:

  • Ahmad Al-Saffar*
  • Russ Bialecki
  • David Baker #
  • Joanne Bowes
  • Ann-Christin Ericsson*
  • Lorna Ewart
  • Silvana Lindgren*
  • Chris Pollard
  • Michael Swedberg*
  • Will Redfern

  # New starter;
  * leaving the organisation