The Innovative Medicines Initiative (IMI)

IMI - Safety Needs and Perspective

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Head of Exploratory Development in Europe
Co-Director of the Predictive Safety Testing Consortium
EFPIA Research Directors’ Group (as deputy of P. Hemling)

Innovative Medicines Initiative Information Day and National Platforms Meeting, Madrid, October 10th 2007
**Agenda**

<table>
<thead>
<tr>
<th>Safety Need - Background</th>
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</thead>
<tbody>
<tr>
<td>Example of Consortium from the Critical Path Initiative (CPI): The Predictive Safety Testing Consortium (PSTC)</td>
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<tr>
<td>Example of a Consortium from the InnoMed Initiative: The PredTox I Consortium</td>
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<tr>
<td>Privileging Synergies over Competition</td>
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<tr>
<td>Safety Topics of interest which could be considered in IMI</td>
</tr>
<tr>
<td>Conclusion</td>
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</tbody>
</table>
What are we trying to solve?

- Increasing cost of innovation
  - greater emphasis on real improvement over existing drugs
  - greater emphasis on safety
  - failure to tackle attrition along the value chain
- Downward pressure on prices
- Pressure to tackle major societal issues
  - environment
  - bioterrorism
  - antibiotic resistance
  - neglected diseases (rare or third world)
- Industry reputation

SAFETY IS A KEY ELEMENT EVERYWHERE!!
The Strategic Research Agenda focuses on the “pre-competitive” bottlenecks in the R&D Process.

Knowledge Management

- Predictive pharmacology
- Predictive toxicology
- Identification of biomarkers
- Patient recruitment
- Validation of biomarkers
- Benefit/Risk assessment with regulatory authorities

Efficacy

Safety

Education & Training
## Global recognition of the problem

<table>
<thead>
<tr>
<th>Europe</th>
<th>USA</th>
<th>Japan</th>
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<tbody>
<tr>
<td><strong>Innovative Medicines Initiative (EU)</strong></td>
<td><strong>FDA Critical Path Initiative</strong></td>
<td><strong>Toxicogenomics Project (J PMA)</strong></td>
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<tr>
<td><strong>InnoMed / PredTox I Project</strong></td>
<td><strong>The Biomarkers Consortium (FNIH/PhRMA/FDA/NIH)</strong></td>
<td><strong>Proteome Factory Consortium (J PMA)</strong></td>
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<tr>
<td><strong>Top Institute Pharma (Netherlands)</strong></td>
<td><strong>Critical Path Institute (University of Arizona)</strong></td>
<td><strong>Large-scale Clinical Trial Network</strong></td>
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<td><strong>Medicamentos Innovadores (Spain)</strong></td>
<td><strong>Predictive Safety Testing Consortium</strong></td>
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<td><strong>Safety Biomarkers (UK)</strong></td>
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Opportunities and threats?

- New technologies (proteomics, lipidomics, imaging, etc.) are allowing quantum leap progress in understanding the biology underlying safety signals.
- The readiness for increased cooperation between stakeholders was never so high (safety finally considered pre-competitive).
  - But...
- Too many parallel initiatives are starting on similar topics (resources are limited; danger of polluting each others results; loss of time, ...)
- Need for Health Authorities to be somehow involved otherwise a lot of work may be lost (not easy).
SAFETY: Making Medicines Safer

Main recommendations from the Strategic Res. Agenda:
- Create a European Centre for Drug Safety Research
- Establish a framework for biomarker development to study human relevance and regulatory utility
- Develop computational methods for predicting toxicity
- Understand relevance of rodent non-genotoxic carcinogenicity and intractable toxicities
- Pharmacovigilance: Develop novel methods of risk prediction and benefit-risk assessment

Expected outcomes:
- Reduced late stage failure
- Better post-marketing risk-benefit analysis
- Higher rate of approval based on improved risk management
- Reduced burden of mandatory post-approval trials
- Faster delivery to patients but with reduced risk
Agenda

• Safety Need - Background

Example of Consortium from the Critical Path Initiative (CPI): The Predictive Safety Testing Consortium (PSTC)

Example of a Consortium from the InnoMed Initiative: The PredTox I Consortium

• Privileging Synergies over Competition

• Safety Topics of interest which could be considered in IMI

• Conclusion
Novartis / FDA CDER Biomarker CRADA

Objectives

- Novartis and FDA work together in a Cooperative Research And Development Agreement:

1. To identify a process by which biomarkers for safety can be qualified for use in regulatory decision-making
2. To qualify kidney safety biomarkers for regulatory decision making in pre-clinical settings
3. To propose the qualification for human
   → Kidney subgroup of the Predictive Safety Testing Consortium (C-Path Institute)
Predictive Safety Testing Consortium (PSTC)

- Announced by HHS/FDA on March 16, 2006 as part of Critical Opportunities List

- The Critical Path Institute (C-Path) is a third party, partner, and project catalyst
  - A non-profit, publicly-funded Institute that serves as a “neutral ground”
  - Founding partners include: FDA, SRI International, and The University of Arizona
  - Executed Memorandum of Understanding with the Food and Drug Administration Dec 16, 2005
  - FDA and EMEA scientists serve as advisors
CPI Opportunity # 46

- 46. Identification and Qualification of Safety Biomarkers.
  - “Collaborative efforts to pool and mine existing safety and toxicology data would create new sources for identification and qualification of safety biomarkers. …”
We are hopeful that as a result of our efforts, the group will contribute data, scientific information, tools, and the regulatory basis to:

- **Validate predictive, pre-clinical animal model biomarkers** aimed at reducing the cost and time of pre-clinical safety studies.

- **Provide potential early indicators of clinical safety in drug development and post-marketing surveillance.**

- **Provide new tools for FDA to assist in regulatory decision making.**
PSTC Goals

• **To cross-qualify pre-clinical animal model biomarkers aimed at reducing the cost and time of pre-clinical safety studies**

• **To use the combined resources, sample sets, novel compounds, and expertise to generate a biomarker data package convincing enough for FDA/EMEA qualification as an approved biomarker**

• **To provide potential early indicators of clinical safety in drug development and post-marketing surveillance.**
  - Note the long-term goal of **translational** biomarkers

• **To develop new tools for FDA and EMEA to assist in regulatory decision making.**
Consortium Members

- Abbott
- Amgen, Inc
- Astra Zeneca
- Boehringer Ingelheim
- Bristol-Myers Squibb
- GlaxoSmithKline
- Iconix Pharmaceuticals
- Johnson & Johnson Pharmaceutical R&D
- Eli Lilly, Inc
- Merck & Co., Inc.
- Novartis
- Pfizer, Inc.
- Roche
- Sanofi-aventis U.S. Inc
- Schering Plough Research Institute
- Wyeth
Regulatory Advisors

**FDA**
- Federico Goodsaid
- James L. Weaver
- Joseph Hanig
- Karol Thompson
- David Jacobson-Kram
- Michael Orr
- Weida Tong
- Felix Frueh
- Wendy Sanhai

**EMEA**
- Spiros Vamvakas
- Jean-Marc Vidal
- Klaus Olejniczak
- Marisa Papaluca-Amati
- Nirosha Amerasinghe
- Peter Kasper
- Romalda Maciulaitis
- Sonja Beken
- Markku Pasanen
- Beatriz Silva Lima
- Bernd Liedert
Role of FDA and EMEA

- Regulatory body participation is key to interactively develop a cross-validation process leading to regulatory qualification.
- FDA/EMEA are not members, but act as advisors and are present in all the working groups except the Membership Subcommittee.
- They may be consulted for input on decisions of the Advisory Committee.
- When appropriate agreements with the FDA (e.g. CRADA) may be developed for specific projects.
- Representatives from the PMDA are now also participating in global conf. calls.
General Criteria for Projects

- Speed up and/or reduce cost of preclinical drug safety evaluation.
- Improve our understanding of mechanisms of toxicity.
- Provide novel tools for troubleshooting compounds that fail studies in preclinical drug safety assessment.
- Provide potential early indicators of clinical safety.
- Have a clear “IP Path”.

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General Approach to Cross Validation

1. Share pre validation work conducted to date within each company

2. Concisely define aims for each cross validation program
   » regulatory significance?
   » goals for how this will impact the critical path initiative?

3. Specific Projects: general flow
   » Define methods and protocols
   » Define commitments and responsibilities of the participants (Project Agreement)
   » Data generation
   » Data analysis <---> Data Management Subcom.
Working Groups and Teams

• Five Injury Area Working Groups
  - Nephrotoxicity
  - Hepatotoxicity
  - Vascular Injury
  - Carcinogenicity
    • Focus on signatures of non-genotoxic carcinogenicity
  - Myopathy
• Data Management Subcommittee
• Translational Team
Types of Analytes Considered

• **Enzymatic assays**
  - E.g. GLDH

• **ELISA assays**
  - Preference for multiplex assays

• **Small molecules**
  - E.g. F(2)-isoprostanes

• **Genomic Signatures**
  - Useful for assessing non-genotoxic carcinogenicity
  - Genomics useful for identifying other candidate biomarkers
Selected PSTC Progress

- **Hepatotoxicity Working Group**
  - Four candidate biomarker assays identified for initial cross-qualification
  - Standard auto-analyzer enzymatic assays

- **Nephrotoxicity Working Group**
  - ELISA assays for urinary biomarkers
  - Data package for biomarker qualification submitted to FDA and EMEA on June 15, 2007
Biomarker Qualification Submission

- Data from 23 compounds for 7 urinary biomarkers (KIM-1, Cystatin C, B2-Microglobulin, Albumin, Total Protein, Clusterin, TFF-3)
- First submission of its kind under the FDA Voluntary Data Submission (VXDS) process
- Joint submission on June 15, 2007 to both FDA and EMEA
- Face to face meetings on July 12, 2007 and Oct 9, 2007
- Almost all outstanding issues addressed
- Decision on submission claims anticipated in November/December, 2007
**All Studies: Proximal Tubular Necrosis**

Area Under Curve:
- Random = 0.5
- **Creatinine** = 0.78
- **BUN** = 0.76
- **Kim-1** = 0.95
- **Clusterin** = 0.90

51 Diseased
292 Controls
All Studies: Glomerular Alteration / Damage

Area Under Curve:

- Random = 0.5
- Creatinine = 0.52
- Urinary Protein = 0.86
- Urinary Cystatin C = 0.91
- Urinary b2-Microglobulin = 0.89

41 Diseased
291 Controls
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FP6 Integrated Project – Innovative Medicines Initiative (IMI)

... Bid Submitted in November-2004

- 2 Consortia with 43 partners
  - PredTox - Predictive Toxicology
    - (see separate slides)
  - AddNeuroMed
    - Discovery of new markers for Alzheimer’s disease

- Project details
  - Total cost: 21’000’000 €
  - Proposal passed evaluation Apr-2005
  - Contract to signed in Dec-2005
  - Duration: ~ 40 months
FP6 Integrated Project – “PredTox”

Ultimate Goals of the Project

• Assess the value of combining results from ‘omics technologies together with the results from more conventional toxicology methods in more informed decision making in preclinical safety evaluation
• Initiate and support the development of scientists within the novel field of Systems Toxicology
• Critically review the value of this approach together with Regulatory Authorities and finally agree upon the approach for their use
<table>
<thead>
<tr>
<th>Companies</th>
<th>Altana</th>
<th>Bayer</th>
<th>Boehringer-Ingelheim</th>
<th>Johnson &amp; Johnson</th>
<th>Lilly (B) - no EU funds</th>
<th>Merck KGaG</th>
<th>Novartis</th>
<th>Novo-Nordisk</th>
<th>Organon</th>
<th>Roche,</th>
<th>Sanofi-Aventis (D)</th>
<th>Sanofi-Aventis (F)</th>
<th>Schering</th>
<th>Serono</th>
<th>Servier</th>
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<tr>
<td>Universities</td>
<td>University of Wuerzburg</td>
<td>Univ. College Dublin</td>
<td>University Hacettepe</td>
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<td>Small and Mid-size Enterprise (SME)</td>
<td>Genedata</td>
<td>Ciphergen - no EU funds</td>
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• In vivo animal studies in rats with up to 16 compounds
  - Study design
    • 5 male Wistar rats per group
    • 2 dose levels and vehicle control group
    • 3 evaluation time points (24 hr, 3 days and 14 days)
  - Investigations
    • Primary targets: liver, kidney, blood, urine
    • “Classical” endpoints in Toxicology studies (e.g. clinical chemistry, histopathology)
    • “omics”-technologies (transcriptomics, proteomics, metabonomics)
• Data management
  • Design, construction and population of a relational DB
  • Data processing and development of biostatistical models
• Mechanistic investigation and biomarker identification and qualification
  • ... using cell and molecular biology methodology
### Co-ordination and Workpackages (WPs)

<table>
<thead>
<tr>
<th>WP</th>
<th>Responsible</th>
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<tbody>
<tr>
<td>Coordination</td>
<td>Friedlieb Pfannkuch; David Tweats</td>
</tr>
<tr>
<td>Contract Issues, Budget and Administration</td>
<td>Paul Crompton, Arttic Consultancy</td>
</tr>
<tr>
<td>3.1.1 Compound Selection</td>
<td>Susanne Schroeder, Altana</td>
</tr>
<tr>
<td>3.1.3 In vivo Study Design</td>
<td>Kirstin Meyer, Schering</td>
</tr>
<tr>
<td>3.2.2 Gene Expression</td>
<td>Laura Suter-Dick, Roche</td>
</tr>
<tr>
<td>3.2.3 Metabonomics</td>
<td>Alexander Amberg, Sanofi-Aventis, D</td>
</tr>
<tr>
<td>3.2.4 Proteomics</td>
<td>Jean-Charles Gautier, Sanofi-Aventis, F</td>
</tr>
<tr>
<td>3.3 Database / IT</td>
<td>Maria Wendt, Genedata</td>
</tr>
<tr>
<td>3.4 Data analysis and modeling</td>
<td>Hans Gmuender, Genedata</td>
</tr>
<tr>
<td>3.5 Mechanistic investigations</td>
<td>Angela Mally, University of Wuerzburg</td>
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WP3.1.1
Compound Selection

• **Requirements**
  – Pharmaceuticals
    • Exhibiting toxicity in the rat after 2 – 4 weeks
  – Morphological endpoints of toxicity
    • Liver: necrosis, cholestasis, steatosis, hypertrophy
    • Kidney: tubular necrosis, crystallization

• **Challenges**
  – Identification of compounds
    • Development discontinued due to liver or kidney toxicity
    • Reference compound for hepat- and nephrotoxicity
  – Qualification
    • Best fit with the requirements
  – Availability of the respective compound
  – Approval by Management and Legal departments
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• **Chemical Effects in Biological Systems (CEBS) programme of the US - NIEHS**
  - Pharmaceuticals involved in the trial; 19 compounds had been studies by October 2005

• **Japanese Consortium on Toxicogenomics**
  - Includes over 100 liver and kidney toxins integrating standard toxicology / pathology endpoints with transcriptomics
  - Results not available before 2010

• **C-Path Institute (Tucson, Arizona, USA)**
  - Predictive Safety Testing Consortium

• **InnoMed**
  - PredTox I
## Comparison of EU FP6 - ‘PredTox’ and C-Path - ‘Predictive Safety’

<table>
<thead>
<tr>
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<th>EU FP6 - 'PredTox' Project</th>
<th>US C-Path Predictive Safety Testing Consortium</th>
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<tbody>
<tr>
<td>Co-ordination</td>
<td>EFPIA (Brussels, B)</td>
<td>C-Path Institute (Tucson, Arizona, USA)</td>
</tr>
<tr>
<td>Scientific contact</td>
<td>Friedlieb Pfannkuch (Roche)</td>
<td>Jacky Vonderscher (Novartis) / Bill Mattes (C-Path)</td>
</tr>
<tr>
<td>Membership</td>
<td>Altana, Bayer, <strong>Boehringer-Ingelheim</strong>, Johnson &amp; Johnson, Lilly (B), Merck KGaG, <strong>Novartis</strong>, Novo-Nordisk, Organon, <strong>Roche</strong>, Sanofi-Aventis (D), Sanofi-Aventis (F), Schering, Serono, Server</td>
<td>Astra-Zeneca, <strong>Boehringer-Ingelheim</strong>, Bristol-Myers Squibb, GlaxoSmithKline, Johnson &amp; Johnson, Merck, <strong>Novartis</strong>, Pfizer, <strong>Roche</strong>, Schering Plough</td>
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<tr>
<td></td>
<td>3 Universities and 1 SME</td>
<td>FDA (as active observer - not member)</td>
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<tr>
<td>Goals</td>
<td>Identification of new biomarkers</td>
<td>Qualification of predictive, pre-clinical animal model biomarkers and Clinical biomarkers</td>
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<td>Investigations on value of new 'omics approaches</td>
<td>Provision of potential early indicators of clinical safety</td>
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<td>Elucidation of mechanisms of toxicology</td>
<td>Molecular Signatures of Toxicities</td>
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<td></td>
<td>Provision of new tools to assist in regulatory decision making</td>
<td>Qualification Process Map for Safety Biomarkers</td>
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<tr>
<td>Focus</td>
<td>Hepato-, nephrotoxicity</td>
<td>Hepato-, nephrotoxicity, genotoxic and non-genotoxic carcinogens; vasculitis</td>
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<tr>
<td>Approach</td>
<td>14 Pharmaceutical compounds after discontinued development and 2 reference compounds</td>
<td>10 Companies to share data, samples, assays to cross-validate panels of markers through process acceptable to HAs to move safety biomarkers from the “Probable Valid Biomarkers” to “Known Valid Biomarkers”</td>
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<tr>
<td>Specific Feature</td>
<td>Data analysis and data integration</td>
<td>Data Integration</td>
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<tr>
<td>Support by Member</td>
<td>EU Commission to project: about € 4'000'000 ~ € 100'000 per year</td>
<td>US Government to C-Path Institute: ($ 5'000'000) ~ $ 25'000 per year + cross-validation studies</td>
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<tr>
<td>Duration</td>
<td>3 years (2005-2008)</td>
<td>open (1st qualified BMs expected in 2007)</td>
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Synergies of EU FP6- ‘PredTox’ and US C-Path- ‘Predictive Safety’

- Both projects focus on the value of conventional and new biomarkers.
- The ‘PredTox’ project is intending to identify new markers of early safety testing in development of new drugs.
- The ‘C-Path Consortium’ puts main emphasis on validation of already available and new biomarkers and their use for regulatory purposes (preclinically & clinically).
- There are many synergies since both projects pursue the same goals with differences only regarding phase of the development process.
- The first step should be that the scientific coordinators of both projects start a mutual discussion on practical aspects of a potential collaboration,
  - e.g. information exchange
  - e.g. further analysis of potential synergies as soon as first results from both projects will become available.
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Safety needs which could potentially lead to Call topics for 2008-2009-...

- PredTox II (qualification in rodents of markers found in PredTox I)
- Validation of Translational Biomarkers from Non-Clinical to Clinical Pharmacology (Process, assays, ....)
- Immunogenicity predictive models and mechanisms
- Predictive models/s signals for non-genotoxic carcinogens
- Immunotoxicity risk factors
- In Silico Predictive expert systems
- Translational safety imaging biomarkers
- Cardiac safety Pharmacology
- ....
<table>
<thead>
<tr>
<th>1</th>
<th>Topic Title</th>
<th>Provide with a clear topic title</th>
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</table>
| 2 | Project description | Describe the envisaged research program  
What approaches are envisioned  
(Maximum 2 pages) |
| 3 | Key Deliverables of the project | What the project aims to achieve after completion  
(Maximum 1 page) |
| 4 | EFPIA Participants in the project | Name EFPIA companies which plan to participate in the project |
| 5 | Role of EFPIA Participants in the project | EFPIA Participants in the project will contribute  
(Maximum 2 pages) |
| 6 | Indicative duration of the project | X years |
| 7 | Indicative total in kind contribution from the EFPIA companies | €X mio |
| 8 | Indicative expectations from the Public Consortium | What are the deliverables expected from the Public Consortium  
(Maximum 1 page) |
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Conclusions

- **IMI is a huge opportunity to discover and develop tools and processes which will allow the various stakeholders in the Drug Development and Health fields to improve the handling of safety signals provided:**
  - that we focus on the essential questions
  - that we are very demanding re. deliverables & timelines
  - that we build on synergies and avoid (bad) competition
  - that we find a way to involve the HAs very early
  - that we can engage strong academic groups to team up with industry