One European Perspective: Changing the Paradigm for Safety Testing of Pharmaceuticals in Europe.

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Disclaimer

The Views expressed in this presentation are of my own responsibility and may not reflect those of my affiliation Institutions
Drug Development from A – Z

Discovery & Screening

In silico
- QSAR; Prediction & Simulation

In vitro
- Mutagenicity (Ames); hERG assay
- Cellular assays

In vivo animal studies

In human Exploratory Trials (ICH M3R2)

Lead Candidate Selection

Preclinical Development (Safety, PoC)
Safety Testing Program

No Stand Alone

Single Dose Studies

Repeated Dose Studies

Additional studies: immunotox; juvenile animals, neurotox

Carcinogenicity

1 life-span + 1 additional model

Genotoxicity

• in vitro
• in vivo

Reproduction Toxicology

• fertility
• embryofetal toxicity
• peri-post natal toxicity

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The Paradigm is Getting Old
How old??

1955 (US) 2014

1957

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1955- USA
Pharmacodynamics (BP, HR, Respiration)
• Acute toxicity (dose response, minimum 3 species)
• sub-acute toxicity (1 or more species; 6-12 weeks)
• Chronic toxicity
• Carcinogenicity (1960s)
• External effects (skin irritation, sensitization)
• Special studies:
  • Reproduction
  • Hematology
  • Absorption / Distribution / Excretion..

1983- Europe (Notice to Applicants)
• Pharmacokinetics
• Single dose Toxicity (2 species)
• Repeated Dose Toxicity (2 species)
  – Sub-acute
  – chronic
• Reproduction Toxicity
• Genotoxicity
• Carcinogenicity
• Other studies

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### Historical background on Safety Testing EUROPE – ICH

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1991</td>
<td>ICH - Harmonisation - New Topics - Revisions</td>
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<tr>
<td></td>
<td>- Core Study Packages Unchanged</td>
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<tr>
<td></td>
<td>- Testing Strategies Reformulated / Updated</td>
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<td>- Following Science / Technology Innovation</td>
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#### Paradigm Enriched but Format Unchanged

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But High Attrition Rates Persist! WHY?

• Insufficient screening?

• Wrong lead candidate selection?

• Insufficient animal predictivity? (PoC, safety)

• Inadequate Clinical Paradigms?

• All those reasons together?
Drug Innovations and Paradigm Adaptations (nonclinical)

- **Biopharmaceuticals:**
  1 species; 6 Month studies; no carcinogenicity (WOE) vitro only acceptable (if nonrelevant species)

- **Biosimilar mAbs:** mostly comparability in vitro

- **Nanopharmaceuticals:** size-based concerns?

- **Advanced Therapies (CTMP; GTMP)**
  risk anticipation; case-based design
Risk Assessment for Advanced Therapies

Risk Management

Effectiveness Measurement

Risk Minimisation & Communication

Risk Identification

Risk Profiling

Quality
Non-Clinic
Clinic

Risk-Based Approach

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NC Paradigm Improvement: what is needed?

• **Efficacy**: Reinforce knowledge on:
  • Disease
  • Target involvement on disease
  • Target biology
  • Target distribution
  • Target mediated cascades
  • Cascades Cross talk

• **Safety**:
  – Models for improved human predictivity

IMPACT ON CLINICAL PARADIGM?

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Re-Thinking Drug Development in Europe: The Innovative Medicines Initiative:

*Joining Forces in the Healthcare Sector*
IMI Nonclinical Safety Projects

• Intensive Joint Research Initiatives towards:
  – In silico: databases Structure-Toxicity relationship
  – In vitro toxicity prediction: liver, kidney, vascular
  – Cancer biomarkers
  – Human cell culturing systems (iPS)
    • Healthy
    • patients
Development of reliable toxicity predictive systems

- 6th release of the Vitic Nexus eTOX database
  831 substances (584 confidential) linked to 1,703 study designs
  (Bayer, Boehringer, Esteve, GlaxoSmithKline, Lundbeck, Novartis, Pfizer, Roche, Sanofi, Servier, and UCB)

- 3rd release of the ChOX database
  411 toxicology-linked targets; 162,287 distinct compounds and 701,181 activities

- Version 1 of the integration system, eTOXsys, was released to all partners
  7 out of 10 companies have already a running system.

- 90 predictive models developed
MIP-DILI  Mechanism based improved prediction of drug-induced liver injury

Summary Work Plan
In vitro models in MIP-DILI

HepG2: Wild type and reporter models Leiden

Human HepaRG Rennes

Primary Human Hepatocytes KaLyCell

Selected currently used in vitro toxicity models (e.g. HepG2, THLE, human heps, BSEP inhibition)

Evaluation via MIP-DILI

Cell models and expertise provided by EFPIA partners

Comparative
- Biology
- Compound Disposition
- Toxicology
using absolute quantification
WP4: Liverpool

Human liver bioreactor Stockholm

Human ES and human iPS-derived hepatocytes Cellartis

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Evaluated 153 potential biomarker candidates for drug-induced injury of the kidney, liver, and vascular system

17 exploratory clinical studies started or completed

> 6500 retrospective samples collected

Dialogue with Regulatory Agencies established

- Providing access to a huge amount of most relevant clinical safety data across all pharmaceutical companies and all major drug classes
- A drug safety signal detection system across global regulatory data is being set up initially with EMA data, driven by IMI and EFPIA
hESCs and iPSCs are Pluripotent: They have the potential to differentiate into all tissue of an adult.
Science is Pushing Paradigm to Shift

- Molecular attributes
- Pharmacology / Target
- Pharmacokinetics (in vitro/in silico)
  - absorption
  - transport
  - metabolism
- Toxicity prediction (MoA and QSARS)
- Toxicity testing
- In vitro systems (human based)
  - healthy condition
  - disease condition

First in Human study
- Exploratory approaches
- PK / PD characterization
- Biomarkers Based
- Efficacy
- Safety

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Which Paradigm Shift?

Discovery & Screening

**In silico**
- Databases on QSAR; Modelling & Simulation
- Omics integration; Systems Biology

**In vitro**
- Mutagenicity (Ames); hERG assay
- iPSCs
- Human cell systems
- 3D cultures
- Organs in Chip

**In human**
- Exploratory Trials (ICH M3R2)

Lead Candidate Selection
Paradigm Shift: Which Path to Take?

• From observational/reactive approach – General toxicity studies in animals then mechanistic

• Into Predictive/proactive approach:
  integrated MoA/in silico/in vitro / (in animal) / in human
A Scientists Drive...

• Scientist profile also changing

  – Scientific Cross Talk
    • Physics
    • Medicine
    • Engineering
    • Electronics
    • Computer systems

Regulators
Regulatory Scientists

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Impact on Regulatory Framework

• Current situation:
  multiple safety guidelines for multiple endpoints
  (mainly animal based)

• The future: strategy oriented guideline (s)
  (integrating omics/in silico/in vitro/in human)
  nonclinical / clinical cross talk
How to “Validate” a New paradigm?

• Test by test?

• Innovative tests vs animal tests?

• Outcomes?:
  innovative program vs human
How to “Validate” a New paradigm?

Outcomes:

i) know molecules:
   innovative program vs human

ii) new molecules (pilot exercises)
   “Paralel Path” : both classical and new paradigm
Thank You!!