Safer Medicines

From bench to FDA, validation of in vitro methods:

who is responsible for independent validation of *in vitro* tests?

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Safer Medicines Trust

Thank OpenTox for the invitation to speak

- Opentox is an Integrating framework
  - "Integrating components creates solutions"
    - QUESTION:
      - **Are these solutions going to gain acceptance? How? What is the path?**

OpenTox Day 1 take home messages

- Integrating preclinical, clinical and new in vitro ADMET information is difficult
- We are building the tools to:
  - Get the unified platform
  - Create uniformly and publicly available databases
  - Build toxicity prediction models
- Questions:
  - Can we avoid doing new studies?
  - What types of studies would move the field towards broader acceptance of new toxicology tools based on human biology as we understand it today?
  - How do we conduct the validation studies so that we see the tests universally accepted before they are outdated (AMES, e.g.)

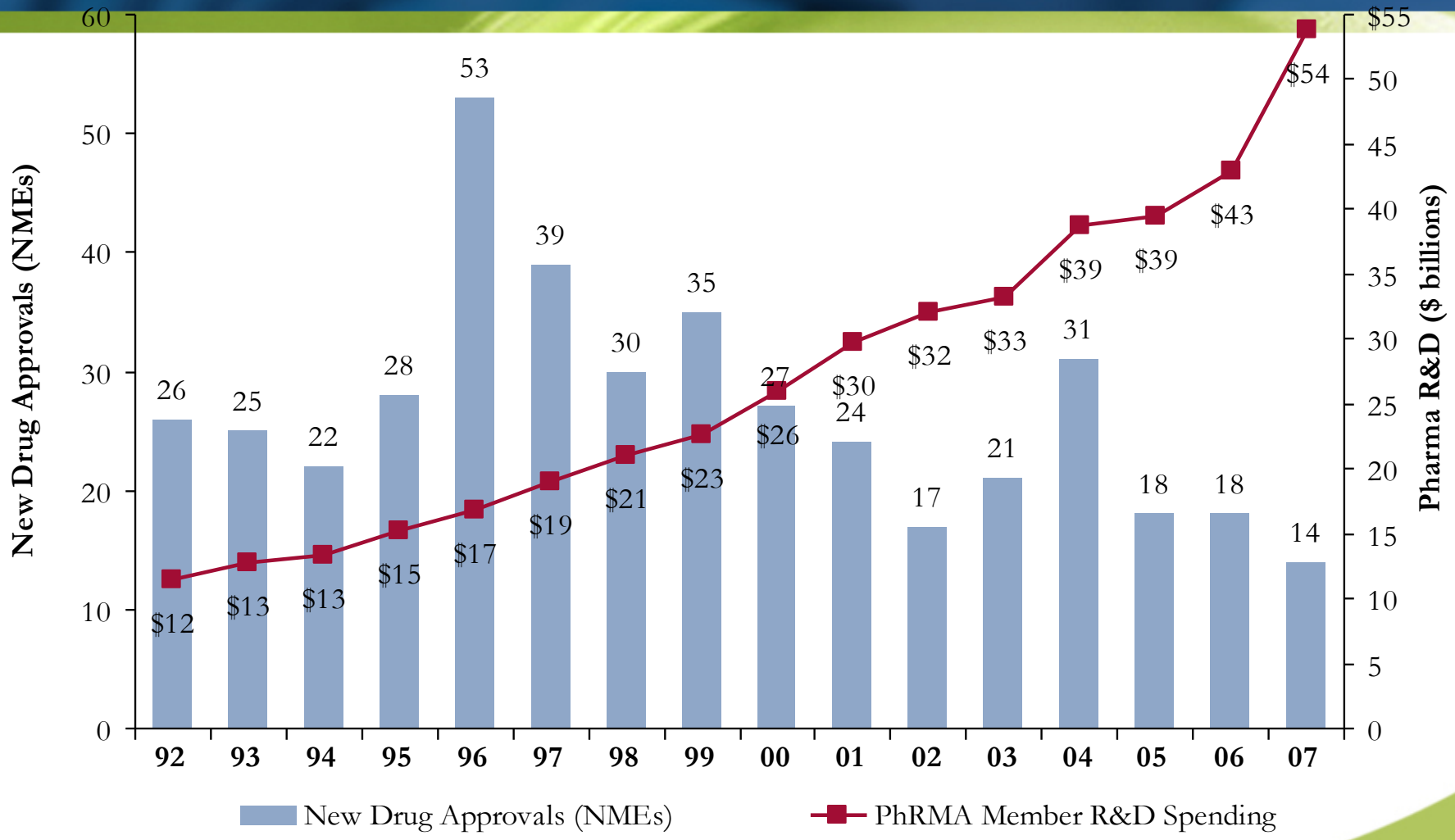
Why Humanize Safety Testing?

Because those taking the medicines are human

The Ideal

- The theoretical ideal is testing in intact humans (healthy volunteers and patients)
- If human responsiveness to new medicines could be modeled *in vitro*, it would represent the best alternative
- We will not know the real predictive value of the *in vitro* testing until the tests are independently evaluated in manner acceptable to all stakeholders, and outcomes and actions agreed upon by all interested parties

The Problem in the Pharma Industry: The R&D Productivity Gap



Source: Burrill & Company; US Food and Drug Administration.
Note: NMEs do not include BLAs

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Why is human safety prediction so poor? The track record of animal hepatotoxicity studies

- **In 2009 alone 110 deaths in the US are linked to Drug-Induced Liver Injury (DILI)**

- Compounds showing liver effects in humans:

  Medline: 710 out of 1061 compounds

  EMEA: 137 out of 157 compounds

- Prediction of human liver effects by rodents and non-rodents.

  [Compounds showing effects in humans but with no reported effects in rodents or non-rodents, i.e. the potential "false negative" rate:

  Medline: 269 out of 710, i.e. 38% of the compounds

  EMA: 70 out of 137, i.e. 51% of the compounds

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Are these odds of causing ADRs in patients our gold standard? Can we do better?

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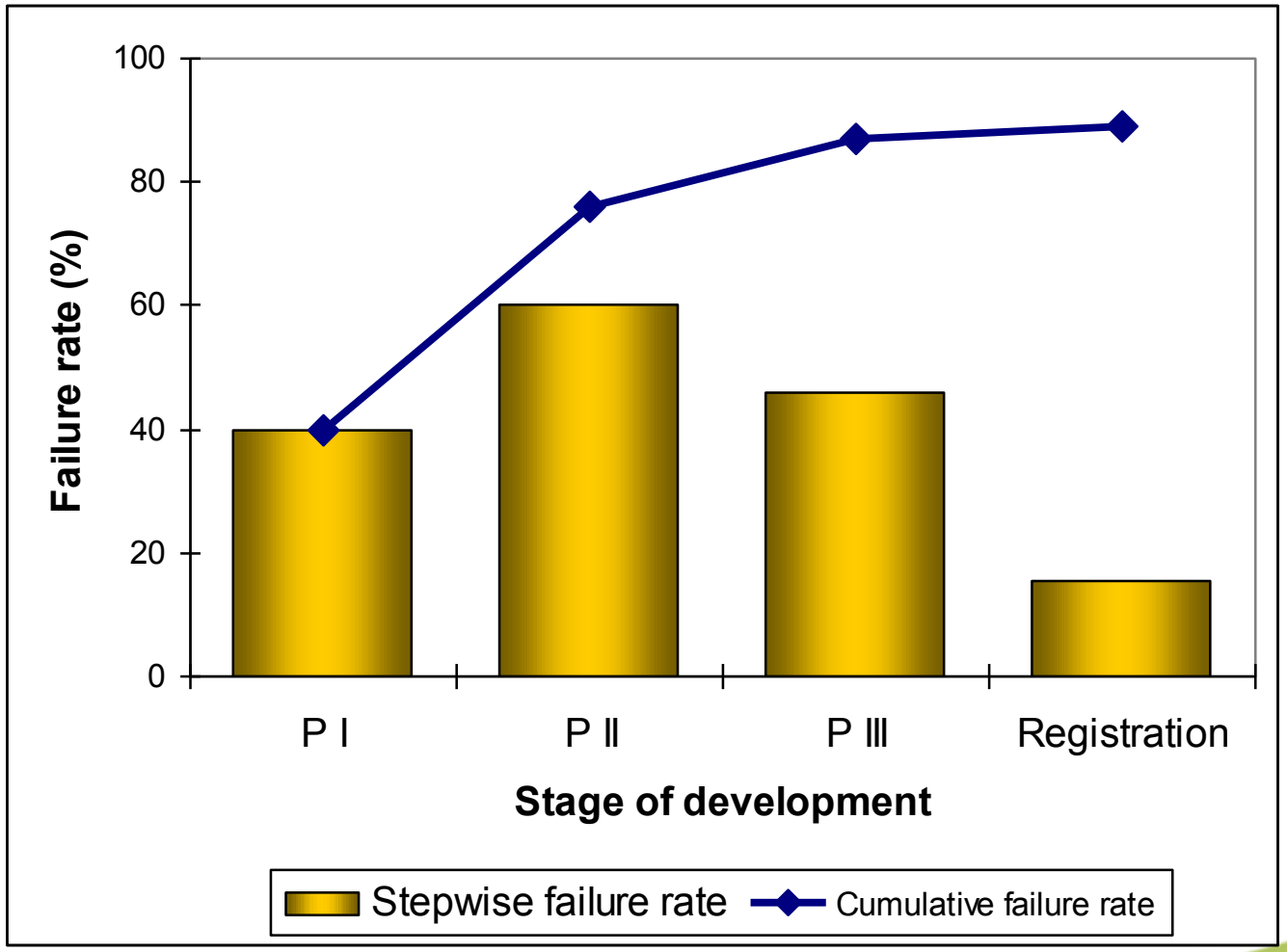
Problem for Patients Safety:
92% of drug candidates fail in human studies



Data from:
Kola & Landis 2004, Nat Rev Drug Disc **3**, 711

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Common Causes of Drug Attrition

Phase	Preclinical	Preclinical	Phase I-III	Phase I-III	Post-Approval
Information:	Causes of attrition	Causes of attrition	Causes of attrition	Causes of attrition	Withdrawal from sale
Source:	ABPI (2008)	Car (2006)	ABPI (2008)	Olson et al. (2000)	Stevens & Baker (2008)
Sample size:	156 CDs stopped	88 CDs stopped	63 CDs stopped	82 CDs stopped	47 drugs
Cardiovascular	24%	27%	35%	21%	45%
Hepatotoxicity	15%	8%	29%	21%	32%
Haematology/BM	3%	7%	3%	4%	9%
Nervous system:	12%	14%	2%	21%	2%
Immunotox;	7%	7%	10%	11%	2%
Gastrointestinal:	5%	3%	2%	5%	2%
Reprotox:	9%	13%	5%	1%	2%
Musculoskeletal:	8%	4%	5%	1%	2%
Respiratory:	1%	2%	2%	0%	2%
Renal:	6%	2%	5%	9%	0%
Genetic tox:	5%	5%	0%	0%	0%
Carcinogenicity:	0%	3%	3%	0%	0%
Other:	4%	0%	2%	4%	2%

Adapted from Redfern WS et al. SOT 2010 Poster 1081 and provided by Tim Hammond

0% 1-9% 10-19% >20%

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Human Cost of Adverse Drug Reactions (ADRs)

- ADRs kill **197,000** EU citizens annually, at a cost of **€79 billion**, according to a 2008 estimate by the European Commission.
- More than **2 million Americans** received emergency hospital treatment in 2009 following ADRs to a prescribed medication.
- It is now reported to cost upwards of **$4 billion** to develop a new medicine.

So… What do we know?

- Pharma is in trouble
  - Increased expense, decreased output of new drugs
  - Industrial consolidation has not helped
- New, safe and effective medicines are getting harder to find
- Animal-based tests alone cannot be relied upon to predict clinical response
- The approved route to establishing safety of new medicines has changed little in over half a century

What do some *think* they know?

- No new drugs possible without the use of experimental animals
- Animal-based safety tests are predicting major human toxicities
- Most clinical safety issues are idiosyncratic in nature
- There are very few if any validated non-animal alternatives
- You can't recapitulate *in vivo* complexity using *in vitro* constructs
- Alternatives are being actively pursued internally by pharma

Ethics of the Current System

- If it is unethical to test new drugs for safety and efficacy in intact humans (volunteers/patients), how can we justify the fact that, in the light of the huge failure rates of new drugs in the clinic, we are in effect already doing it?

  Let us be honest.

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No new drugs without experimental animals

UK Department of Health position document (2012)

"Without the judicious use of animal studies, we would have no modern drugs."

http://transparency.dh.gov.uk/2012/03/30/response-to-safer-medicines-campaign/

No new drugs without experimental animals

Understanding Animal Research (was Research Defence Society)

Why are animals used in research?

Most of the medicines we have come from animal research. Often science doesn't need to use animals, but for many key questions they are crucial. They will help millions with conditions such as cystic fibrosis, Alzheimer's disease, spinal cord damage and parasitic infections like malaria.

http://www.understandinganimalresearch.org.uk

/

Animal-based safety tests not that bad

Use of animals in medical research

The MRC considers the use of animals to be essential in biomedical research in order to better understand the living body and what goes wrong in disease, and to develop safe and effective ways of preventing or treating those diseases.

http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Useofanimals/index.html

Drugs 'should carry animal testing labels'

Medicines tested on animals should be labelled as such to educate the public about the benefits the research can have, Lord Robert Winston has claimed.

http://www.telegraph.co.uk/science/science-news/8858219/Drugs-should-carry-animal-testing-labels.html

Most clinical safety issues are idiosyncratic

A major impediment to the study of the mechanisms of IDRs is the paucity of valid animal models, and if we had a better mechanistic understanding, it should be easier to develop such models.

Uetrecht J (2007) Idiosyncratic drug reactions: current understanding. *Ann Rev Pharmacol Toxicol*, **247**, 513-539

Very few validated non-animal alternatives

To date, more than 30 non-animal alternative methods for assessing safety have been scientifically validated and two thirds of these have been accepted by the regulators according to AltTox.

http://www.understandinganimalresearch.org.uk/how/the-three-Rs/alternatives-and-replacements/

Validation - What do we *really* want to know?

Not: Does a new test 'tick all the boxes?'

But: "Is a new test at least as good as, or ideally better than, an existing one?"

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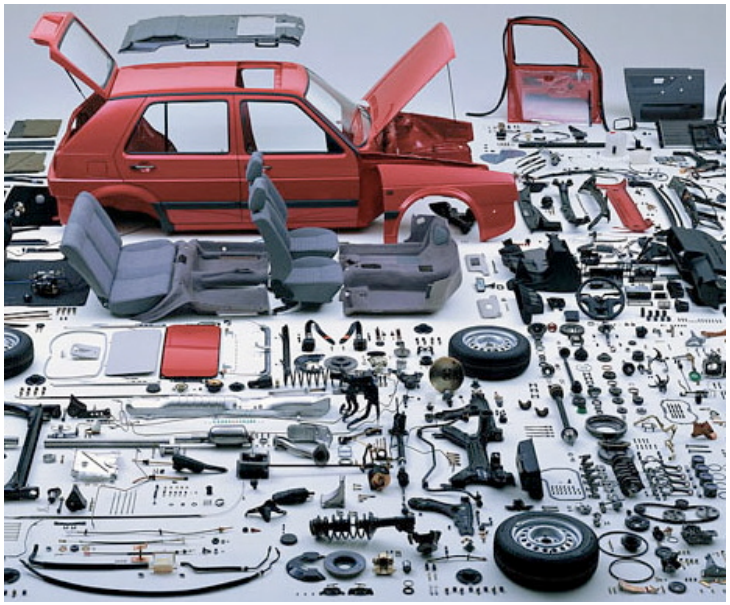
Impossible to recapitulate *in vivo* systems using *in vitro* constructs



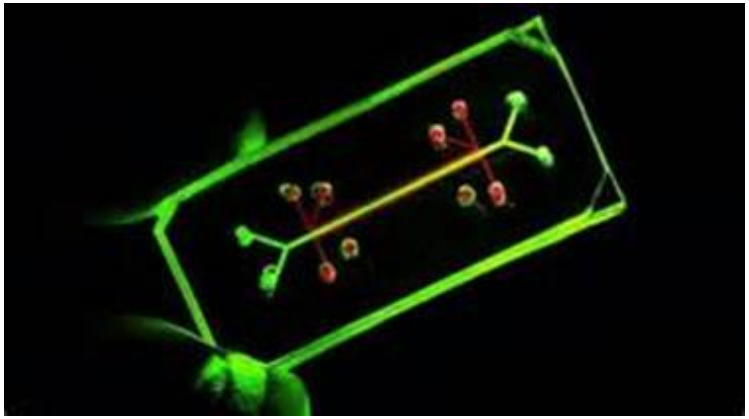
Undoubtedly true, but in complexity and physiological relevance, human-based *in vitro* test systems are making huge progress

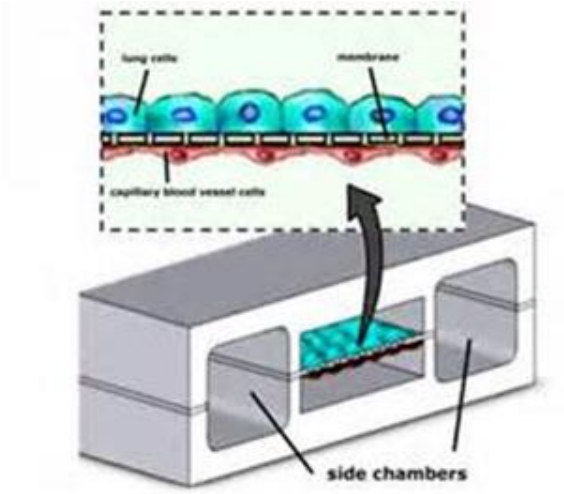
What sort of tests?

The availability and use not only of human cells and tissues, but also of human stem cells opens up many opportunities for studying cell/ tissue actions and interactions in *in vitro* constructs

What sort of tests? A glance at the future…

Now many integrated heterogeneous *in vitro* systems constructed available and/or under development, e.g., organ-on-a-chip





Validation
'As good as' or 'better than' – how to establish?

- Properly designed and controlled studies, comparing outcomes

- There is a wealth of data on the outcome of animal-based testing – ie clinical experience - so how would alternative, human-based approaches fair?

Validation
'As good as' or 'better than' – how to establish?

- Identify drugs that have achieved regulatory approval following a clean bill of health in pre-clinical animal-based testing, but that have subsequently gone on to cause ADRs in humans
- For each such drug identify a structurally and/or functionally similar drug that does not cause the same ADRs in humans
- Submit the pairs of drugs to a range of human-based *in vitro* tests to determine whether such tests can identify problems not identified by the approved animal-based methods
- This is the basis of a **Safer Medicines Trust** Proposal

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- A UK-based charity whose aim is to improve patient safety by encouraging a change in the way we test new medicines through an increased focus on human-based test methods

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Putting patient safety first

Patient Safety

Understanding Causes of Harm

Technologies Predicting Harm

Validating Technologies

Assays Becoming Part of Regulatory Process

Why then do human *in vitro* data seldom feature in drug submissions?

Pharma:

- "The regulators demand animal data"
- "We want to keep things simple and not generate data that may muddy the water"

Regulators:

- "We'd be happy to review such data if pharma would present them"

- ☐ A classical vicious circle
- ☐ How to break out?
- ☐ Who moves first?

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How to effect progress in an industrial regulatory process? – an historical perspective

- In the 19th century cotton production was only considered viable because of slave labour – **legislation** forced a change
- Clean Air Acts 1956, 1968, 1993, 2012 have transformed industrial air pollution - **legislation**
- Health & Safety at Work Act 1974 has dramatically reduced the number of workplace accidents - **legislation**
- The rapid evolution of the motor car was only brought about by force of regulation (safety, fuel efficiency, environmental pollution) - **legislation**
- The REACH legislation re cosmetics – **legislation**

Why no change in medicines R&D?

- Because nobody wants to take responsibility, in case things go wrong
  - (*no pressure from regulation*)

- You cannot be criticized for failure if you followed instructions, even if those instructions are outmoded, outdated and discredited
  - (*no pressure from regulation*)

- *In vitro* skin constructs have achieved regulatory approval, and they *are* used by drug companies to identify possible skin irritancy, but those companies still rely on animal data in their drug submissions
  - (*no pressure from regulation*)

So who should be responsible?

We all have a role:

- Patients, clinicians and governments (ie society) should not accept 2nd rate medicines
- There should be incentives for academics and industry to actively explore and develop better methods of safety testing
- Industry should work closely with regulators
- Governments should take note and 'encourage' regulators to insist on more effective methods

The bottom line

If we wait for change to occur organically, we'll wait for ever

So who should be responsible?

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A Human Alternative

- While there is little doubt about the need for improvement, it is widely held that suitable human-based methods are either unethical (in vivo), or do not exist (in vitro).
- Is that really true?

Solution: Addition of Species-appropriate Testing, but…

- Qualification / Validation a bottleneck.
- No agency wants to "own" the validation process.
- New committees at EMA, FDA, NIH and DARPA are formed, but…
- It takes too long to get a method qualified and validated.
  - Example: it took 15 years for AMES test to be approved by FDA!
- In the meantime, the existing preclinical methods have not been subjected to independent validation process.
- The question should not be whether a new method is 100% sensitive and specific, but whether it can provide information that existing methods do not, bringing the combined approach to be more predictive of human biology.

Back to Human Alternatives

- Are there really no human-based in vitro tests that can add reliable information about safety and efficacy of new drugs in man?

- While admittedly, few such tests have achieved formal validation by ECVAM & ICCVAM, how many of the existing animal-based tests would pass such demanding evaluation (any?).

- Would it not be more prudent at this stage to ask whether the introduction of a new test (of which there are many) can provide any improvement in the industry's current patently inadequate ability to predict clinical safety?

The Need for Evidence

- Safer Medicine Trust's aim is to provide independent comparative evaluation of human-based *in vitro* methods already available.

A Study

- We have designed a study to determine whether a range of human-based *in vitro* tests can identify human toxicities that have been missed by the currently used preclinical methods.

- If they can, their addition to existing paradigms could identify human toxicities earlier, and provide some insight into the value of non-human-based data.

- The proposed study is not intended as a thorough validation study, but instead as a qualification study

Outline of Study

- 6 high profile compounds with human toxicities* not identified by current testing regime.
- All positive control compounds are withdrawn in at least one geographic region (US, Japan and/or EU) for reasons of AEs, all negative controls are marketed
- Each compound partnered by a structurally or functionally related compound devoid of the clinical toxicity.
- All 12 compounds to be tested blind in a range of human-based *in vitro* tests

* *Cardiovascular, liver, kidney and skeletal muscle.*

Proposed Compounds' Toxicities

Positive Control	Negative Matched Control
QTc interval prolongation, arrhythmias due to hERG channel blockade	No side effects noted
Mitochodrial damage: Rhabdomyelosis, myopathy, liver	mild muscle cramps, rare abnormal liver tests
Heart valve defects	No side effects noted
Heart attacks	No side effects noted
Kidney damage, Haemolytic anaemia	Rare: tendon ruptures, tendonitis, liver failure, hERG
Liver injury	Rare: abnormal liver and heart tests
Liver damage	No side effects noted

Funding

- It is proposed that the study will be supported by a consortium consisting of government and regulatory organizations, technology providers and pharmaceutical industry.
- Safer Medicines Trust serves as a catalyst in this validation work

Management of Study

- The study to be run by representatives of the Pharma consortium, led by an independent Project Manager (identified).
- Compound control (weighing, anonymising & supply) to be managed by an independent company (identified).
- Data to be analysed by independent organization (identified).
- Study to be complete within 12 months.

Final Reporting

- Final data to be reported on completion in peer-reviewed publication(s).
- FDA and EMA meetings and submissions to discuss the results and actions are being discussed
- If appropriate, also via open forum such as conference.

Selected Technologies

biopta
human tissue experts

ChanTest™
THE ION CHANNEL EXPERT

Some of the selected technologies

BioSeek
A division of DiscoveRx

insphero

CeeTox
In vitro models to predict toxicity

APREDICA
contract research at the pace of discovery

GE Healthcare

Cerep

Current progress

- OpenTox to do the data analysis upon completion of the study
- EPA ToxCast is running selected compounds in Phase IIII ToxCast study (data to be released for early analysis in Q2'2014)

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Thank you.