

Humanizing toxicity testing in the 21st century: who should be responsible for introduction of human biology-based tests into the regulatory process?

Robert Coleman PhD DSc
Scientific Director UK



Why Humanize Toxicity Testing?

- Because too many compounds are slipping through the 'safety net'
- Because we may be losing valuable drugs (false positives)
- Because patients are human

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 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?

- There would be no new drugs without the use of experimental animals
- Animal-based safety tests are really not that bad
- Most clinical safety issues are idiosyncratic in nature
- There are very few validated non-animal alternatives
- It is impossible to recapitulate the functioning of any whole integrated organism using *in vitro* constructs
- Alternative approaches (in UK at least) are the remit of the NC3Rs

What is the truth about humanized testing?

- 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 ideal
- We don't know how valuable *in vitro* testing can be, because nobody has really looked

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?”

'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 – clinical experience, so how would alternative, human-based approaches fair?

'As good as' or 'better than' – a proposed approach

- 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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Safer Medicines Trust

PO Box 62720, London SW2 9FQ - 020 8265 2880 - info@SaferMedicines.org - www.SaferMedicines.org

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

Putting patient safety first

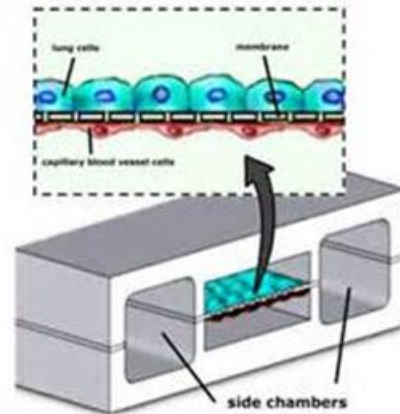
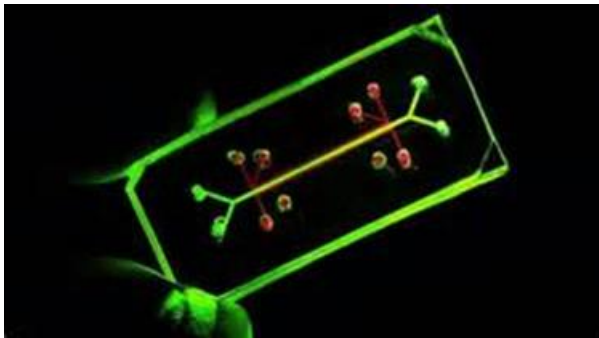
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What sort of tests?

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



- The availability and use of human stem cells opens up many opportunities for studying cell/tissue actions and interactions in *in vitro* constructs

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

Pharma: “The regulators demand animal data”

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?

So, who should be responsible for introduction of human biology-based tests into regulatory process?

- 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**

So, legislation and regulation

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

If we wait for change to occur organically, we'll wait for ever, so ultimately governments must insist on change