Developing Methods and Technologies to Ensure Safe and Effective Medicines

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Outline

- Who we are
- Drug safety
  - Current process / Why innovate?
  - Barriers / Progress to change
- Asks

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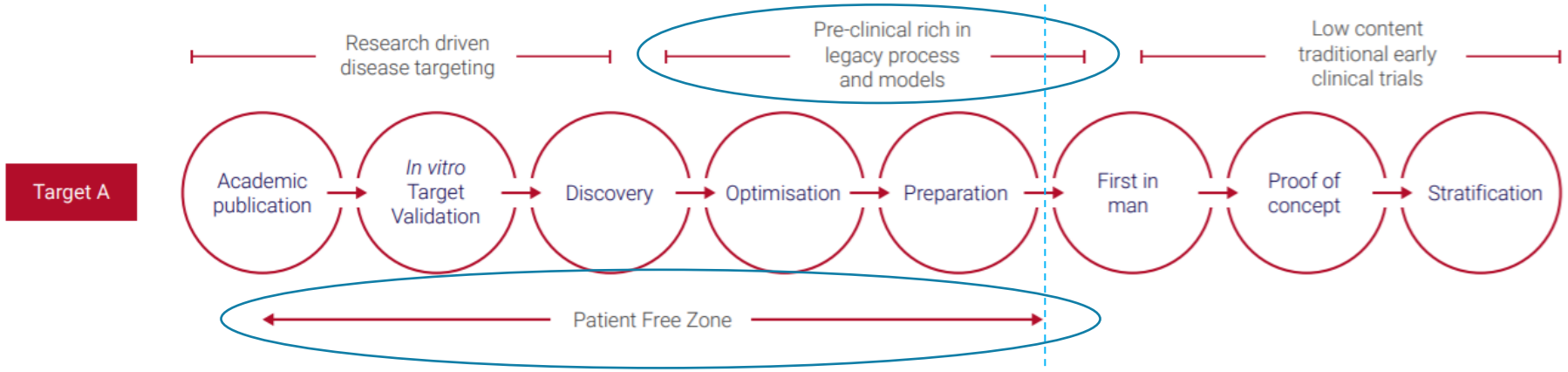
Safer Medicines Trust

- An independent patient safety charity
- Our aim is to make medicines safer, by encouraging a change in the way they are tested, from a system based on animal tests to one based on human-relevant science
- See: www.SaferMedicines.org

Drug safety

….. the preclinical research process is patient free, relying on animal models of disease and toxicology as poor approximations of humans…



- Legacy processes and models are flawed with >90% of drugs failing

  - need to retool the R&D model[1]

- Adverse drug reactions now 4th-6th leading cause of death in western world

1. State of the Discovery Nation 2018 and the role of the Medicines Discovery Catapult. Joint report by the BioIndustry Association and the Medicines Discovery Catapult, January 2018

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Drug safety

- Many hundreds of licensed drugs cause undesired side effects in humans
- These cause many serious illnesses, including fatality (10,000 people in UK/year)…
- …and are not predicted by safety testing undertaken in animals, or in early clinical trials
- New drugs currently require prolonged testing in large numbers of people before they are licensed for use

Data from FDA labels:

WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS
Zidovudine capsules have been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease *[see WARNINGS AND PRECAUTIONS (5.1)]*.

WARNING: HYPERSENSITIVITY REACTIONS
Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir.

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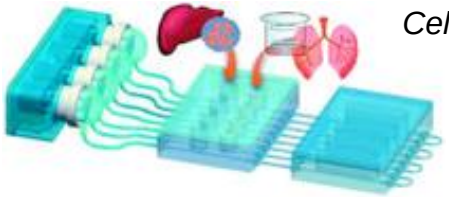
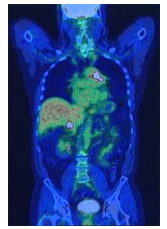
Human-relevant models

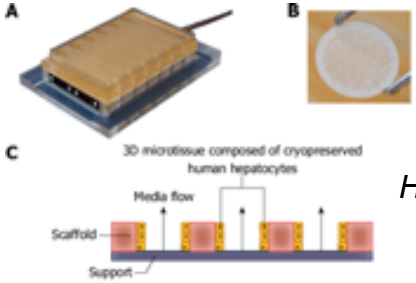
- Human-relevant experimental models use cells from human tissues, maintained under biologically relevant conditions
- Now used routinely to study many different human diseases, to explore disease susceptibility, and to design and test novel drug treatments
- **And** to predict and avoid human adverse effects of drugs that cannot be detected in animal studies
- Computational data analysis tools are used to enable accurate prediction of human in vivo responses from human-relevant models



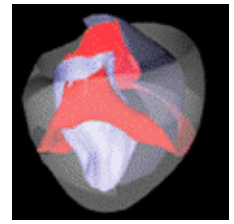
Cell/tissue culture, 2D and 3D models

Microdosing

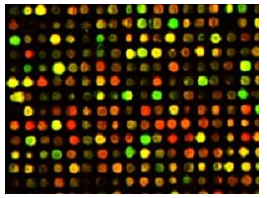




Human "organoids“ or “Organ-on-Chips”



Bioinformatics/ Mathematical modelling and systems biology



‘Omic’ technologies

Imaging technologies

Population studies

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Some human-relevant models

COVID-19:

Busquet F, Hartung T, Pallocca G, Rovida C, Leist, M. Harnessing the power of novel animal-free test methods for the development of COVID-19 drugs and vaccines. Archives of Toxicology (2020) 94:2263–2272 https://doi.org/10.1007/s00204-020-02787-2

Inflammation in obesity:

Ahluwalia A, Misto A, Vozzi F, Magliaro C, Mattei G, Marescotti MC, et al. (2018) Systemic and vascular inflammation in an in-vitro model of central obesity. PLoS ONE 13(2): e0192824. https://doi.org/10.1371/journal.pone.0192824

Influenza and Staphylococcus aureus super-infection:

Bruchhagen C, van Krüchten A, Klemm C, Ludwig S, Ehrhardt C. In Vitro Models to Study Influenza Virus and Staphylococcus aureus Super-Infection on a Molecular Level. *Methods Mol Biol*. 2018;1836:375-386. doi:10.1007/978-1-4939-8678-1_18

Hepatitis virus infection:

Verrier, Eloi R et al. "Cell Culture Models for the Investigation of Hepatitis B and D Virus Infection." *Viruses* vol. 8,9 261. 20 Sep. 2016, doi:10.3390/v8090261

Cardiotoxicity of drugs:

Blinova K, Dang Q, Millard D, Smith G, Pierson J, Guo L, et al. International multisite study of human-induced pluripotent stem cell-derived cardiomyocytes for drug proarrhythmic potential assessment. Cell Reports. 2018;24(13):3582-92. doi: 10.1016/j.celrep.2018.08.079

Liver toxicity of drugs:

Proctor, W.R., Foster, A.J., Vogt, J. et al. Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury. Arch Toxicol 91, 2849–2863 (2017). https://doi.org/10.1007/s00204-017-2002-1

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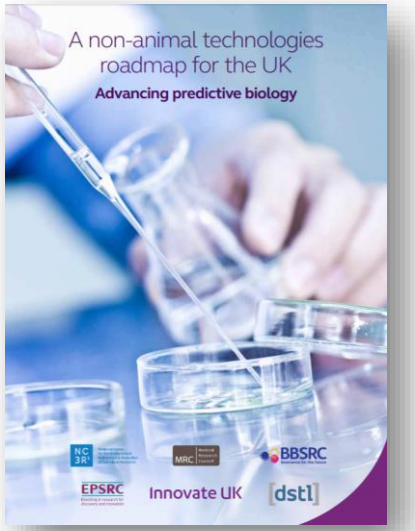
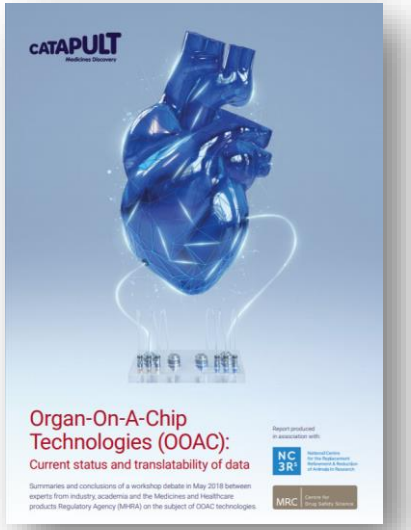
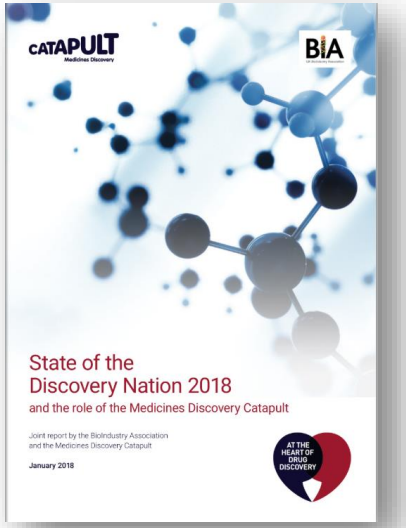
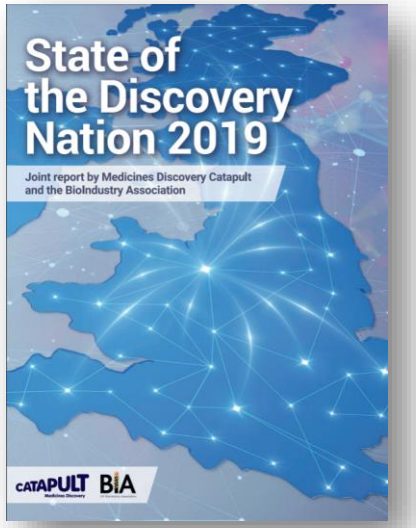
Roadmaps to New Approach Methodologies (NAMs)

UK

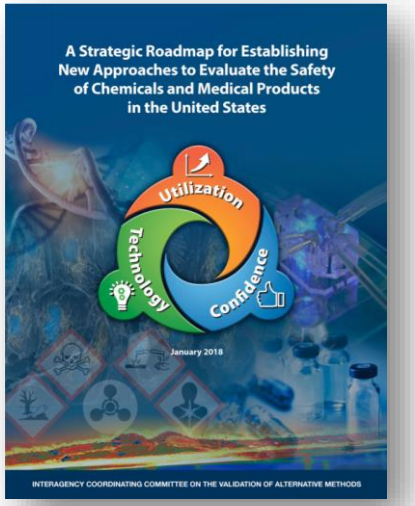


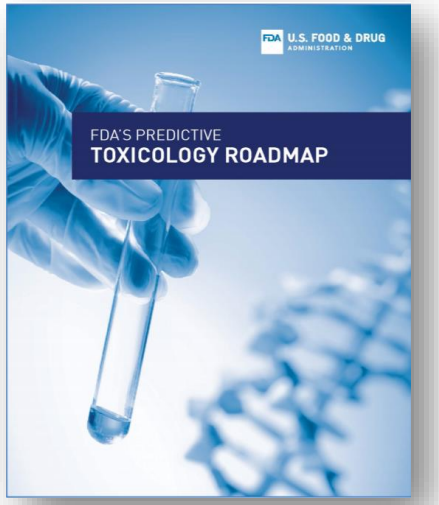


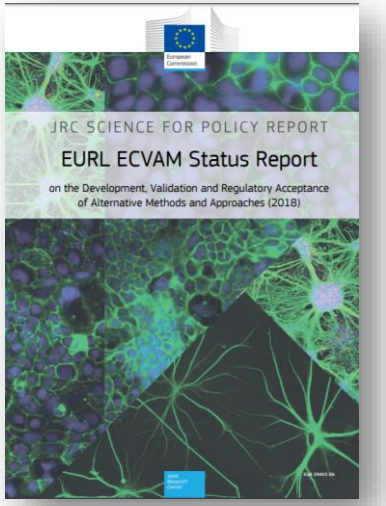




ICCVAM **FDA** **EU**







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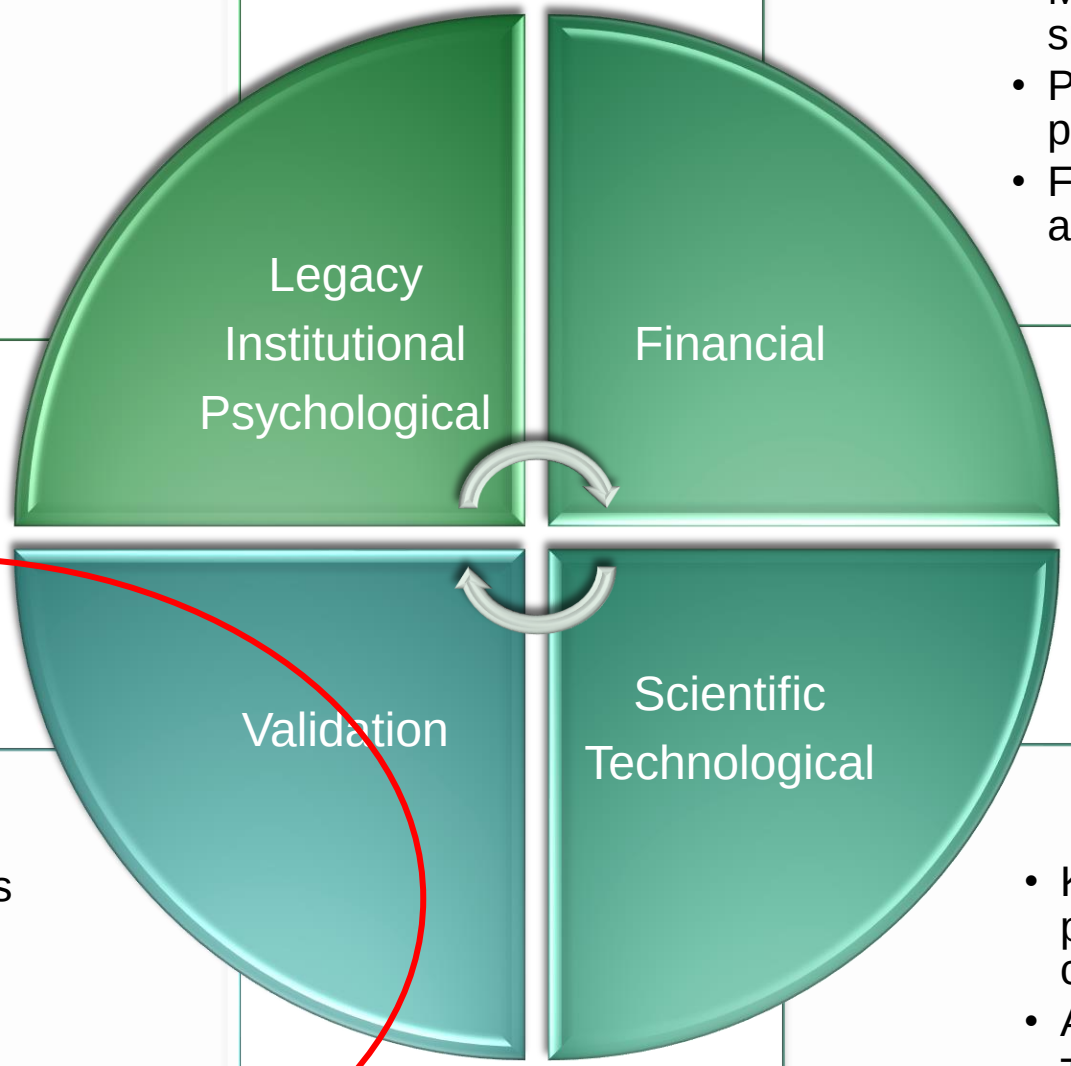
Barriers to change

- Resistance to change
- Status quo bias
- Historical data
- Education

- Multi billion £ animal supply industry
- Pharma liability protection
- Funding of NAMs vs animal methods



- Applicability domains
- Context of use
- QVIVE
- Regulation and implementation

- Knowledge gaps (tox pathways, disease cause)
- Assay development
- Technology limitations

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Progress – Validation & Implementation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

- Applicants encouraged to apply in parallel to the EMA and FDA
- Specify intended use, DD context, scientific rationale
- 6 weeks of public consultation. Publicly available 15 days after final opinion
- EMA/CHMP organise training and amend relevant guidelines
- ~190 day process
- MHRA process – Innovation Office

MHRA

Innovation office enquiry form

Your query will be reviewed by our experts and you will receive an email response within 20 working days, depending on the complexity of the query and the availability of key experts and specialists.

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ANIMAL FREE RESEARCH UK
CERTARA Simcyp
CN-BIO INNOVATIONS
cyprotex AN EVOTEC COMPANY
dtl dermal technology laboratory
IBST Institute of Bio-Sensing Technology
Kirkstall
LORD DOWDING FUND FOR HUMANE RESEARCH
SAFER MEDICINES TRUST
UPM
UNIVERSITY OF PORTSMOUTH

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https://www.humanrelevantscience.org/white-papers/

ASKs

Ability to challenge <u>non</u> fit-for-purpose regulations and propose new approach methodologies and solutions **collaboratively**

Clearly defined **processes** to enable adoption of innovative technologies into medicines regulation process

An **agile system supporting innovation** for safer medicines and regulatory processes **reflecting this dynamic field**

"Future proofing regulation"

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