Non-animal approaches in support of medicinal product development: Setting the scene

Safety Working Party, EMA

London, UK

05.10.2017

Sonja BEKEN

famhp
federal agency for medicines and health products

.be

Introduction

Current preclinical testing paradigm was established 30 years ago

70% of human toxicity in clinical trials is predicted by preclinical studies (Olson et al 2000, Regul. Toxicol. Pharmacol 32; 56-67).

More recent review by Tamaki et al 2013 (J. Toxicol. Sci. 38; 581-598) demonstrates that 48% of human ADRs are predicted in non-clinical testing

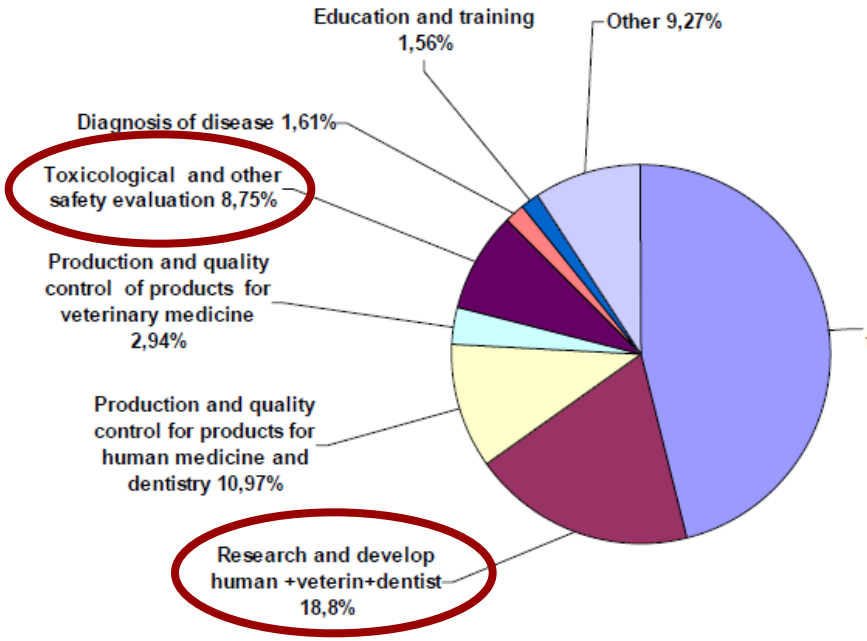
Classical paradigm based largely on descriptive toxicology, not MOA-based

Main drivers for change

- **Better prediction of human relevant effect – efficacy and safety**
- **Animal welfare considerations -3Rs**

Animal experimentation in Europe

Purposes of experiments

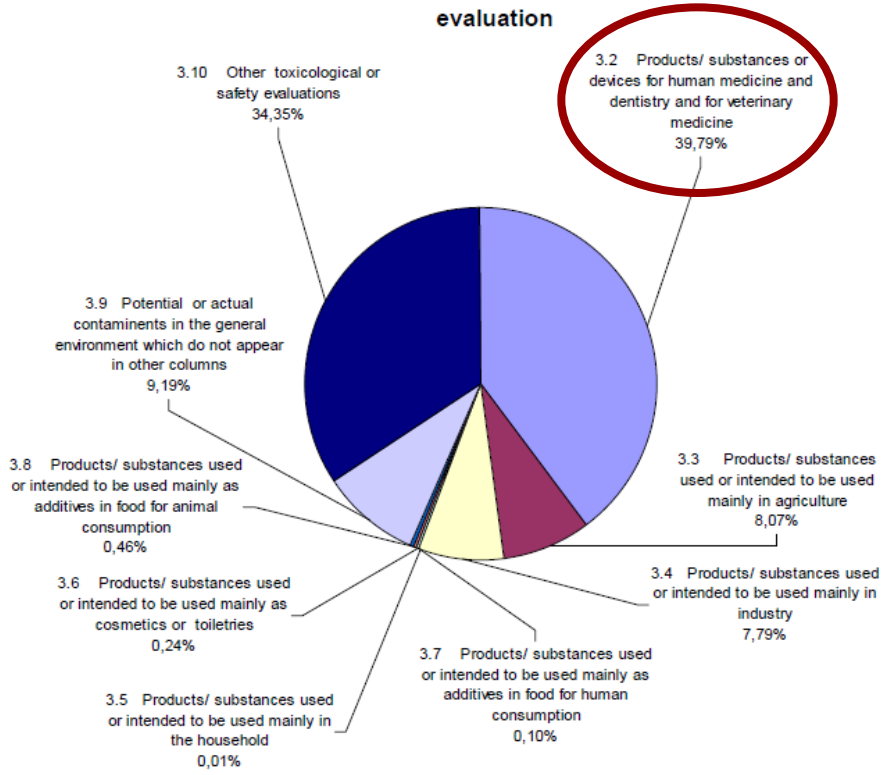


Animals used in toxicological or other safety experiments

2011:

~11.5 million of animals used in 27 Member States

Number of animals used in toxicological and other safety evaluation



Directive 2010/63/EU of the European Parliament and of the Council

of 22 September 2010 on the protection of animals used for scientific purposes

Article 4 clearly states that:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure .

Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.

Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.

Article 13 states that:

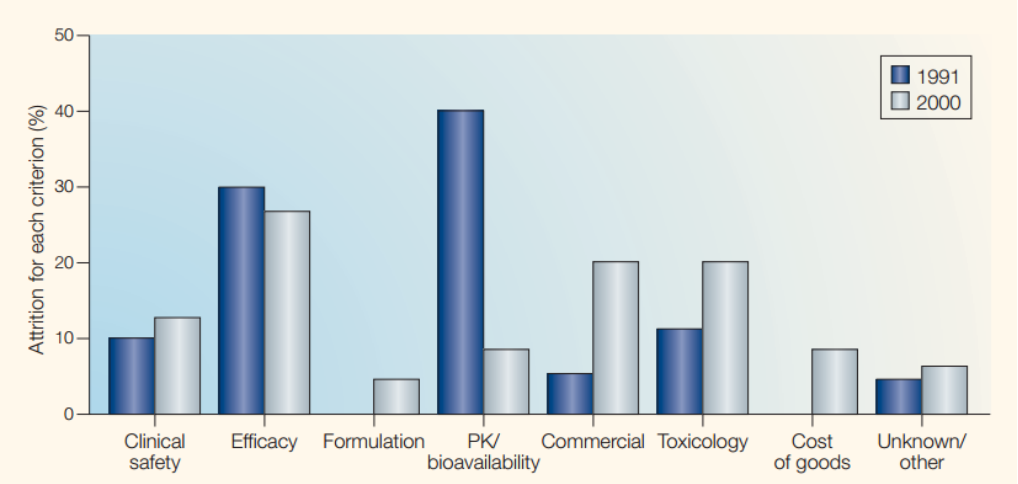
1. *Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.*
2. *In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected:*
   - *(a) use the minimum number of animals;*
   - *(b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm;*
   - *(c) cause the least pain, suffering, distress or lasting harm;*

   and are most likely to provide satisfactory results.

Main reasons for drug attrition

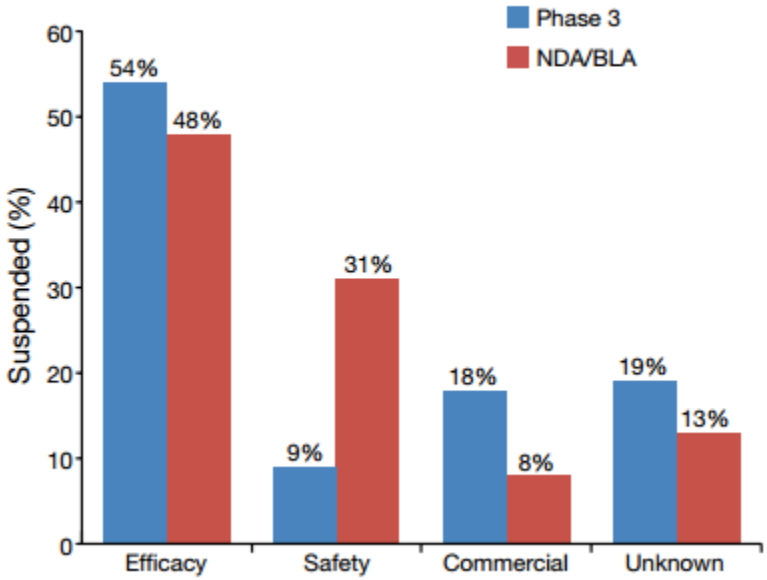
Kola and Landis 2004

Nature Review drug Discovery 3, 711-715



Hay et al, 2014,

Nature Biotechnology 21; 40-541



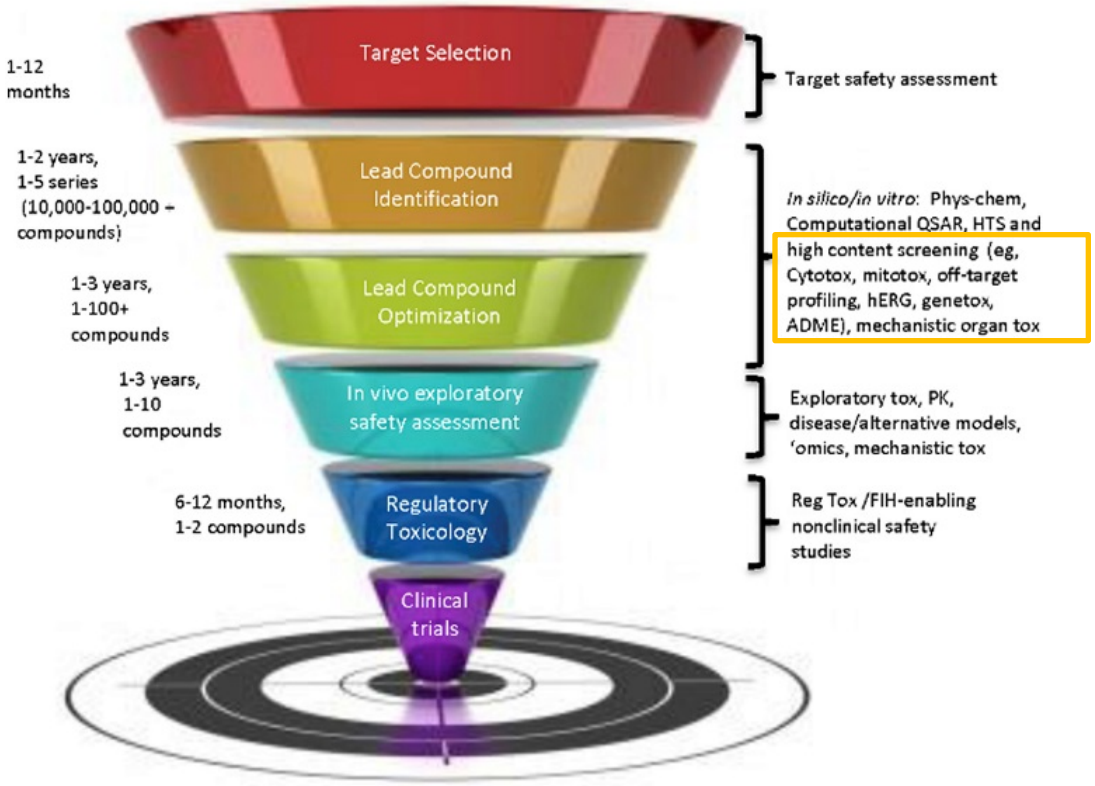
Hornberg et al 2014

Drug Discovery Today 19; 1131-1136

Most noted safety reasons for withdrawal of marketed drugs:

- ***Liver toxicity***
- ***Cardiovascular toxicity***
- ***CNS effects***

In vitro methods in drug development



Butler et al, 2017
Regulatory Toxicology and Pharmacology 87; S1-S15

Confidence in assay specificity and sensitivity:
DILI, Cardiovascular toxicity >>> CNS, lung, adapative immune system

Confidence in prediction of human clinical adverse effects based upon *in vitro* alone decreases with:

- highly complex organisation of organs
- significant genetic variation
- large variation in toxicological phenotypes
- lack of well annotated organ-specific toxicants

Moving beyond discovery towards regulatory acceptance of novel methods

Early tox / compound screening:

in-house validation by companies, NO regulatory involvement

Exploratory / mechanistic studies for regulatory decision-making:

regulatory acceptance based upon demonstrated scientific validity

Pivotal (guideline-driven) studies:

formal regulatory acceptance, different modalities:

- *historically introduced in vitro models*
- *transition from exploratory/mechanistic screening models to pivotal studies based on accumulating experiences (review of databases)*
- *targeted replacement of established animal study by in silico or in vitro model(s) requires "formal" validation*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches

Draft Agreed by JEG 3Rs	**March 2014**
Draft agreed by SWP, SWP-V, BWP, IWP and EWP-V	By July 2014
Adoption by CVMP for release for consultation	11 September 2014
Adoption by CHMP for release for consultation	24 September 2014
Start of consultation	3 October 2014
End of consultation (deadline for comments)	31 December 2014
Adopted by JEG 3Rs	19 October 2016
Adopted by CVMP	8 December 2016
Adopted by CHMP	15 December 2016

This guideline replaces the Position on Replacement of Animal Studies by in vitro Models (CPMP/SWP/728/95).

Keywords	***3Rs, regulatory acceptance, testing approaches, non-clinical, quality, safety, efficacy, human medicinal products, veterinary medicinal products, validation, replacement, reduction, refinement***

Guideline describes:

- regulatory acceptance
- a new procedure for submission and evaluation of a proposal for regulatory acceptance of 3R testing approaches
- scientific and technical criteria for regulatory acceptance of 3R testing approaches (incl. Safe Harbour)
- pathways for regulatory acceptance of 3R testing approaches

Guideline on the principles of regulatory acceptance of 3Rs testing approaches

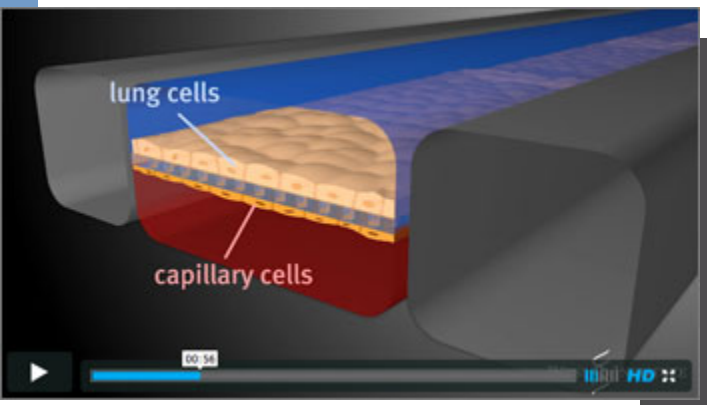
Regulatory acceptance

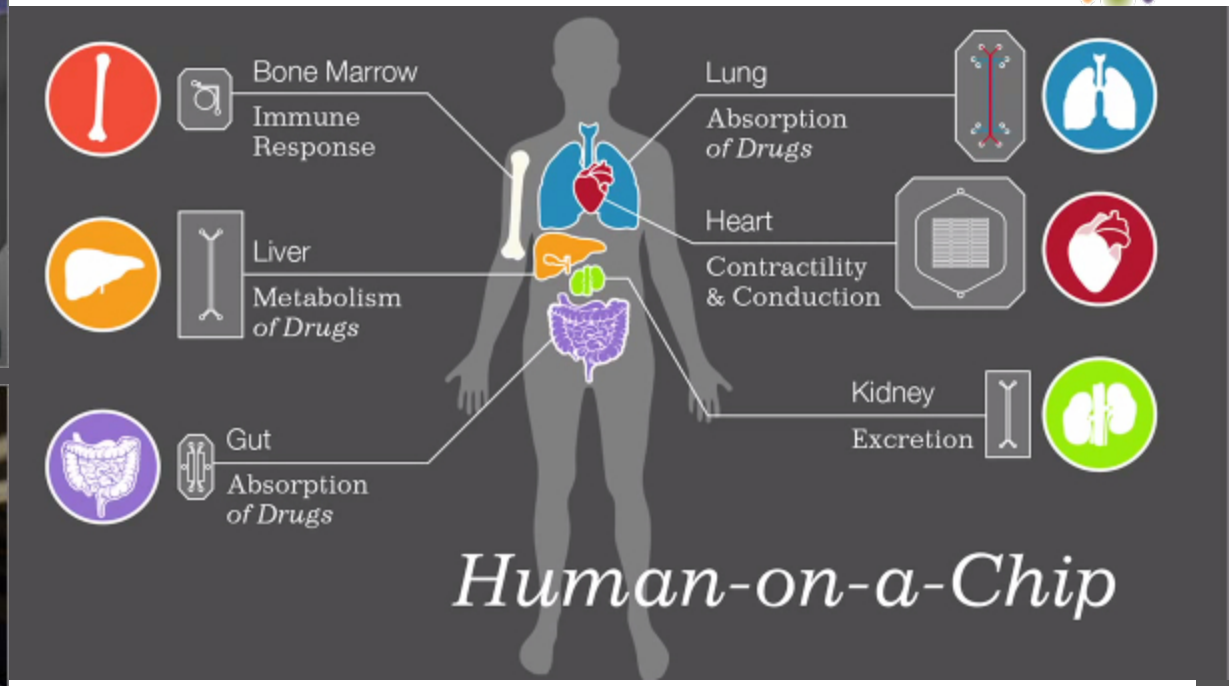
- the incorporation of a new 3R testing approach into a regulatory testing guideline
- on a case-by-case basis: the acceptance by regulatory authorities of new approaches not (yet) incorporated in testing guidelines but used for regulatory decision making

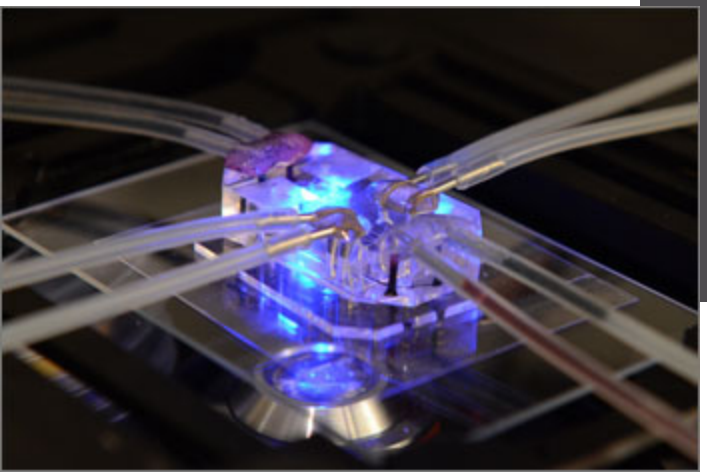
Criteria for regulatory acceptance

- Defined test methodology (protocol, endpoints)
- Relevance within a particular context of use (including accuracy)
- Context of use (including limitations). For example, demonstration that the new or substitute method or testing strategy provides either new data that fill a recognised gap or data that are at least as useful as, and preferably better than those obtained using existing methods.
- Reliability/robustness
- Voluntary submission of data obtained by using a new 3Rs testing approach can be made in parallel with data generated using existing methods (safe harbour)

Technological progress – organ-on-chip



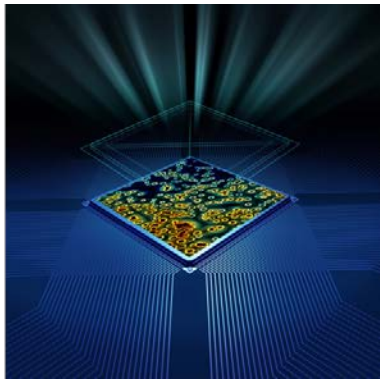


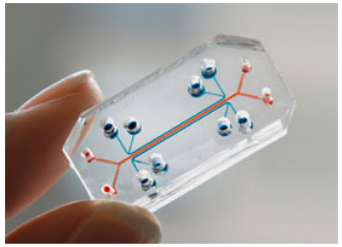


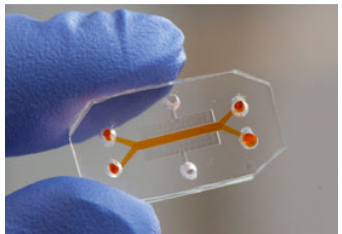
DARPA

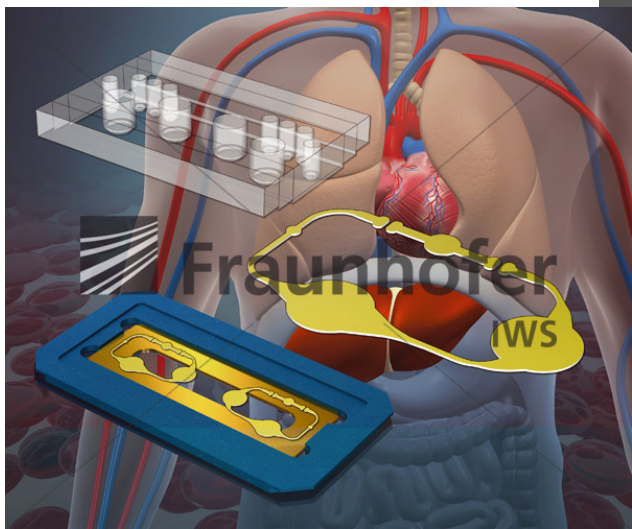
NATIONAL INSTITUTES OF HEALTH

FDA









What is needed?

Regulatory science to be kept in pace with technological developments.

Past and current regulatory revisions, whilst being mostly reformatting of the existing requirements (excl. biosimilars) has led to improved predictive power and higher implementation of the 3Rs.

BUT there is room for improvement!

Regulatory non-clinical testing should evolve to mechanistic based safety and efficacy testing – quid upgrading exploratory safety testing

For this close interaction between multiple stakeholders is needed to ensure qualification of fit-for-purpose methods and science-driven, mechanism-based testing strategies

24-28/8/2014,
Prague,
Czech Republic

Scientific Session I-3b

Human-on-a-chip – advancing regulatory science through innovation and worldwide networking for alternative testing

Statement of Intend

Taking into account the large scale projects ongoing on a global scale with regards to the human-on-a-chip technologies and the potential interest for global regulatory authorities of different sectors, it is considered important that a systematic mechanism for exchange of information is being set up. The latter should take advantage of the collaborative initiatives already established for different sectors (e.g. EMA/FDA qualification exercises, ICH, ...). Such a forum could also allow for cross sectorial discussions on qualification criteria and performance standards in order to foster possible qualification ….

So here we are ….

Objectives for today's workshop

- Mapping of state of the art for organs-on chips
- Common understanding of benefits and limits of organs-on-chips
- Identification of gaps in non-clinical safety testing and how organs-on chips could address these
- Exchange of information between developers, users and regulators
- Facilitate regulatory acceptance of innovative 3R methods for a defined context of use for the approval of safe and effective medicines.


IF EVERYONE IS MOVING
FORWARD TOGETHER,
THEN SUCCESS TAKES CARE
OF ITSELF. ~ Henry Ford ~

Contact

Federal Agency for Medicines and Health Products – FAMHP

Place Victor Horta 40/40
1060 BRUXELLES

tel. + 32 2 528 40 00
fax + 32 2 528 40 01
e-mail welcome@fagg-afmps.be

www.afmps.be

Your medicines and health products, our concern

famhp

10 years

.be