Public Conference
"Advancing the 3Rs for Regulatory Testing of Medicines"

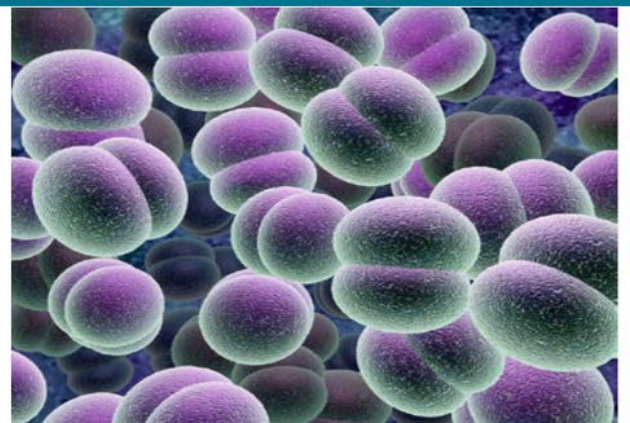
famhp federal agency for medicines and health products

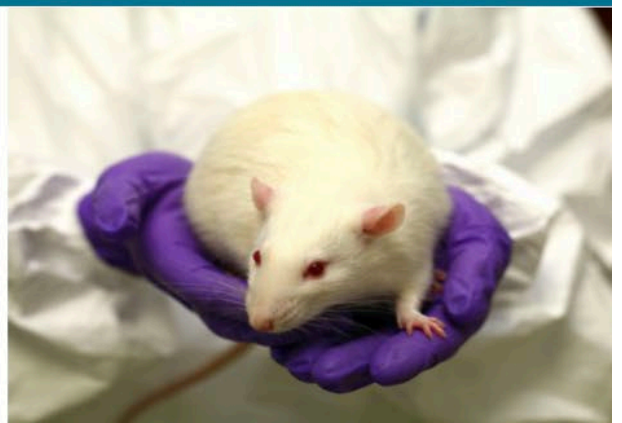
be EU belgium24.eu

Kirsty Reid

Director Science Policy, European Federation of Pharmaceutical Industries and Associations

31 January 2024

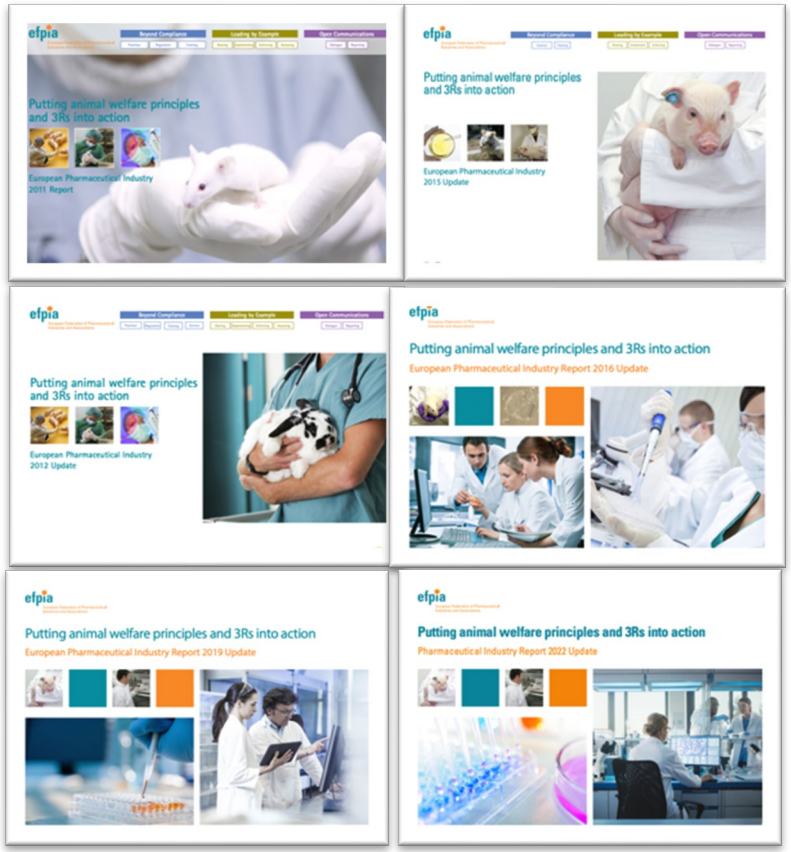





About us

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 37 national associations and 40 leading pharmaceutical companies, with a growing number of small and medium-sized enterprises (SMEs). EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.

PHARMA INDUSTRY AND THE 3RS



Phasing-In New Approach Methodologies

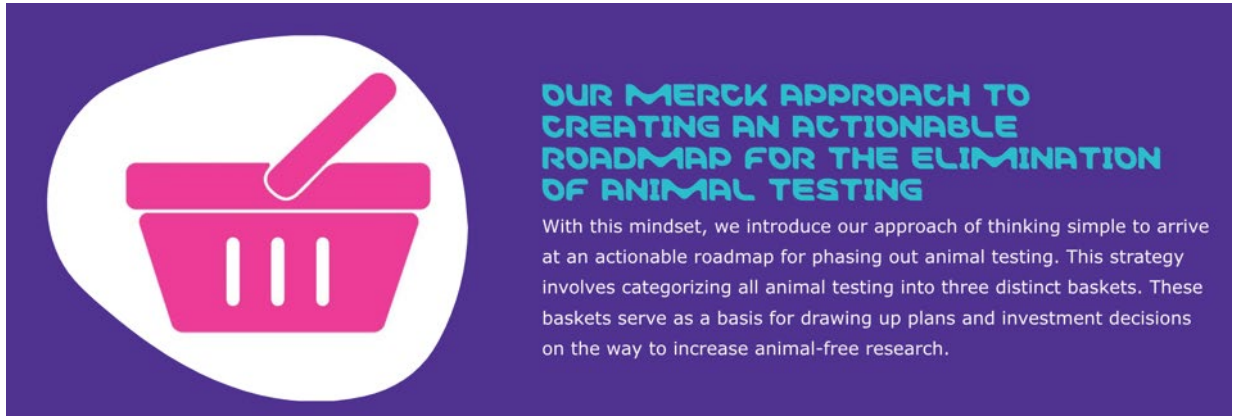
EFPIA members are committed to the **science-based phase-in of methods to replace the use of animals for scientific purposes** and the deletion of animal tests which are obsolete or redundant. EFPIA members aim to lead progress on this by engaging in a wide range of practical activities to help drive the development, uptake and promotion of non-animal technologies (NATs) and new approach methodologies (NAMs) so that these can be phased-in as soon as it is scientifically possible to do so.

*More than medicine

TURNING SCIENCE INTO NEW MEDICINES
RESPONSIBLE INNOVATION
IMPROVING HEALTH
ECONOMIC IMPACT

Company driven initiatives

MERCK



novo nordisk®

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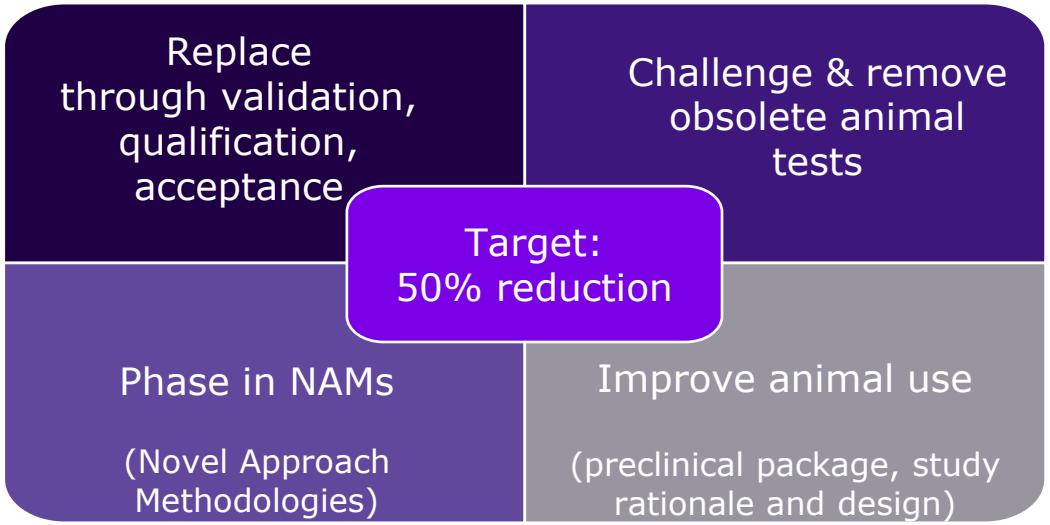
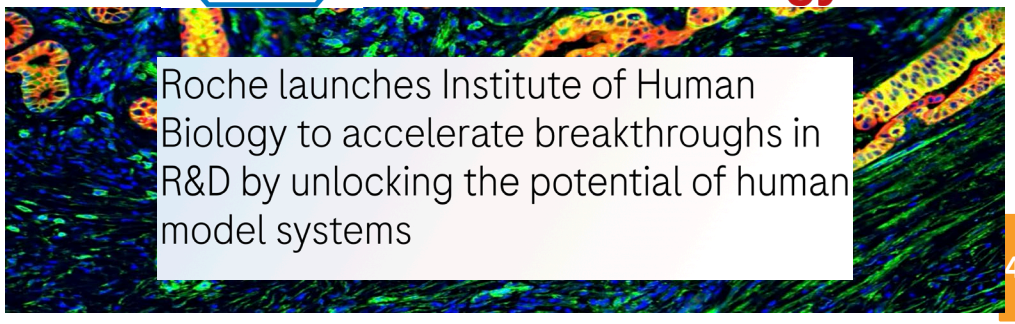


Roche

Institute of Human Biology



Collaboration and joining forces: Industry and NGOs

The Animal Welfare Body
a catalyst for progress

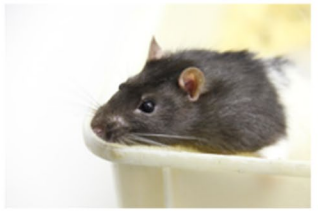
A meeting convened by EFPIA and the RSPCA,
with input from FELASA and EFAT

EFAT

Friday, 18 June 2021: 13.00 - 17.00 CEST

How the pharmaceutical
industry is working to avoid
and replace the use of animals
for scientific purposes

Thursday 22 June 2023



Accelerating Global Deletion of the Abnormal Toxicity Test.
Planning common next steps.

A workshop organized by AFSA/HSI and EFPIA in collaboration with IABS
October 14th, 2021 // 12:30 – 16:45 CET
On Zoom

Agenda

Time	Topic	Presenter
12:30	**Welcome** Opening remarks	AFSA & EFPIA
12:40	**Keynote speeches** **Q&A**	• Dr. Gastineau Thierry (SANOFI PASTEUR, Global Quality Head of Innovation, Culture & Engagement) • Dr. Catherine Milne (EDQM, Head of section Biological Standardisation)
13:20	**Roundtable: Global perspectives on ATT deletion**	**Session to be moderated by:** EFPIA **Panelists:** EFPIA, DCVMN, WHO, US FDA, HealthCanada, Bill & Melinda Gates Foundations
14:10	*Break*	
14:15	**Open session: Many countries, many approaches, how far are we for a global alignment?**	**Session to be moderated by:** IABS **Panelists** Industry and Regulatory representatives from Japan, China, Russia, India, Indonesia, Korea
15:40	*Break*	
15:50	**Collaborative session: defining next step**	**Session to be moderated by:** IABS
16:20	**Final remarks**	DCVMN and Bill & Melinda Gates Foundation
16: 35	**Next Steps**	AFSA and EFPIA

How the pharmaceutical industry is tackling
'severe' suffering in animals used in science

A meeting convened by EFPIA and the RSPCA

Wednesday 26 January 2022: 14:30 - 16.00 CET

Collaboration = Progress

The European Partnership for Alternative Approaches to Animal Testing (EPAA) aims to replace animal testing by innovative, non-animal testing methods/New Approach Methodologies (NAMs), to reduce the number of animals used and to refine procedures where no alternatives exist, or are not sufficient to ensure the safety of substances (the '3R principle'). The partners are pooling knowledge and resources to accelerate the development, validation and acceptance of alternative approaches at national, European and global levels.

The European Partnership for Alternative Approaches to Animal Testing

The European Partnership for Alternative Approaches to Animal Testing

National Centre for the Replacement Refinement & Reduction of Animals in Research

EPAA/NC3Rs Webinar

Re-evaluating the need for chronic toxicity studies with therapeutic monoclonal antibodies (mAbs): weight of evidence and further 3Rs approaches

Monday 17 April 2023 – 14.00-15.30 (BST)

Under an EPAA supported and funded project, a consortium of 14 pharmaceutical companies, the Medicines Evaluation Board (MEB) and the NC3Rs evaluated whether a 6-month toxicity study is still necessary to assess the long-term safety of mAbs. Hear about two recent papers with key results and recommendations.

Agenda and registration: https://nc3rs.org.uk/events/nc3rsepaa-webinar

Pioneering Better Science

ELSEVIER

Biologicals

Volume 78, July 2022, Pages 17-26

Meeting Report

Accelerating Global Deletion of the Abnormal Toxicity Test for vaccines and biologicals. *Planning common next steps.* A workshop Report

Laura Viviani [a], Kirsty Reid [b], Thierry Gastineau [c], Catherine Milne [d], Dean Smith [e], Robin Levis [f], Dianliang Lei [g], Mark van Ooij [h], Philippe Alexandre Gilbert [i], Joris Vandeputte [j], Jianxun Xie [k], Leena Madhuri [l], Shahjahan Shaid [m], Vaughn Kubiak [j], Rajinder Suri [n], Takuo Mizukami [o], Yoshihisa Shirasaki [p], Xiantang Li [q], Ying-Ying Zhou [r], Alla Trapkova [s]... Antoniana Ottoni [ah]

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https://doi.org/10.1016/j.biologicals.2022.06.003

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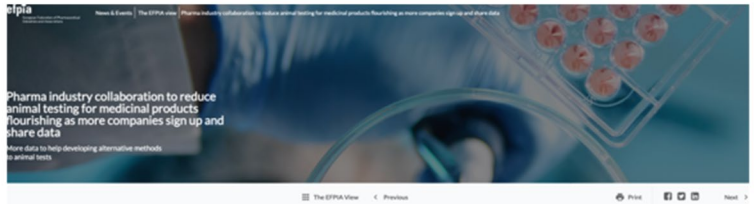


Pharma industry collaboration to reduce animal testing for medicinal products flourishing as more companies sign up and share data

More data to help developing alternative methods to animal tests

Pharma industry collaboration to reduce animal testing for medicinal products flourishing as more companies sign up and share data

17.05.23

A voluntary non-profit collaboration which kicked off a year ago between four pharmaceutical companies(1) - supported by EFPIA – and the European Chemicals Agency which could ultimately lead to a decrease in animal testing is today being hailed a success.

The contribution pilot project has expanded considerably with three further companies(2) signing up and now over 500 tests - containing physicochemical, toxicological and ecotoxicological substance data - have been uploaded containing information about the hazard properties of 94 substances.

The data is made publicly available and can be used to help develop new approach methodologies, decreasing the need for the use of animals in research.

More information is available on the ECHA webpage

Since the adoption of the EU legislation governing animal use, EFPIA and its members have been publishing reports to visibly highlight industry actions on putting animal welfare principles and the 3Rs (replace, refine, reduce) into action(3). This illustrates a continued drive to reduce the number of animals used, refine experiments to minimise the impact on animals, and replace animal experiments wherever possible with alternatives.

Kirsty Reid, Director Science Policy, EFPIA, said:

"EFPIA members are engaging in a wide range of practical activities to help drive the development, uptake and promotion of non-animal technologies and methodologies as well as working across numerous projects to improve animal welfare. The ongoing success of this joint collaborations is another step closer to phasing in these new ways of working to reduce and refine – and ultimately stop animal testing wherever possible."

Regulatory Toxicology and Pharmacology 138 (2023) 105329

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

ELSEVIER

Re-evaluating the need for chronic toxicity studies with therapeutic monoclonal antibodies, using a weight of evidence approach

Hsiao-Tzu Chien [a,s,1,2], Helen Prior [b,1,2], Laura Andrews [c], Leon van Aerts [a,1], Annick Cauvin [d], David O. Clarke [e,1], Kaushik Datta [f], Maggie Dempster [g,1], Noel Dybdal [h,1], Wendy Freebern [i], Lolke de Haan [j,1], Danuta Herzyk [k,1], Adam Hey [l], Thomas Kissner [m], Sven Kronenberg [n,1], Michael W. Leach [o,1], Donna Lee [b], Katrin Schutte [p], Fiona Sewell [b,1], Kevin Trouba [i,1], Peter Ulrich [q], Lucinda Weir [r,1,3], Peter van Meer [a,1,3,*]

Health Public Private Partnerships - IMI and IHI

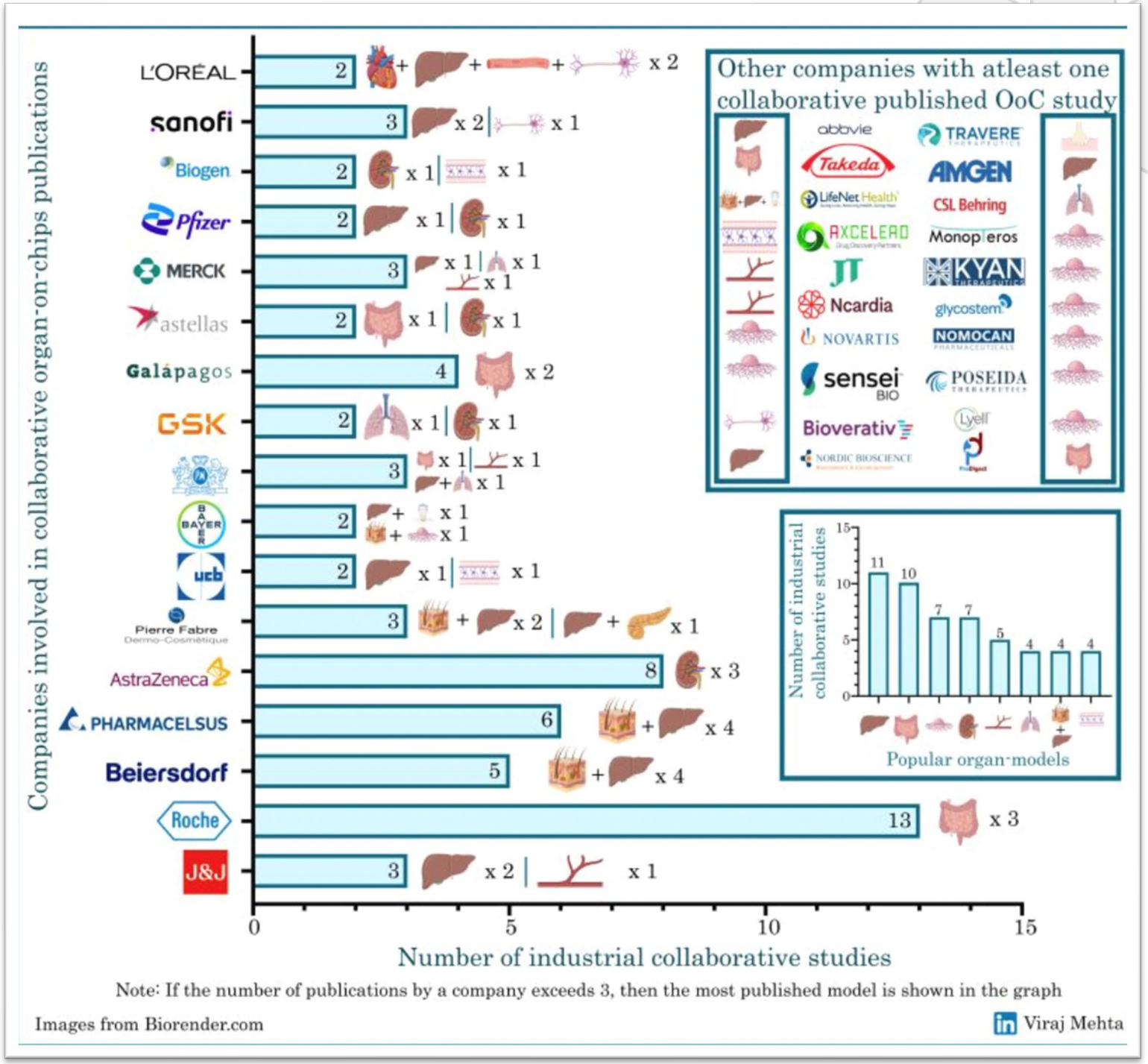
IMI projects have led to development & validation of 34 *in vitro* models and tools; 70 robust animal models; 316 *in silico* models; 12 novel imaging techniques; 95 novel robust assays and 1500 stem cell lines

- **Improved safety predictivity of new drug candidates**
- **Data Precision Innovations**
- **Regulatory modernisation**
- **High-Quality Data Sharing**
- **Further "3R" contributions:**
  - Animal study data replaced with data from *in silico*-based methods, precise validated biomarkers, and modern cellular assays.

Two-stage topics (IHI call 4) - 08 November 2023
Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical safety assessment

Single-stage topics (IHI call 5) - 16 January 2024 – 3 proposals submitted
Accelerating the implementation of new approach methodologies and other innovative non-animal approaches for the development, testing and production of health technologies

Organ On A Chip in drug development



Industry efforts to minimise use of non-human primates

- Pharma industry is working hard to **reduce and refine NHP** use as much as possible
- **Long-term goal** : encourage the adoption of **global best practices for minimizing the use of NHPs in nonclinical safety studies with international regulatory acceptance**

EMA reflection paper

In 2023, EFPIA surveyed 26 members to Identify possibilities for Reduction or Replacement of NHP. Detailed information shared and discussed with the EMA

IMI and IHI collaborations

eTRANSAFE

Virtual Control Groups

Presentation S401 – Phase-in of non-animal methods by the pharmaceutical industry, WC12, Niagara 2023

Joint collaborations aimed at minimising non-human primate use in drug development

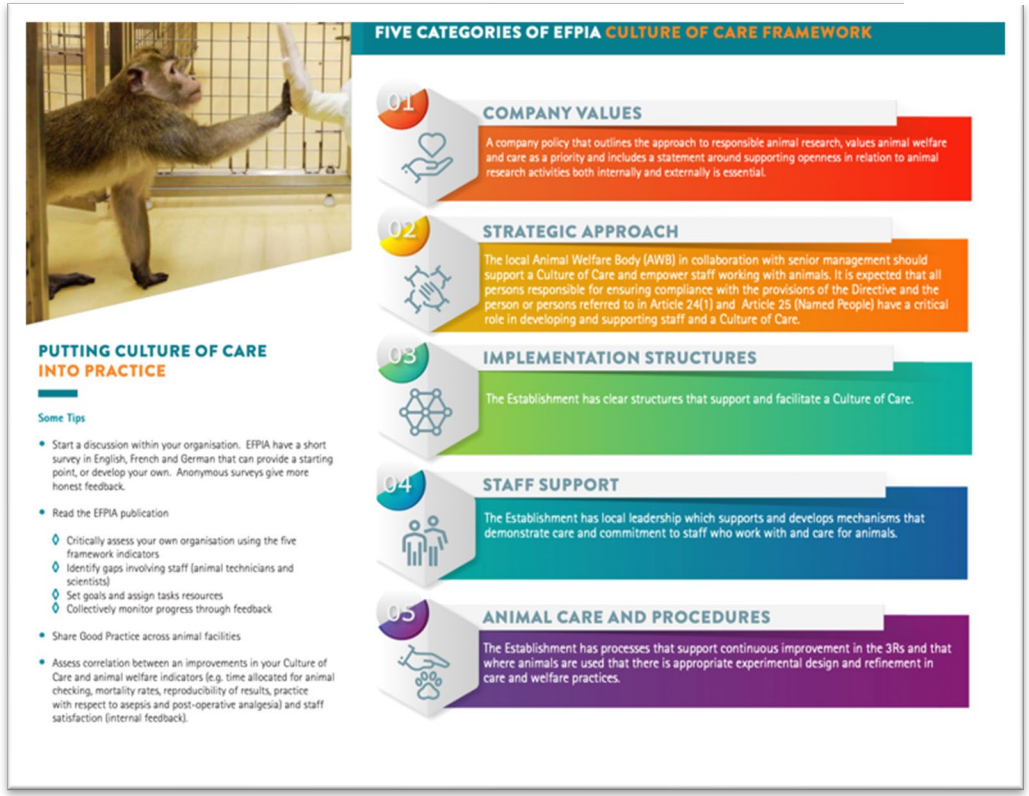
epaa The European Partnership for Alternative Approaches to Animal Testing

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

CBG MEB MEDICINES EVALUATION BOARD

efpia

Promoting a culture of care



Where ICH* guidelines contribution to 3Rs

ICH guidance	Subject Matter	Contribution to 3Rs
ICHS1	Carcinogenicity	Replacement of 2-year mouse studies with shorter duration transgenic mouse studies. Replacement of 2-year rat studies with a weight of evidence approach.
ICHS2	Genotoxicity	Refinements to include in vitro genotoxicity testing.
ICHS3A	Toxicokinetics	Reduction in sampling regimens through micro-sampling and reducing satellite animals.
ICHS4	Chronic toxicity	Reduced need for multiple long duration chronic toxicity studies by guiding 6-month duration in rodents and nine month duration in non-rodent.
ICHS5	Reprotoxicology	Reduction in reprotoxicology studies through describing circumstances when reprotoxicology studies are not warranted or can be deferred. Guidance on the utility of in vitro, ex vivo or non-mammalian assays to reduce or replace in vivo animal testing.
ICHS6	Biologicals	Reduction of number of species required for general toxicity testing from two to one. Replacing carcinogenicity studies with weight of evidence. Eliminating the need for ADME studies.
ICHS7B/ E14	Safety Pharmacology	Integrated Q&A guides on refinement to in vivo studies to improve quality and sensitivity of animal data leading to reduction in animals number. Furthermore, introduction of in vitro and in silico assays might reduce the early in vivo assessment and provide greater confidence in success for drugs progressing toward in vivo assessment, further reducing the overall animal usage.
ICHS8	Immunology	Weight of evidence decision making approach to stream-line immunological animal testing
ICHS9	Oncology	Refined packages for chronic general toxicity, reprotoxicology, metabolite safety, impurity management and carcinogenicity. Eliminating the need for abuse liability, combination studies, lactation or placental transfer studies.
ICHS10	Phototoxicity	Consideration throughout on use of non-animal methods to reduce animal testing in accordance with 3Rs. Circumstances when phototoxicity testing is not warranted. UV absorbance and chemical photo-reactivity tests (e.g. 3T3) to reduce in vivo phototoxicity testing.
ICHS11	Paediatric	Refinements to design, strategy and timing to reduce animal testing.
ICHS12	Biodistribution	Includes recommendations to facilitate the development of gene therapy products while avoiding unnecessary use of animals – mainly driven by reducing the number of animals required for biodistribution studies.
ICHM3	Non-clinical safety	Reduces use of animals in accordance with 3R principles by creating general guidance for minimally acceptable safety packages including, for example, substantially reduced packages required for exploratory clinical trials or scenarios where reprotoxicology packages can be deferred to late development.
ICHM7	Mutagenic impurities	The guidance describes in silico and in vitro approaches that should be used to reduce the necessity for in vivo testing.
ICHQ5	Viral Safety of biotechnology products	Replacement of in vivo assays with Nucleic Acid amplification Techniques (NATs) such as PCR assays or Next Generation Sequencing (NGS) approaches such as massive parallel sequencing or deep sequencing multi-step nucleic acid-based technology.

* The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

EDQM and the European Pharmacopoeia

History of 3Rs at Ph. Eur. Commission (Human and Veterinary)

2012
- Reduction of unnecessary use of animals in pertussis vaccines
- Adoption of 80 veterinary vaccine monographs reducing the number of animals used in testing

2014
- ELISA alternative introduced in *Assay of hepatitis A vaccine*

2015
- Revision of testing strategy for extraneous agents
- Revision of general monograph *Vaccines for veterinary use (0062)*: reduction of animal testing for veterinary vaccines
- Provision for additional systems for monitoring of production consistency and *in vitro* alternatives

2016
- New chapter in Ph. Eur: *Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines*
- Revised *Monocyte-activation test,* an alternative to pyrogen testing

2017
- Suppression of the Test for Abnormal Toxicity from 49 monographs of the European Pharmacopoeia

2018

Replacement of the Histamine sensitisation test (HIST) for residual pertussis toxin testing

2019
- Review of toxicity testing requirements for tetanus vaccines for which three animal tests have been suppressed

2020
- Review of veterinary vaccine monographs to promote the 3R principles

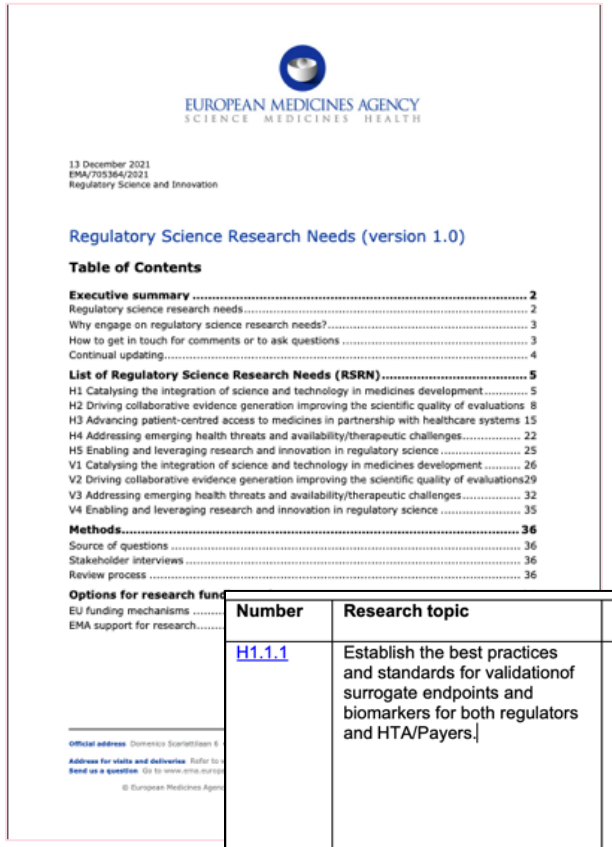
Next? 2026 Pyrogenicity

Share your proposals for replacement of *in vivo* methods: The Ph. Eur. Commission welcomes any data supporting the replacement of the remaining *in vivo* methods and proposals for replacement methods, both of which can be sent to the Commission Secretariat

Optimising Impact of regulatory relevant results generated in precompetitive research consortia: IMI/IHI experience

The Challenge

- Hundreds of potentially relevant results already generated and planned
- Regulatory validation/ acceptance drives use and modernisation of R&D
- The process needs to be accelerated
- Full qualification is the “Holy Grail” but may not always be the best use of everyone resources



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2021
EMA/705364/2021
Regulatory Science and Innovation

Regulatory Science Research Needs (version 1.0)

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03 May 2022
EMADOC-1700519818-808373
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of IMI PREFER

Draft agreed by Scientific Advice Working Party (SAWP)	30 September 2021
Adopted by CHMP for release for consultation	14 October 2021[1]
Start of public consultation	15 October 2021 [2]
End of consultation (deadline for comments)	25 November 2021[3]
Adopted by CHMP	22 April 2022

Keywords	Qualification of Novel Methodologies, IMI PREFER, Patients Preference studies

Number	Research topic	Objectives	Expected impact	projects (including IMI, IHI, Other)
H1.1.1	Establish the best practices and standards for validationof surrogate endpoints and biomarkers for both regulators and HTA/Payers.	To review and describe the evidentiary standards for novel endpoints and biomarkers by EMA and HTA (and potentially payers). To gain an understanding of how standards differ among regulators and HTA/Payers and the evolution of these over time. To evaluate, in collaboration with HTAs, payers and patients, the impact of treatment on clinical outcomes measuredby biomarkers and developjoint standards for biomarker development. Todevelop guiding principles for surrogate endpoint validation that are acceptable to regulators, HTA and	Greater clarity in terms of data requirements and facilitating the developmentof novel endpoints, biomarkers and their qualification. Increased understanding and harmonisation (where appropriate) among stakeholders for novel endpoint and biomarker qualification. Ensuring a shared understanding aboutthe clinical relevance of biomarkers used in developments, and widening their acceptability amongst stakeholders to ultimately facilitate drug development (e.g., improving the speed, cost, objectivity, validity, reliability of clinical trials) with biomarkers used as surrogate endpoints.	MACUSTAR NECESSITY PRISM AIMS2TRIAL HARMONY IDEA FAST MOBILISE-D SUMMIT Hypo-RESOLVE

Solution

- Set up of a **focus group with the EMA** to reflect on how to **optimise regulatory validation / acceptance processes** and use in research and regulatory practice of results generated by precompetitive consortia based on IMI examples but applicable across all precompetitive collaborations

Objective

- Reflect and deliver recommendations and a roadmap on
  - What type of regulatory validation/acceptance and level of evidence is best suited for different results and context of use?
  - How to adapt the current regulatory acceptance mechanisms to cope with the large number of potential applications? Need to create a new pathway for assessing clusters of assets or other alternative solutions?
  - Assess financial, expertise, and process implications (including regulatory engagement in projects)

efpia

Next steps for Pharma

Initiate the Merck example across companies to identify recommendations for a roadmap