

Public Conference  
“Advancing the 3Rs for Regulatory Testing of Medicines”



**Kirsty Reid**

Director Science Policy, European Federation of Pharmaceutical Industries and Associations

31 January 2024



# About us

“

*Wherever the art of Medicine is loved, there is also a love for of humanity.*

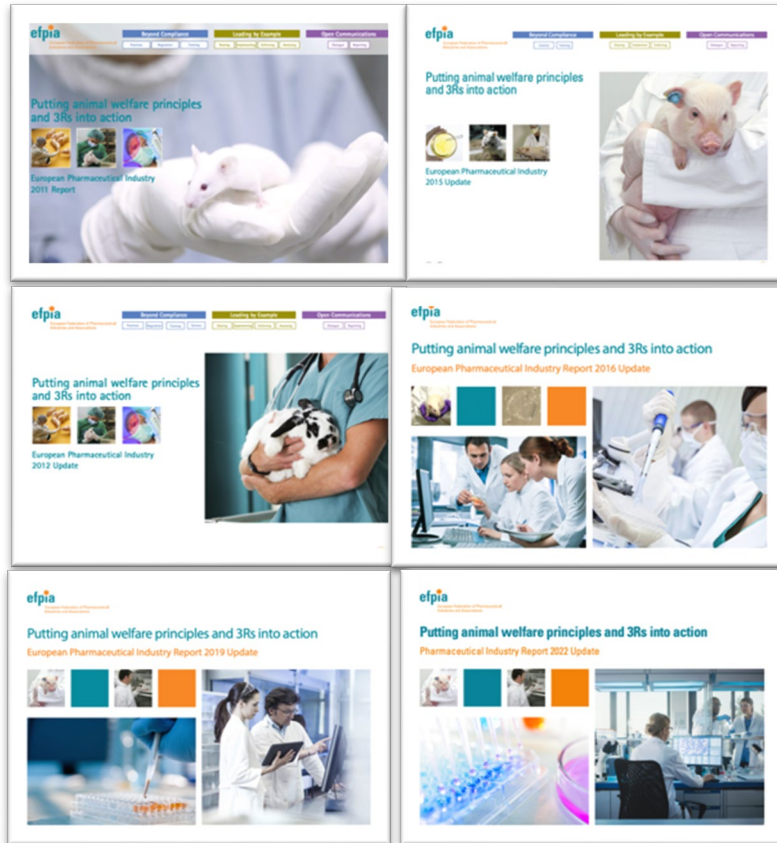
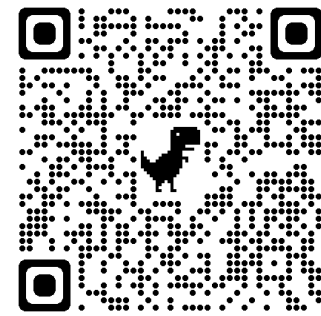
– Hippocrates

”

## **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



# Company driven initiatives

**MERCK**



## OUR MERCK APPROACH TO CREATING AN ACTIONABLE ROADMAP FOR THE ELIMINATION OF ANIMAL TESTING

With this mindset, we introduce our approach of thinking simple to arrive at an actionable roadmap for phasing out animal testing. This strategy involves categorizing all animal testing into three distinct baskets. These baskets serve as a basis for drawing up plans and investment decisions on the way to increase animal-free research.

**sanofi**

Replace through validation, qualification, acceptance

Challenge & remove obsolete animal tests

Target:  
50% reduction

Phase in NAMs  
(Novel Approach Methodologies)

Improve animal use  
(preclinical package, study rationale and design)



### press release

#### Novo Nordisk to expand R&D presence in greater Boston area

Bagsværd, Denmark, 2 March 2023 – Novo Nordisk just announced plans to expand its research and development (R&D) presence in the greater Boston metro area, creating one of its largest R&D hubs outside of Denmark. This new hub, which will leverage the company's existing presence in Lexington, Cambridge and Watertown, Massachusetts, will be home to the majority of Novo Nordisk's US-based research and development activities.

*Novo Nordisk is expanding its efforts within MPS development. Establishing a dedicated unit in Boston with the sole purpose of accelerating the development and implementation of MPS in drug our discovery efforts. This will increase translation and further reduce animal use.*



## Institute of Human Biology

Roche launches Institute of Human Biology to accelerate breakthroughs in R&D by unlocking the potential of human model systems

# 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


 





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 14<sup>th</sup>, 2021 // 12:30 – 16:45 CET  
On Zoom

**Agenda**

Time	Topic	Presenter
12:30	Welcome	AFSA & EFPIA
12:40	Opening remarks Keynote speeches Q&A	<ul style="list-style-type: none"> <li>Dr. Gastineau Thierry (SANOFI PASTEUR, Global Quality Head of Innovation, Culture &amp; Engagement)</li> <li>Dr. Catherine Milne (EDQM, Head of section Biological Standardisation)</li> </ul>
13:20	Roundtable: Global perspectives on ATT deletion	Session to be moderated by: EFPIA Panelists: EFPIA, DCVMM, 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 DCVMM and Bill & Melinda Gates Foundation
16:20	Final remarks	
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.

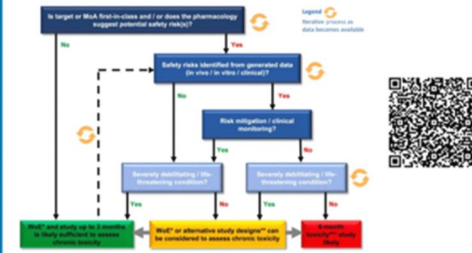


## EPAA/NC3Rs Webinar

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/nc3rsepa-webinar>

Pioneering Better Science



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

Show more

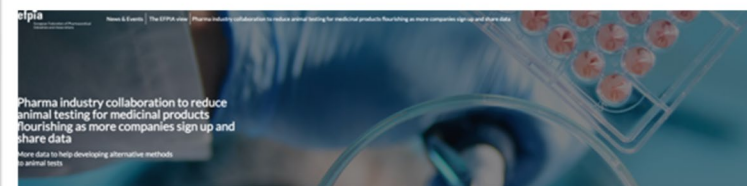
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Pharma industry collaboration to reduce animal testing for medicinal products flourishing as more companies sign up and share data

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

17.05.22

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

The contribution of this project has expanded considerably with three further companies (2) signing up and now over 100 tests - containing physicochemical, toxicological and environmental substance data - have been replaced 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, EPAA 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 minimize the impact on animals, and replace animal experiments wherever possible with alternatives.

Kirsty Reid, Director Science Policy, EPAA, said:

"EPAA 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 collaboration 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](http://www.elsevier.com/locate/yrtph)



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


Hsiao-Tzu Chien<sup>a,\*,1,2</sup>, Helen Prior<sup>b,1,2</sup>, Laura Andrews<sup>c</sup>, Leon van Aerts<sup>a,1</sup>, Annick Cauvin<sup>d</sup>, David O. Clarke<sup>e,1</sup>, Kaushik Datta<sup>f</sup>, Maggie Dempster<sup>a,1</sup>, Noel Dybdal<sup>b,1</sup>, Wendy Freebern<sup>1</sup>, Lolke de Haan<sup>1,1</sup>, Danuta Herzyk<sup>h,1</sup>, Adam Hey<sup>1</sup>, Thomas Kissner<sup>h,1</sup>, Sven Kronenberg<sup>h,1</sup>, Michael W. Leach<sup>h,1</sup>, Donna Lee<sup>h</sup>, Katrin Schutte<sup>h</sup>, Fiona Sewell<sup>h,1</sup>, Kevin Trouba<sup>h,1</sup>, Peter Ulrich<sup>g</sup>, Lucinda Weir<sup>r,1,3</sup>, Peter van Meer<sup>a,1,3,\*</sup>

# 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.



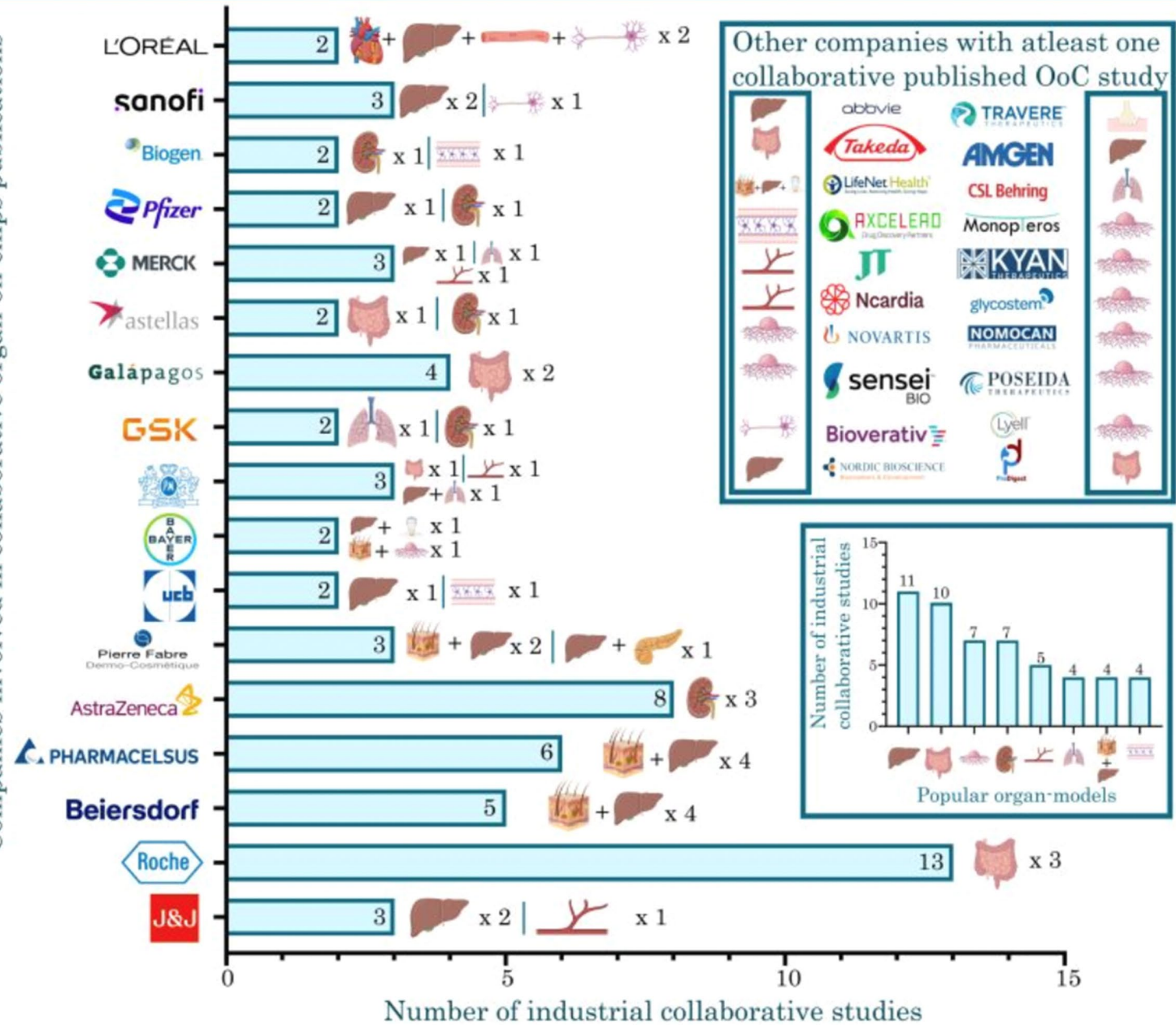
**Two-stage topics (IHI call 4) - 08 November 2023**  
Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical safety assessment



**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

Companies involved in collaborative organ-on-chips publications



Note: If the number of publications by a company exceeds 3, then the most published model is shown in the graph



# 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



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



# Promoting a culture of care





**REFERENCES**

If you are just starting to work with Culture of Care, this is a good reference to begin with:

- <https://norecopa.no/CoC/quick-start-guide>
- [https://ec.europa.eu/environment/chemicals/lab\\_animals/pdf/endorsed\\_awb-nc.pdf](https://ec.europa.eu/environment/chemicals/lab_animals/pdf/endorsed_awb-nc.pdf)

If you have some experience working with Culture of Care and want to get more inspiration, here's a selection of resources:

- <https://norecopa.no/CoC/resources>
- The European Federation of the Pharmaceutical Industry and Associations' Research and Animal Welfare Group: Assessing and benchmarking 'Culture of Care' in the context of using animals for scientific purpose. <https://doi.org/10.1177/0022367219887998>
- Communicating the Culture of Care - how to win friends and influence people. <https://www.rspca.org.uk/webContent/static/images/Downloads/CommunicatingTheCultureOfCare.pdf>
- 3Rs-Related and Objective Indicators to Help Assess the Culture of Care. Animals <https://doi.org/10.3390/ani1109069>

**LIVING YOUR CULTURE OF CARE** efpia

A positive Culture of Care is required for good animal science and supports staff to do their best work.

A Culture of Care, when using animals for scientific purposes, supports continuous improvement in:

- animal care and welfare
- support and recognition of staff involved directly and indirectly in the animal care and use programme
- scientific quality and integrity
- openness and transparency

A Culture of Care goes beyond meeting legal requirements. These organizations' values promote respectful attitudes and behaviour towards animals and co-workers.

This leaflet is designed to raise awareness around Culture of Care and how to support it in your organisation. It is based on the EFPIA Research and Animal Welfare group publication for assessing and benchmarking 'Culture of Care'.

**THE FOUR KEY COMPONENTS OF A CULTURE OF CARE**


A Culture of Care is not directly required in the Directive 2010/63. However, Climate of Care is recognised as one of the roles of an effective Animal Welfare Body (see the reference section). A working document on Animal Welfare Bodies and National Committees to fulfil the requirements under the Directive.



**CULTURE OF CARE IS THE RESPONSIBILITY OF EVERYONE INVOLVED IN ANIMAL ACTIVITIES**

ANIMAL FACILITY MANAGEMENT, VETERINARIAN, SENIOR LEADER, CHEMIST, STUDY PLANNER, ANIMAL SCIENTIST, ANIMAL TECHNICIAN, HEAD OF RESEARCH, STUDY DIRECTOR, STATISTICIAN, SAMPLE ANALYST, INSTITUTIONAL OFFICIAL, ENGINEER, MANAGER, PROJECT LEADER, BIOLOGIST





**PUTTING CULTURE OF CARE INTO PRACTICE**

**Some Tips**

- Start a discussion within your organisation. EFPIA have a short survey in English, French and German that can provide a starting point, or develop your own. Anonymous surveys give more honest feedback.
- Read the EFPIA publication
  - Critically assess your own organisation using the five framework indicators
  - Identify gaps involving staff (animal technicians and scientists)
  - Set goals and assign tasks/resources
  - Collectively monitor progress through feedback
- Share Good Practice across animal facilities
- Assess correlation between an improvements in your Culture of Care and animal welfare indicators (e.g. time allocated for animal checking, mortality rates, reproducibility of results, practice with respect to asepsis and post-operative analgesia) and staff satisfaction (internal feedback).

**FIVE CATEGORIES OF EFPIA CULTURE OF CARE FRAMEWORK**

- COMPANY VALUES**  
A company policy that outlines the approach to responsible animal research, values animal welfare and care as a priority and includes a statement around supporting openness in relation to animal research activities both internally and externally is essential.
- STRATEGIC APPROACH**  
The local Animal Welfare Body (AWB) in collaboration with senior management should support a Culture of Care and empower staff working with animals. It is expected that all persons responsible for ensuring compliance with the provisions of the Directive and the person or persons referred to in Article 24(1) and Article 25 (Named People) have a critical role in developing and supporting staff and a Culture of Care.
- IMPLEMENTATION STRUCTURES**  
The Establishment has clear structures that support and facilitate a Culture of Care.
- STAFF SUPPORT**  
The Establishment has local leadership which supports and develops mechanisms that demonstrate care and commitment to staff who work with and care for animals.
- ANIMAL CARE AND PROCEDURES**  
The Establishment has processes that support continuous improvement in the 3Rs and that where animals are used that there is appropriate experimental design and refinement in care and welfare practices.

# Where ICH\* guidelines contribution to 3Rs

ICH guidance	Subject Matter	Contribution to 3Rs
ICH S1	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.
ICH S2	Genotoxicity	Refinements to include in vitro genotoxicity testing.
ICH S3A	Toxicokinetics	Reduction in sampling regimens through micro-sampling and reducing satellite animals.
ICH S4	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.
ICH S5	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.
ICH S6	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.
ICH S7B/ 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.
ICH S8	Immunology	Weight of evidence decision making approach to stream-line immunological animal testing
ICH S9	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.
ICH S10	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.
ICH S11	Paediatric	Refinements to design, strategy and timing to reduce animal testing.
ICH S12	Biodistribution	<u>Includes recommendations to facilitate the development of gene therapy products while avoiding unnecessary use of animals</u> – mainly driven by reducing the number of animals required for biodistribution studies.
ICH M3	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.
ICH M7	Mutagenic impurities	The guidance describes in silico and in vitro approaches that should be used to reduce the necessity for in vivo testing.
ICH Q5	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.

# 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

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 <sup>1</sup>
Start of public consultation	15 October 2021 <sup>2</sup>
End of consultation (deadline for comments)	25 November 2021 <sup>3</sup>
Adopted by CHMP	22 April 2022

<b>Keywords</b>	Qualification of Novel Methodologies, IMI PREFER, Patients Preference studies
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The image shows the cover page of the document 'Regulatory Science Research Needs (version 1.0)'. It features the EMA logo and the text 'EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH'. The document number is EMA/705364/2021. The title is 'Regulatory Science Research Needs (version 1.0)'. Below the title is a 'Table of Contents' section listing various topics and their page numbers, such as 'Executive summary', 'List of Regulatory Science Research Needs (RSRN)', and 'Methods'. At the bottom, there is contact information for the official address and a note about the document being available in multiple languages.

Number	Research topic	Objectives	Expected impact	projects (including IMI, IHI, Other)
H1.1.1	Establish the best practices and standards for validation of 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 measured by biomarkers and develop joint standards for biomarker development. To develop guiding principles for surrogate endpoint validation that are acceptable to regulators, HTA and Payers.	Greater clarity in terms of data requirements and facilitating the development of novel endpoints, biomarkers and their qualification. Increased understanding and harmonisation (where appropriate) among stakeholders for novel endpoint and biomarker qualification. Ensuring a shared understanding about the 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 NECESSARY 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)

# Next steps for Pharma

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

Sort all animal using activities into 3 baskets as a basis to create roadmaps towards phasing out the use of animals in research:

basket 1



Animal testing for which alternative technologies have already been developed or which are not scientifically necessary

→ Implement Roadmap with Milestones

basket 2



Animal testing for which there are concrete ideas and hypothesis for the development of alternative methods

→ Prioritization of R&D Efforts and Business Cases

basket 3



Animal testing for which there is still no concept of how they can be replaced by animal-free methods: Greatest innovation potential

→ Evolution of Science and Blue Ocean Opportunities

Investment priority: Replace

Investment priority: Refine