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3Rs initiatives – a view from Industry

EMA Veterinary Medicines Info Day 2026

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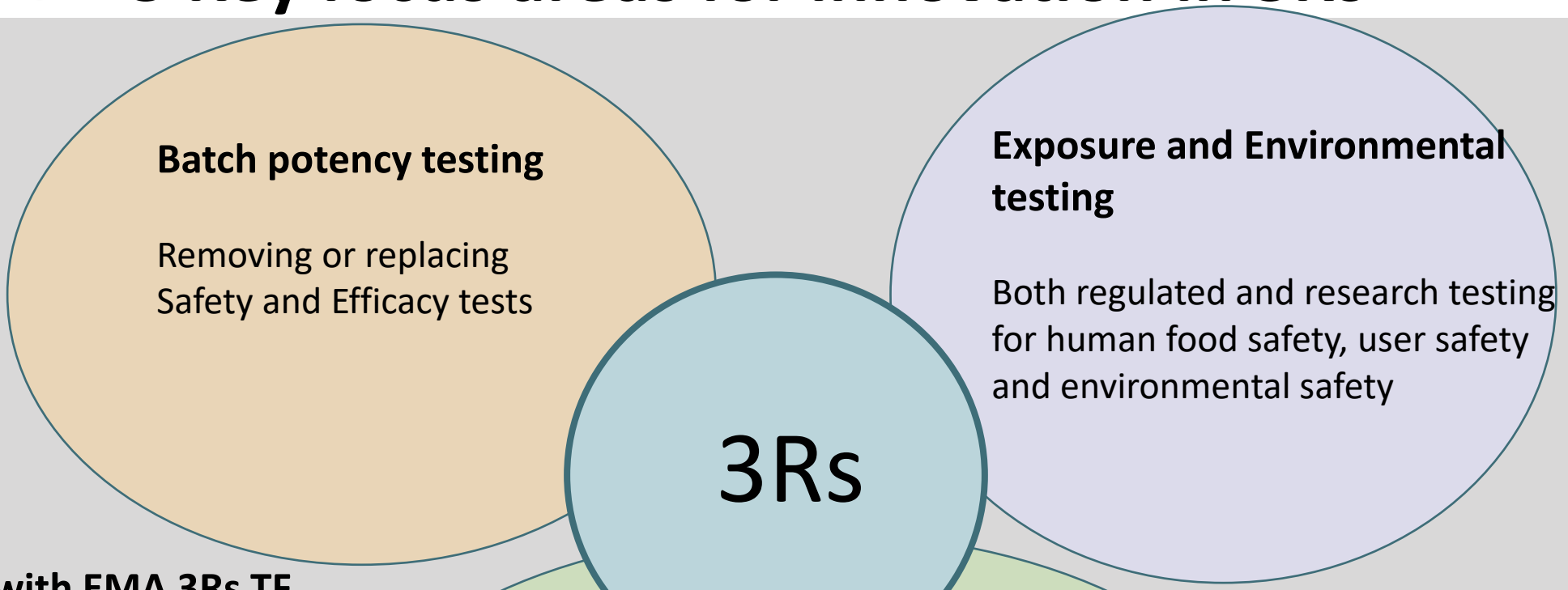
3 Key focus areas for innovation in 3Rs



Work with EMA 3Rs TF on targeted 3Rs topics and guidance in addition to cross-sectorial collaboration – supporting innovation in NAMs

Leverage 3Rs dedicated topics for Innovation Task Force (ITF) and SciAd

European Citizen's Initiative (ECI) Save Cruelty Free Cosmetics - Commit to a Europe Without Animal Testing - and EC response

1) Protect and strengthen the **cosmetics animal testing ban**. Initiate legislative change to achieve consumer, worker, and environmental protection for all cosmetics ingredients without testing on animals for any purpose at any time.

2) Transform EU chemicals regulation. Ensure human health and the environment are protected by managing chemicals without the addition of new animal testing requirements.

- Commission launched a roadmap project to outline milestones and specific actions over short and long term

3) Modernise science in the EU. Commit to a legislative proposal **plotting a roadmap to phase out all animal testing** in the EU before the end of the current legislative term.

- The Commission is proposing **a set of action points** to accelerate the reduction of animal testing in research, education and training, including activities that will increase cooperation with Member States.
- The Commission will continue to support research on alternatives to animal testing with **substantial funding.**

Roadmap expected to be final in 2Q26

Commission Communication in response to the ECI

Sectorial legislation

- Human medicines – Directive 2001/83/EC and Regulation 726/2004/EC: takes into account fully Dir2010/63/EU
- Alternative testing approaches that have not been formally validated can be accepted by responsible authorities (EMA or NCA)
- Abridged marketing authorisation applications (generics and biosimilars) / + informed consent applications can rely on preclinical studies of MA of reference medicinal product from originator

- New Human medicines legislation just completed trilogues - **We expect to see all of this within new Human Pharma legislation and NAMs definition in Biotech Act**
  - Strengthening 3Rs across life cycle of medicinal product
  - Strengthens current rules by adding obligations for MAA or MAH and by facilitating alternative testing approaches
  - Encourages cooperation between agencies and NCA in assessing substances, facilitating data sharing and carrying out joint non-clinical studies
  - Aims to future proof legislation to allow use of alternatives

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Batch release testing

3Rs Opportunities in Batch release testing

- **Supporting training for regulators on approaches to developing and transitioning to *in vitro* batch testing**
  - Support predictable and efficient regulatory timelines
  - Is there also value in industry training for SMEs etc?
- **Ph.Eur chapter 5.2.14 provides good guidance for industry**
  - Development of VICH GL should help globally
- **Health for Animals global 3Rs TF**
  - Working on improved working in WOAH terrestrial manual chapters to support 3Rs in batch release
- **Endotoxin testing – transitioning from LAL to rFC/rCR**
  - Represents a global strategic and validation challenge

Pyrogen testing

- Ph.Eur has new chapters for Pyrogen testing 5.1.13
- Rabbit Pyrogen test (RPT) has been removed and replaced with Monocyte Activation test (MAT) and Bacterial endotoxin test (BET)
- In Vet med we generally use BET only
  - Current BET method is LAL which uses Horseshoe crab blood
  - Ph.Eur now includes fully *in vitro* method rFC (recombinant Factor C) (Ph.Eur.2.6.32)
  - Push from EDQM to eventually remove LAL method for BET also
- Switching LAL to rFC for BET is an extensive exercise for industry
  - Companies should all be looking at how to make this switch
  - Expect long term issues with LAL reagents
  - 3Rs and sustainability benefit
  - Need to ensure consistent supply and access to rFC testing kits and supporting technology

Joint EDQM-EPAA Symposium: Pyrogen testing 2.0: Ethical, Evolving and Eco-friendly – Implementing safe, rapid, state-of-the-art and sustainable non-animal approaches worldwide, 25-26 February 2026 - European Directorate for the Quality of Medicines & HealthCare

Promoting the implementation of BINACLE Assay for Tetanus Vaccines Safety Testing (18 months)

Project Leaders:

Industry: Shahjahan Shaid (GSK), Emmanuelle Coppens (Sanofi); **EU Commission**: Katrin Schutte (DG ENV)

Supported by Laura Viviani (EPAA/Sciethiq)

Objectives:

Provide practical recommendations on how to overcome the complexities/difficulties related to the assay's critical reagents

Develop working instructions describing the key general steps to perform the BINACLE Assay for Tetanus neurotoxin

Share the working instructions and the practical recommendations in a dedicated online global workshop

Impact:

- Replace an obsolete animal-based test from the product release strategy
- Significantly reduce the lead time for the release of Tetanus-containing vaccines
- Improve supply chain resilience for one of the key pediatrics vaccines worldwide
- Support the implementation of the BINACLE assay within both human and veterinary vaccines manufacturers in Europe and globally, completing the over two decades of work to develop a full in vitro assay for the Tetanus component of multivalent or monovalent vaccines, substituting one of the few remaining safety in vivo tests that is still in use for routine vaccine Quality Control
- Multi-stakeholders engagement, data and knowledge sharing will facilitate adoption by manufacturers, acceptance by health authorities globally and update of regulatory guidance and pharmacopoeia monographs for Tetanus vaccines

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Exposure and Environmental safety testing - AhE Sector specific Roadmap

Animal Health Europe 3Rs roadmap

Regulatory Landscape

Starting point

- EU Regulation (2019/6) requires rigorous safety, quality, efficacy standards.
- MA requires submission of full dossiers to regulators.
- Animal-based data still required for some toxicity, safety, potency, PK/PD endpoints.

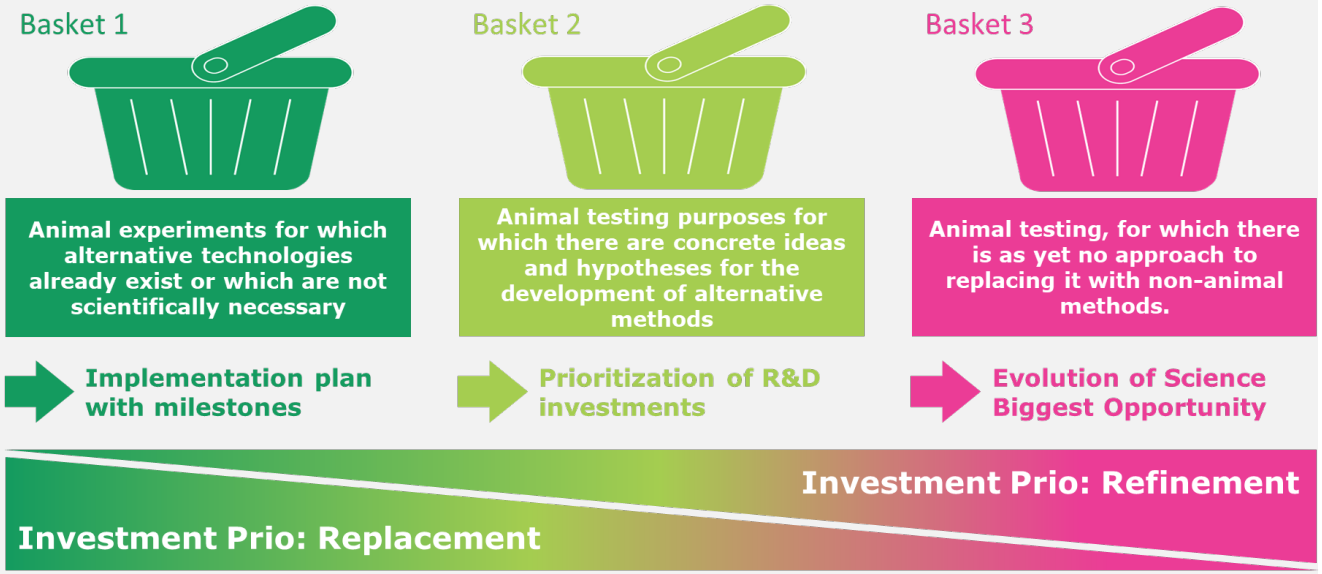
Working towards collaborative approach with EMA 3Rs WP and IMRWG3Rs

EFPIA roadmap for reference

efpia-recommendations-on-phasing-out-animal-testing-for-chemical-safety-assessments.pdf

Where Do Alternatives Exist?

- "3 baskets" system:
  - Basket 1 (NAMs exist/accepted),
  - Basket 2 (NAMs in development),
  - Basket 3 (no NAMs).
- Traffic light system for quick reference.
- Targeted research drives progress.



Basket diagram from EFPIA – AhE proposes an adapted version of this

Identify Progress and Challenges

- Good progress: Acute toxicity, irritation, sensitization, and some batch safety.
- Less progress: Repeat/chronic/repro/developmental toxicity, batch potency, environmental endpoints.
- Global misalignment leads to duplicate testing, regulatory delays, and costs.

Frontiers | Advancing human health risk assessment: the role of new approach methodologies

Strategic Priorities

- Develop NAMs for repeat/chronic toxicity, batch potency/safety, reproductive toxicity and environmental safety.
  - Make proposals for NAMs regulatory acceptance and/or validation for regulatory use
- Improve progress mapping and harmonization.
  - Visibility on what's been accepted is important
  - Utilise parallel scientific advice, VICH and IMR3RsWG to enhance global alignment

Invest in collaborative research and drive regulatory updates.

Recommendations for Action

- Detailed, actionable plan with milestones.
- Focus funding, address data gaps, harmonize metrics.
- Enhance mutual recognition and global guidelines.
- Roadmap sets a feasible direction: minimize animal use, maintain scientific rigor, drive global alignment.
- Success relies on collaboration, investment, clear policies, and committed stakeholders.

Qualification of an alternative to OECD TG 203 Fish Acute Toxicity test

Aim:

Regulatory acceptance by the EMA of OECD TG 236 (Fish Embryo Acute Toxicity Test) as an ethical Alternative for OECD TG 203 (Fish Acute Toxicity Test)

Ambition:

Accommodate the pressing EC goal to phase out acute fish toxicity testing within 2 years, by evaluating/qualifying the OECD TG 236 for VMP APIs

How:

- EPAA-coordinated Safe Harbour project with EMA, safeguarding confidentiality and without affecting past, current, or future approvals
- Industry partners generate GLP comparative datasets for fish embryo toxicity using APIs which have existing acute fish toxicity data; submit findings via EMA/CVMP Safe Harbour
    - Proposed funding by EPAA/EC with industry contributing through FTEs
    - Industry will select suitable APIs with historical fish toxicity data
    - Industry will place and monitor embryo toxicity testing and evaluate outcomes
- Regulators evaluate the evidence and recommend whether to accept OECD TG 236 as an alternative to TG 203

Opportunities in Safety NAMs

- **Participating in EPAA Partners forums example - exposure assessment**
  - Promoting the use of PBPK modelling, QIVIVE, and other ways to assess data
  - Represented in follow-up project
- **Engaging with the PARC consortium collaboration through EPAA**
  - Many important cross-sectoral aspects that can impact Animal Health – for example NGRAroute (task 2,2), where stakeholder engagement is critical as new technology evolves to support this approach, but also to ensure this approach does not result in additional safety factors that could impact withdrawal periods

Partnership for the Assessment of Risks from Chemicals | Parc (eu-parc.eu)

- **Exploring the use of big data and AI to reduce animal use in safety assessment**
  - Can data from historical control groups be used to reduce animal numbers (already being explored in Human Health)

    Hartung T (2023) Artificial intelligence as the new frontier in chemical risk assessment.

    Front. Artif. Intell. 6:1269932. doi: 10.3389/frai.2023.1269932

EPAA review of regulatory requirements for a second (non-rodent) species in repeated-dose toxicity studies: Identifying 3Rs opportunities

- Regulations on human safety assessment may require testing in rodent and a second, non-rodent species to identify potential health hazards not detected in rodent studies. However, the design of non-rodent repeated-dose toxicity studies has limitations and lack sensitivity.
- The added value of non-rodent studies depends on the context of use. For example, it has been shown that these studies provide no benefit to risk assessment of PPP in most cases.
- Multiple initiatives are actively developing 3Rs opportunities to reduce and ultimately replace non-rodents. New approach methodologies (NAMs) may assist in determining sensitivity and human relevance of non-rodent species prior to testing.

- The EPAA established a cross-sector working group to map these initiatives and actions in the context of the European Commission's Roadmap for phasing out animal testing for chemical safety assessment

VICT3R

Developing and implementing Virtual Control Groups to reduce animal use in Toxicology Research

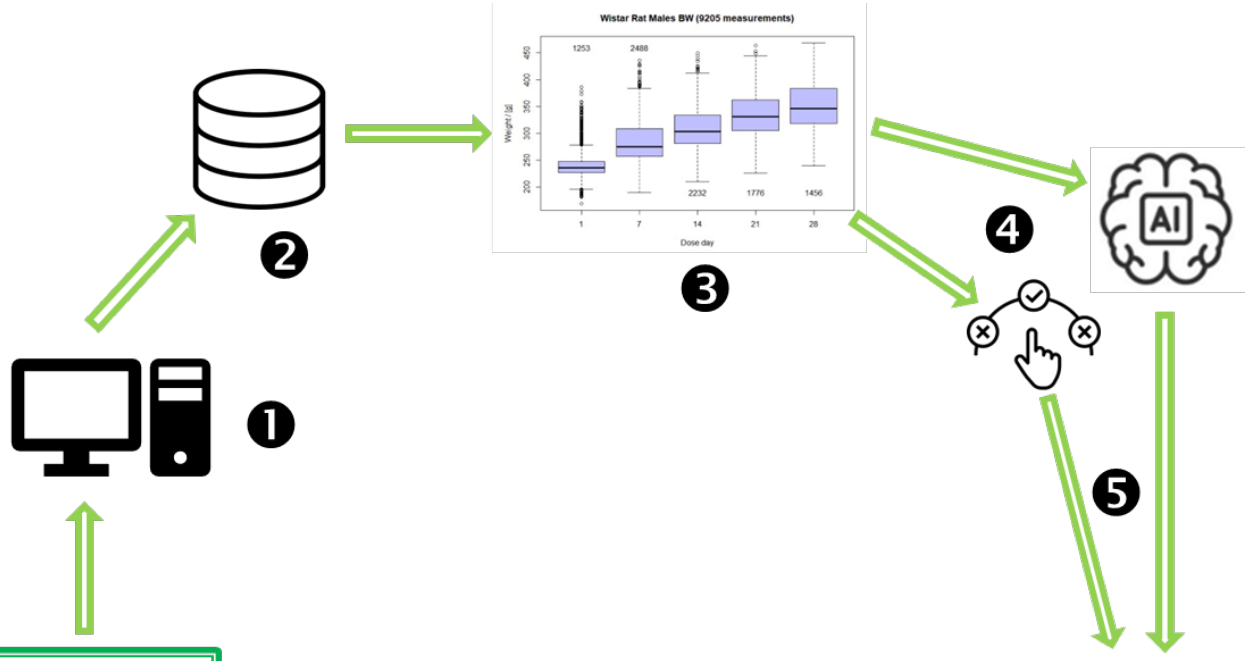
IHI VICT3R – Project Overview

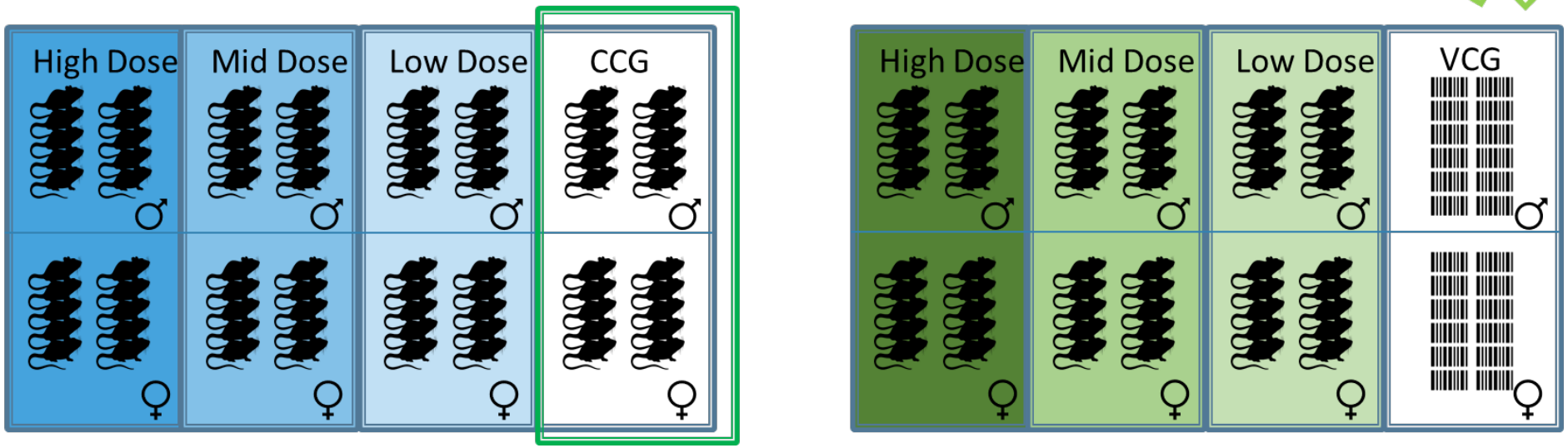
Developing and Implementing Virtual Control Groups to Reduce Animal Use in Toxicology Research

This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101172693. The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, Europa Bio, MedTech Europe, and Vaccines Europe and Instem Scientific Limited.
Funded by the European Union, the private members, and those contributing partners of the IHI JU. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the aforementioned parties. Neither of the aforementioned parties can be held responsible for them.

The VCG Concept

1. Collection of historical data from CCG (concurrent control groups)
2. Shared repository of data from CCG
3. Data curation and characterization
4. Generation of Virtual Control Groups (VCG)
5. Use of VCG in new studies





Adapted from Steger-Hartmann et al. 2020, ALTEX; https://doi.org/10.14573/altex.2001311

The VICT3R Community

Academic institutions (6)

Universitat Pompeu Fabra Barcelona

Fraunhofer ITEM

technische universität dortmund

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Universität Konstanz

VUB VRIJE UNIVERSITEIT BRUSSEL

SMEs (8)

SYNAPSE Research Management Partners

grit42

MEDBIO INFORMATICS
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Industry Partners (23)

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Incyte

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instem
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BSL Bioservice
MUNICH

ucb Inspired by patients. Driven by science.

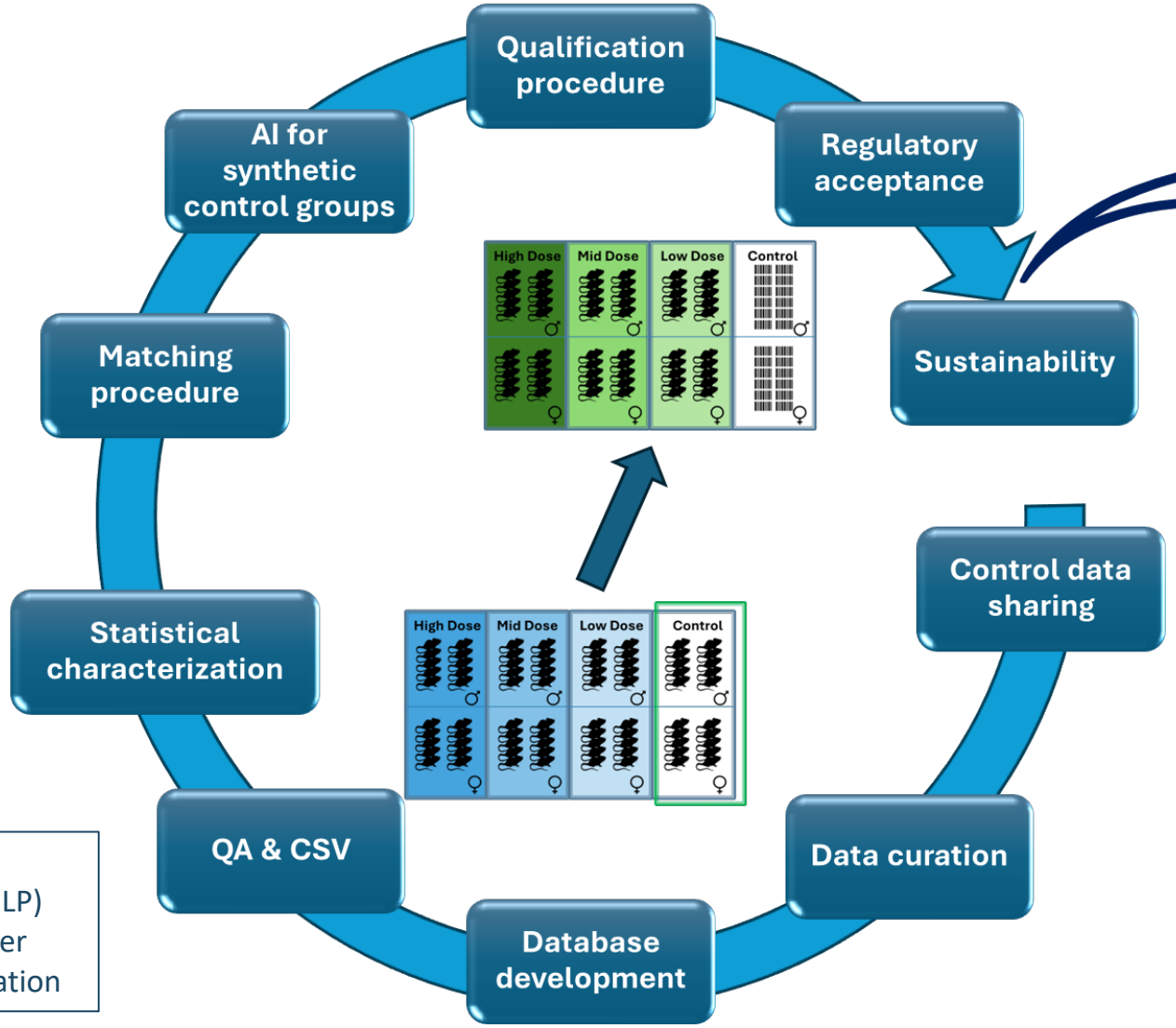
abbvie

GSK

SERVIER
moved by you

zoetis

Process, Outcome & Impact



- ✓ Ethical: reduced animal numbers (3R)
- ✓ Economic: lower animal costs
- ✓ Scientific: improved study interpretation and safety assessment
- ✓ Environmental: reduced pollution and energy consumption

QA: quality assurance (GLP)
CSV: computer system validation

Contexts of Use (CoU) in EMA SAWP Qualification Process

EMA qualification steps

Three steps for the implementation of the VCG concept were identified for the EMA qualification procedure, which are assigned to three Contexts of Use (CoU).

Final qualification

The final qualification will depend on the outcomes of the CoU I-III and EMA feedback.

CoU III

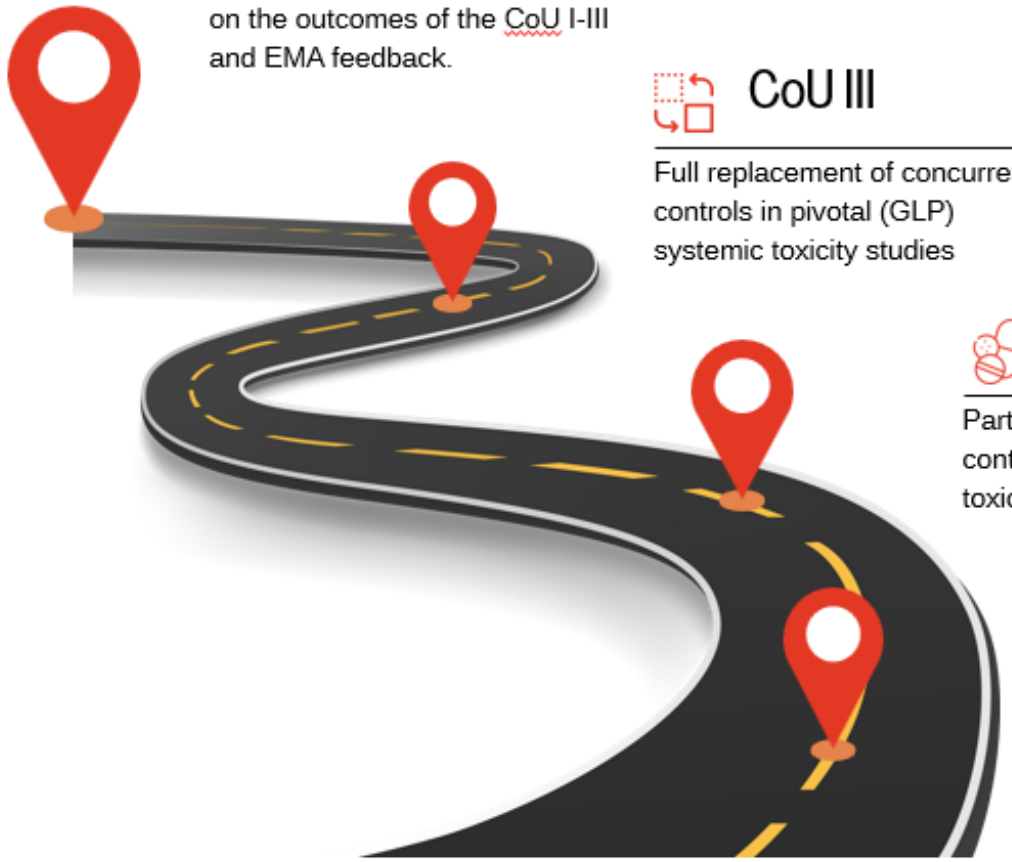
Full replacement of concurrent controls in pivotal (GLP) systemic toxicity studies

CoU II

Partial replacement of concurrent controls in pivotal (GLP) systemic toxicity studies

CoU I

Application in dose-range finding (DRF) non-GLP studies



Where we currently are

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Discovery Research

Areas of early research for Animal reduction

- Using RWE/Big Data and AI analysis tools to leverage existing data in discovery
- Using modelling technology to predict *in vivo* activity on early screening
- Exploring the use of external control arms in studies
- Working to understand *in vitro/ex vivo* models for disease or organs

  for early screening for toxicity and understanding mechanism of action

  Establishment and Characterization of Novel Canine Organoids with Organ-Specific Physiological Similarity

  Christopher Zdyrski, Vojtech Gabriel, Oscar Ospina, Hannah Wickham, Dipak K. Sahoo, Kimberly Dao, Leeann S. Aguilar Meza, Leila Bedos, Sydney Honold, Pablo Piñeyro, Jonathan P. Mochel, Karin Allenspach

  bioRxiv 2022.07.15.500059; doi: https://doi.org/10.1101/2022.07.15.500059

- Refinements to avoid challenge studies in early vaccine research

Commitment to Animal welfare and the 3Rs

- Our products directly support animal health and welfare
- Commitment to achieve animal free batch release testing
- Commitment to engage with regulatory and academic and cross sectorial projects to reduce or replace animal use in exposure and environmental studies
- Committed to reducing animal use in early research wherever possible
- Follow 3Rs principles in all we do

How can we do more and better?

Need for communication from regulators on what has been accepted

Training for industry (esp SMEs) on how to use and approach NAMs

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Thank you!