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

Agenda

Welcome - Kirsty Reid, EFPIA and Barney Reed, RSPCA	
14.30	Update on the RSPCA's 'Focus on severe suffering' initiative - Barney Reed, RSPCA
	Tackling severe suffering within the context of EFPIA's vision, aims and activities - Kirsty Reid, EFPIA
Case study examples - approaches to avoiding and reducing severe suffering	
14.50	A new group housing approach for non-human primates in metabolism studies - John Kendrick, Labcorp
15:05	Refining and reducing animal use in challenge potency tests - Emmanuelle Coppens, Sanofi
15:20	Refining animal use in Maximum Tolerated Dose studies - Thomas Bertelsen, Novo Nordisk
Questions and panel discussion	
15:35	Challenges and progress towards avoiding and reducing severe suffering
15:55	Concluding comments
16:00	End

This webinar aims to:

- Illustrate our **shared ambition** for reaching a point where no animal used in research or testing experiences ‘severe’ suffering
- **Showcase steps the pharmaceutical industry is taking** to review, reduce and avoid ‘severe’ suffering
- Discuss the current challenges in achieving **further progress**
- **Encourage collaboration and activity** within EFPIA member’s and other organisations towards this goal

Update on the RSPCA's 'Focus on severe suffering' initiative

Barney Reed
Senior Scientific Manager
Animals in Science Department
RSPCA

FOCUS ON SEVERE SUFFERING

BARNEY REED

ANIMALS IN SCIENCE DEPARTMENT

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Within the UK and the European Union, ‘severe’ procedures are those where animals used in science are likely to experience:

- severe pain, suffering or distress
- long-lasting moderate pain, suffering or distress, or
- severe impairment to their wellbeing or general condition

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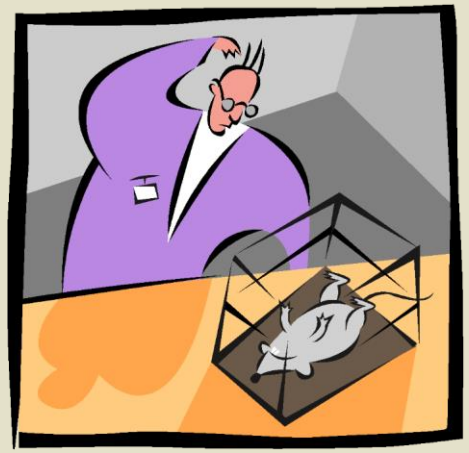
e.g. Annex VIII of EU Directive 2010/63

Causes of severe suffering



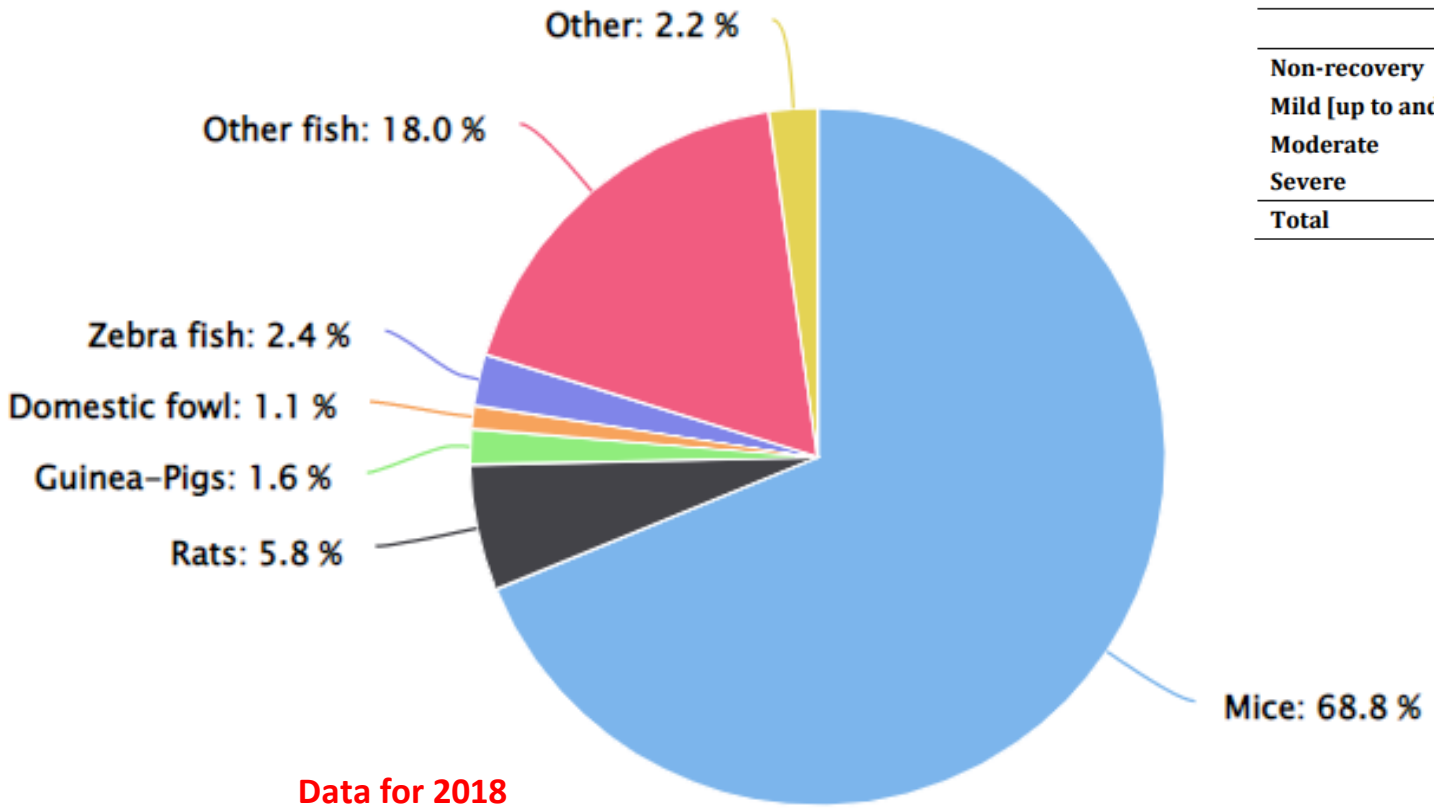
THREE MAIN REASONS

- Animals may be used in studies of diseases or conditions that can cause severe suffering
- A combination or series of less severe factors can combine to lead to an increase in overall suffering
- Where animals die unexpectedly, or where the death of an animal is used an ‘endpoint’ of the study

+1M **

procedures involving severe suffering each year within UK and EU

** based on latest available data



Data for 2018

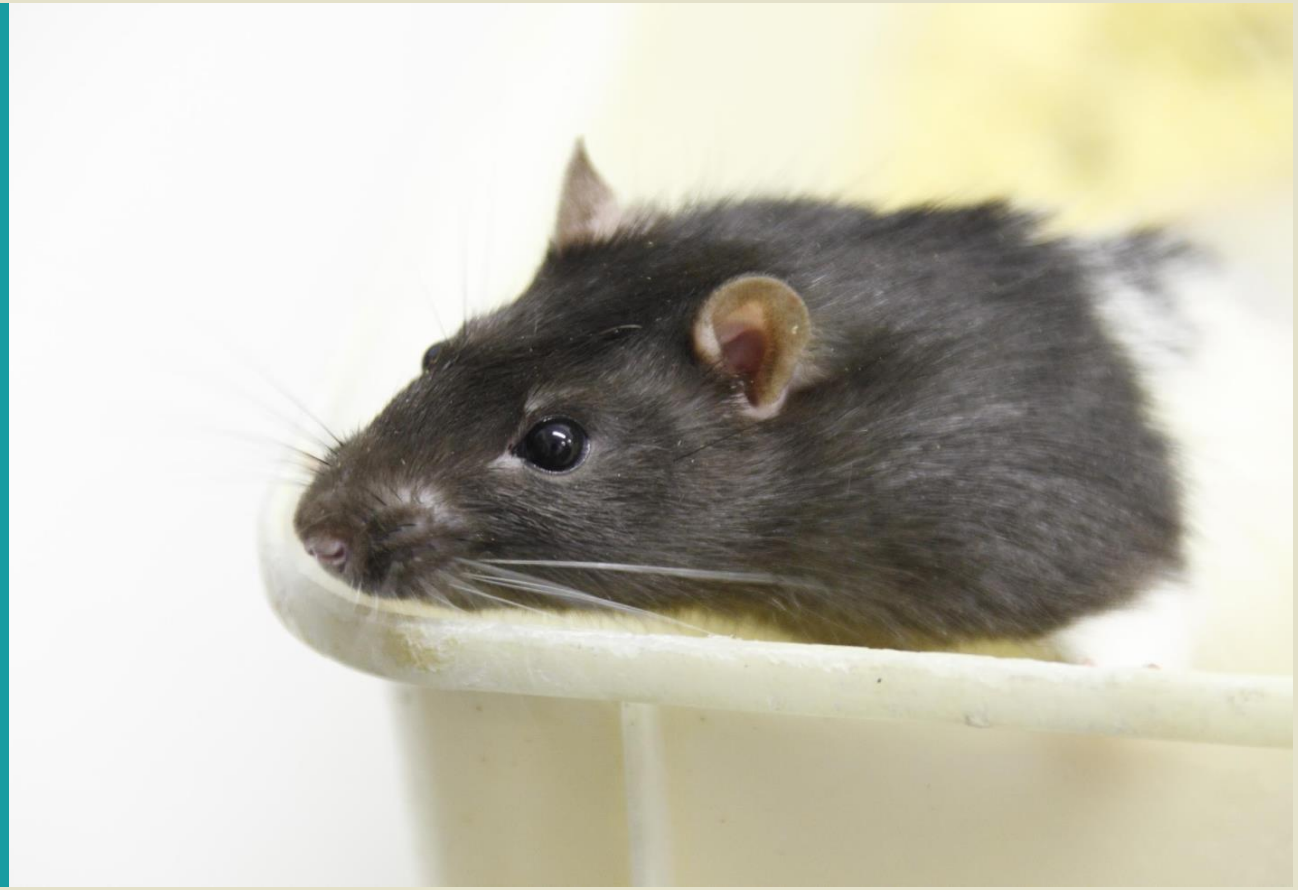
	2017	2018 (EU)	2018 (EU-28 incl. NO)
Non-recovery	6% (621,054)	6% (534,999)	6% (612,094)
Mild [up to and including]	51% (4,865,721)	49% (4,522,747)	50% (5,469,214)
Moderate	32% (3,071,828)	34% (3,096,460)	34% (3,658,621)
Severe	11% (1,023,138)	11% (983,237)	10% (1,064,925)
Total	**100% (9,581,741)**	**100% (9,137,443)**	**100% (10,804,854)**

https://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

10M

animals across the world experience severe suffering each year

*estimate



All laboratory animal suffering is a concern, but reducing and avoiding 'severe' suffering should be a top priority

- ✓ Ethical and animal welfare benefits
- ✓ Legal requirements to minimise suffering
- ✓ Public concerns about harms to animals
- ✓ Scientific benefits - better welfare means better science

Our initiative

Since 2012, the RSPCA has been **working collaboratively** with the scientific community in the UK and internationally, to initiate and promote a range of activities aimed at identifying and promoting **practical steps** which will help people to **reduce** or, ideally, **avoid** 'severe' suffering.

FOCUS ON SEVERE SUFFERING

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NEW DATA PUBLISHED ON 'SEVERE' SUFFERING IN THE UK AND EU

15th July 2021

The most up-to-date data currently available on the use of animals in research and testing in the UK, and the EU, was published on 15 July 2021. This information is important for openness and transparency and can also help to focus 3Rs efforts more effectively. Below is a summary of the data relating to the number of animals reported to have experienced 'severe' suffering, and in which areas of science.

The mouse is the species most likely to experience 'severe' pain, suffering, distress or lasting harm. In both the UK and EU, batch potency testing of vaccines and other substances (such as botulinum toxin) for quality control purposes is the category responsible for the most uses of animals reported as 'severe'.

UK

Data for 2020
Source: Home Office. See Tables 3.1 and 3.2 of the Data Tables associated with the Statistics of scientific procedures on living animals, Great Britain 2020 – published 15 July 2021.

Summary

58,499 experimental procedures using animals (4% of the total) were reported as causing 'severe' pain, suffering, distress or lasting harm.

44,093 – for regulatory purposes *(9% of all use for regulatory purposes was 'severe')*
10,867 – in basic research
3,511 – in applied research

Main categories of research and testing involving severe suffering

(data shown represent the number of 'procedures' undertaken that were reported as causing 'severe' suffering)

35,997 – Batch potency testing *(represents 61.5% of all experimental procedures involving animals that were 'severe')*
2,592 – Nervous system
2,567 – Immune system
1,512 – Human infectious disorders
1,479 – Batch safety testing
1,303 – Oncology

Which animals experienced the most 'severe' suffering?

(data shown represent the number of 'procedures' undertaken involving those animals)

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focusonseveresuffering.co.uk/latest

EXAMPLES OF POTENTIALLY 'SEVERE' PROCEDURES

Batch potency testing of vaccines (where control animals experience 'severe' disease symptoms) **and other biologics** e.g. botulinum toxin, for regulatory purposes

Studies involving infectious disease models, including the development of vaccines or other treatments, where animals may experience 'severe' disease symptoms

Various tests involved in regulatory toxicology, including ecotoxicology, especially where animals may become moribund or die

Monoclonal antibody production using the mouse ascites method – NB this method has not been used in the UK since 2012 but is still used elsewhere in the world

Some cancer models – involving large tumours, resection, bone metastasis, brain tumours, pancreatic tumours

Some heart disease models – myocardial infarction induction; monocrotaline (MCT)-induced pulmonary arterial hypertension; transverse aortic constriction/banding

Multi-organ failure models

Demyelination of the central nervous system (CNS)

Models of motor neurone disease (MND)

Spinal cord injury models

Neuroscience studies using non-human primates, involving the cumulative effects of numerous surgeries, regular and long periods of restraint, and/or fluid or food control

Tamoxifen as an inducer of gene function

Irradiation with reconstitution of bone marrow

Cerebral malaria in rodents

Pancreatitis models

Expert Working Groups

- Seizures, convulsions and epilepsy
- Experimental autoimmune encephalomyelitis (EAE)
- Rheumatoid arthritis
- Sepsis
- Spinal cord injury
- Bone marrow ablation and reconstitution

- Avoiding mortality

Events

- **Brussels**, Belgium - 2016
- **Berlin**, Germany - 2017
- **Stevenage**, UK - 2019
- **Athens**, Greece - 2019

- **Manchester**, UK - 20 April 2022
- **Stockholm**, Sweden - 24/25 August 2022

100s of participants: regulators, scientists, veterinarians, animal technologists and care staff, members of Animal Welfare Bodies and National Committees etc.

Website

PERCEIVED OR ACTUAL REGULATORY REQUIREMENTS

The OECD recognises that *'with increasing knowledge and experience, investigators in animal research will be able to identify more specific, early humane endpoints in the form of clinical signs for impending death or severe pain and distress. This would permit international harmonisation of these humane endpoints'*. **Researchers and establishments should challenge regulatory bodies to accept evidence that death can be predicted and to accept data from tests in which humane endpoints have been defined and implemented.**

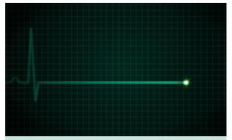
PREDICTING ANIMAL DEATHS

There is always scope to better predict mortality, and to challenge any assumptions that a proportion of deaths is 'inevitable' or that endpoints cannot be refined. Perceptions about the ability to predict death often change; for example, telemetered body temperature using microchips has improved the ability to define humane endpoints and avoid severe suffering in a number of fields. It is good practice to keep up with the literature and to identify any new approaches that may be suitable for trialling at the facility.

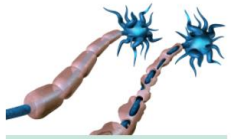
ACTIONS FOR THE AWERB (OR EQUIVALENT BODY)

The AWERB, AWB, IACUC or AEC should ask for explanations of humane endpoints, including how they are defined, refined and implemented. They can also ask to see, and discuss, animal 'fate' data, including a breakdown of animals humanely killed as part of the experiment, found dead, killed because they are close to a humane endpoint, or because they are not needed (surplus). This will allow the institution to monitor wastage, identify where endpoints may need to be revised and see where additional welfare monitoring should be applied.

For further information about humane endpoints, see www.humane-endpoints.info and www.nc3rs.org.uk/humane-endpoints.

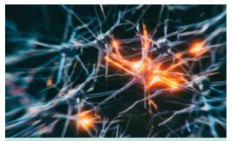


Avoiding mortality
Hawkins et al. (2019)
Avoiding mortality in animal research and testing.
ISBN: 978-0-901098-17-7A

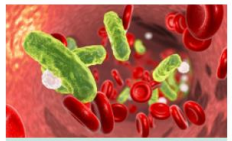


Experimental Autoimmune Encephalomyelitis (EAE)
Wolfensohn et al. (2013)
Reducing suffering in experimental autoimmune encephalomyelitis (EAE).
Journal of Pharmacological & Toxicological Methods 67, 169-176

Rheumatoid arthritis
Hawkins et al. (2015)
Applying refinement to the use of mice and rats in rheumatoid arthritis research.
Inflammopharmacology 23, 131-150



Seizures, convulsions and epilepsy
Wolfensohn et al. (2013)
Reducing suffering in animal models and procedures involving seizures, convulsions and epilepsy.
Journal of Pharmacological & Toxicological Methods 67, 9-15



Sepsis
Lilley et al. (2015)
Refinement of animal models of sepsis and septic shock.
Shock 43, 304-316

Spinal cord injury
Lilley et al. (2020)
Refining rodent models of spinal cord injury.
Experimental Neurology 328, 113273

CUMULATIVE SEVERITY

Apart from experimental procedures and their impacts, each animal experiences many other **events during their lifetime** – including transport, marking for identification, capture, handling, restraint, laboratory housing and husbandry, and humane killing. Some of these events can be anxiety-inducing, painful or distressing, and may affect the animal's ability to cope with experimental procedures.

It is important to consider how the effects of all these events may interact with one another. The term 'cumulative severity' is often used, but harms do not 'accumulate', or simply add up – although animals may become sensitised to certain procedures (e.g. repeated injections), so the distress associated with each one is increased. As another example, if recovery time is not sufficient following stressful events (such as cage cleaning and change) before conducting a procedure, then the severity of the procedure may increase. The cumulative impact of some procedures (e.g. surgery without the most effective perioperative analgesia regime) may be long-lasting or permanent.

Alternatively, animals may habituate (become used) to repeated procedures, which can reduce suffering, especially if they can be trained using positive reinforcement techniques to avoid restraint.

It is critically important not to make subjective assumptions about cumulative severity either increasing or decreasing – expert input and monitoring systems are both necessary to ensure that the animal's **lifetime experiences** are understood and that welfare issues, and refinements, are identified.

Regarding severe suffering, two key questions are:

Might a procedure that does not prospectively appear to be severe, actually end up being severe in practice, because of cumulative effects?

Can we use the concept of cumulative severity to make multiple refinements (or 'marginal gains'), which will combine to significantly reduce severity?

For more information, see section 3.3. of the UK Animals in Science Committee **review of harm-benefit analysis**

◂ SEVERE PROCEDURES

MORTALITY ▸

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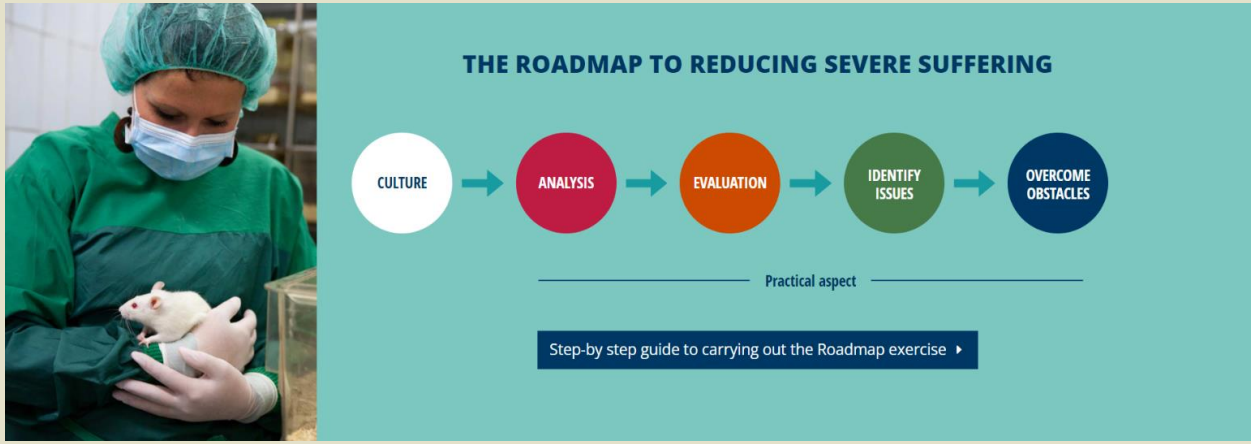
lasa Laboratory Animal Science Association

LAVA Laboratory Animals Veterinary Association A division of the British Veterinary Association

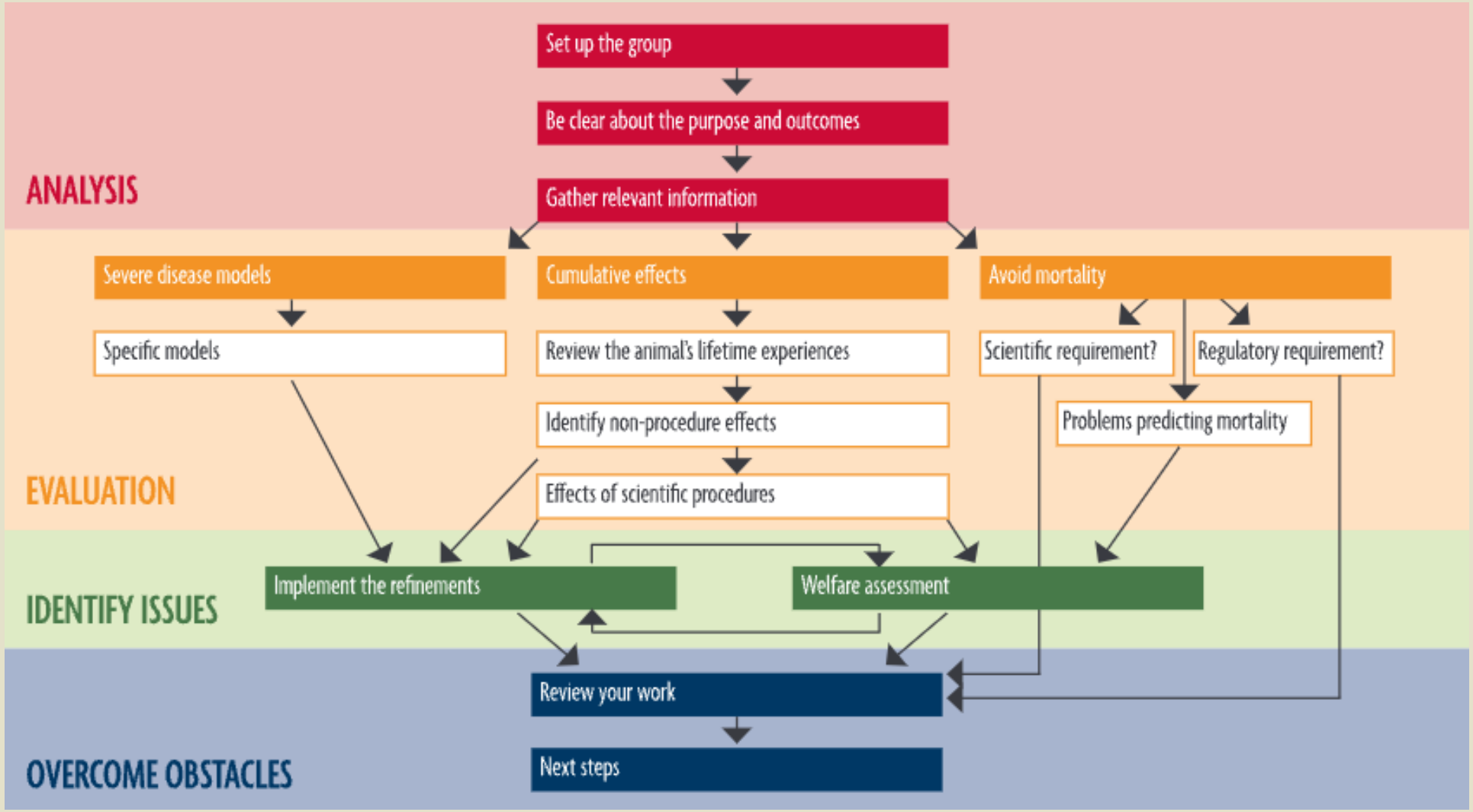
iat

A commitment to address severe suffering

- Agreement as a priority area for attention and action
- Institutional strategy and responsibilities
- Setting of clear objectives



- Consider as part of the ‘Culture of Care’


ANALYSIS
Set up the group
Be clear about the purpose and outcomes
Gather relevant information
Severe disease models
Cumulative effects
Avoid mortality
Specific models
Review the animal's lifetime experiences
Scientific requirement?
Regulatory requirement?
Identify non-procedure effects
Problems predicting mortality
EVALUATION
Effects of scientific procedures
IDENTIFY ISSUES
Implement the refinements
Welfare assessment
Review your work
OVERCOME OBSTACLES
Next steps

Examples of questions to consider

- Why is severe suffering needed? Is there a robust scientific justification?
- Is the ‘model’ translatable? How significant are the proposed benefits of the work?
- Could the protocol be run with a moderate severity limit?
- Is there a regulatory requirement for the experimental design and ‘endpoint’? Can this be challenged?
- Are welfare assessment and monitoring protocols optimised?
- What more could be done to mitigate impacts on animals?

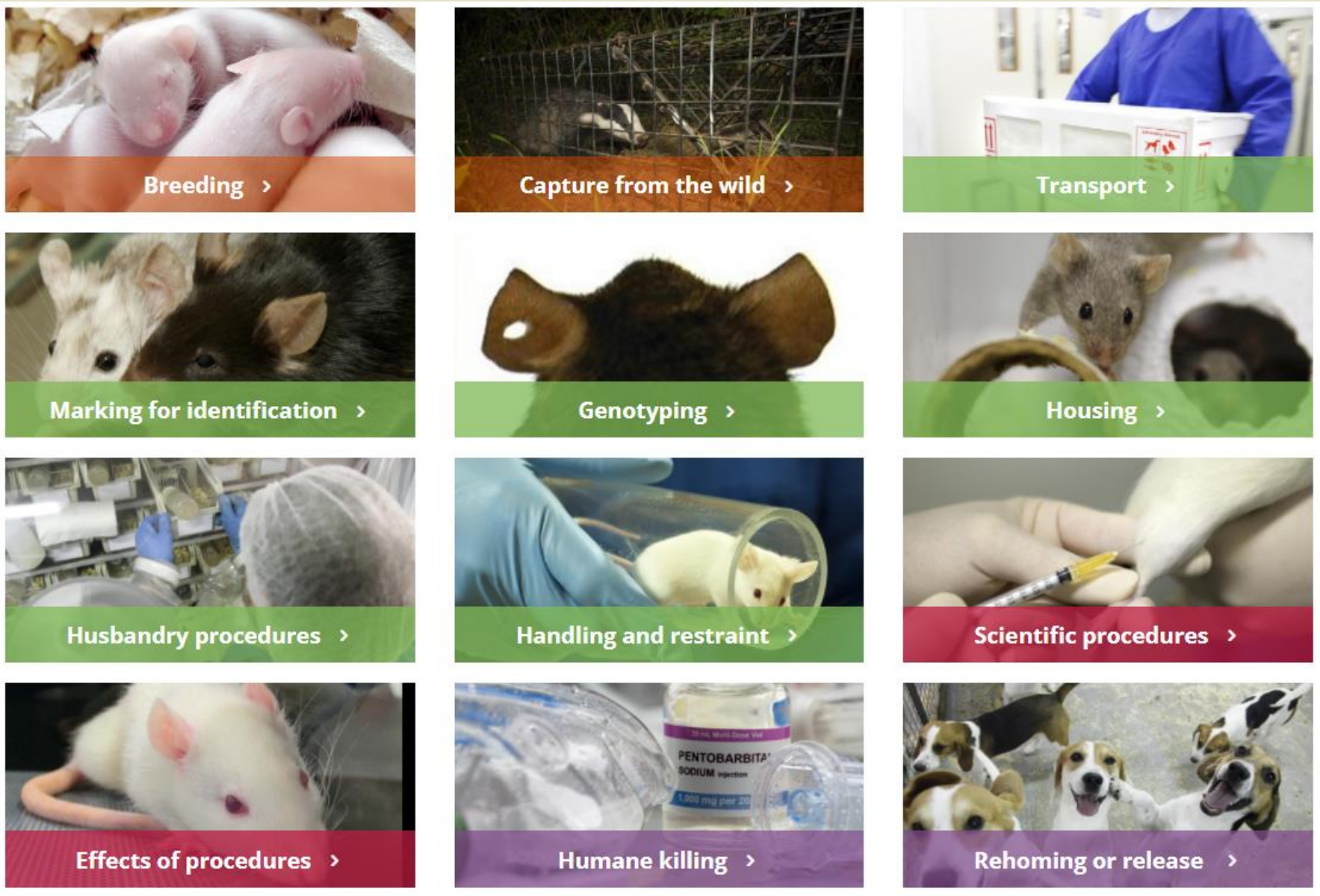
What does this study involve doing to the animals?	What will the animals experience? How much suffering might it cause? What might make it worse?	How will suffering be reduced to a minimum?	
	Adverse effects and indicators of these	Methodology and interventions	Humane endpoints
Administration of rheumatoid arthritis inducer	Capture and restraint – distress. Aggression, vocalisation, unwilling to be caught. Administration i.d. or s.c. – pain. Flinching, vocalisation, aggression. Pain or ulceration around injection site. Attention to site, reduction in nest quality, body weight/food intake reduction,	Competent, empathetic capture (e.g. not by tail) and handling, habituate to handling and restraint. Use gaseous anaesthesia for i.d.; inject into rump, not tail base (if tail base is painful, restraint by the tail will hurt). Minimise volumes and doses, use multiple sites if large volumes. Ensure injectate formulated to minimise adverse effects Inject into rump (less risk of ulceration); never inject into the foot; if attention paid to site apply topical anaesthesia and review	Humane endpoints with respect to administration of inducer in general: - Ulceration that is painful, shows no signs of healing or becomes infected. - If an ulcer reaches >5 mm, the vet or senior animal technologist should be informed and consulted about treatment. Animal should be humanely killed if no signs of healing within 3 days.

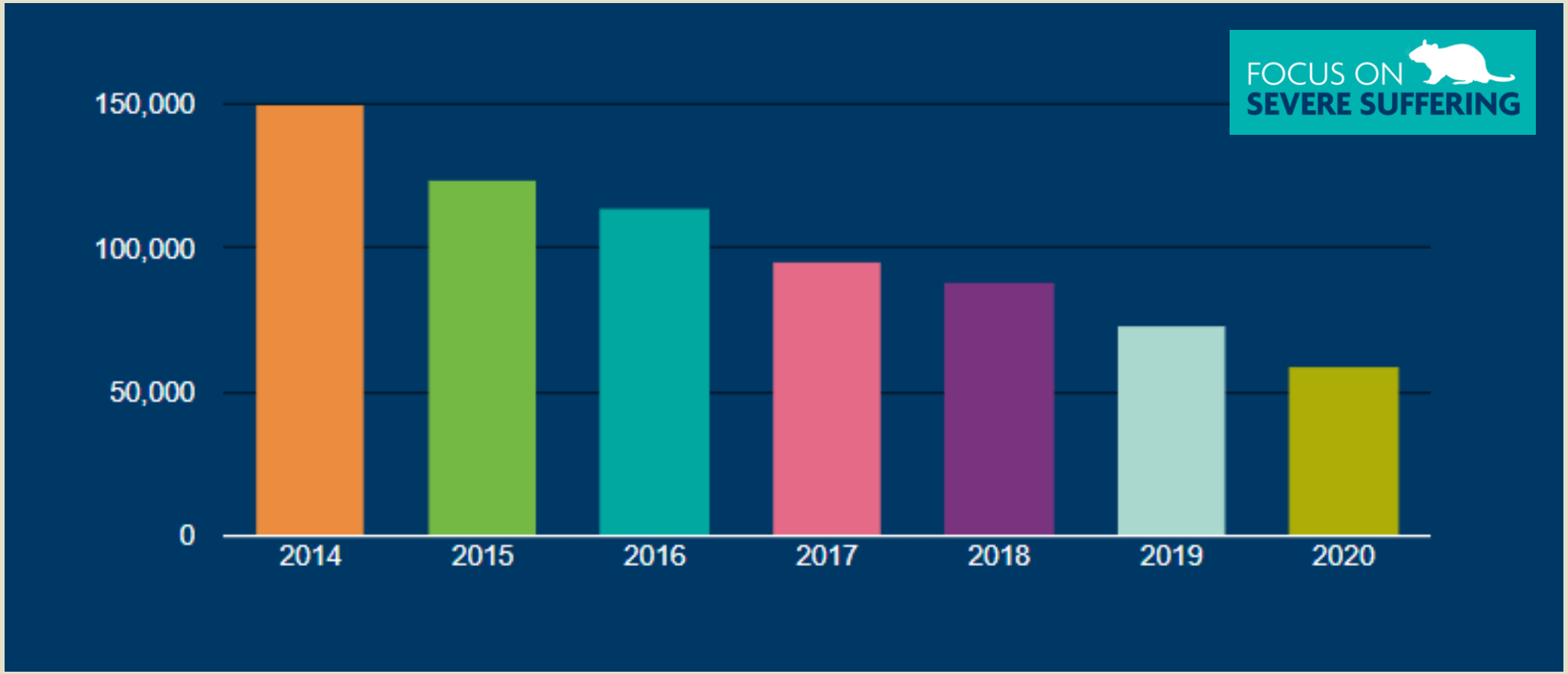
ce of the animal	Welfare issues	Ways of mitigating these
ored in-house. Supply and are carefully matched and animals provided with litter, nest boxes and nesting material. Cages are cleaned weekly.	Distress due to separation of dam and pups at weaning.	Ensure removal from dam is appropriately timed and keep litters together wherever possible. Review frequency of cage change (e.g. fortnightly?) to ensure cage is sufficiently clean but with minimal disturbance.
Once, between rooms within the same building before procedures begin.	Stress and anxiety due to movement.	Move in home cages, minimise distance, think about timing, ensure sufficient time to recover before any other interventions or procedures.
Animals are identified using microchips, which involves capture and restraint for insertion.	Distress due to restraint, short term pain of chip insertion.	Trial less aversive capture techniques (see below). Research pros and cons of sedating or anaesthetising mice. Ensure adequate checks in case of longer term discomfort.

Sourcing

Transport

Marking for identification


Breeding ›
Capture from the wild ›
Transport ›
Marking for identification ›
Genotyping ›
Housing ›
Husbandry procedures ›
Handling and restraint ›
Scientific procedures ›
Effects of procedures ›
Humane killing ›
Rehoming or release ›



61% reduction

in experimental procedures causing severe suffering in the **UK** since 2014

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

Tackling severe suffering within the context of EFPIA's vision, aims and activities

Kirsty Reid
Director Science Policy
EFPIA

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

The pharmaceutical industry members of EFPIA:

- Are fully committed to the principles of **3Rs**;
- Continue to support the objectives of the **Directive 2010/63/EU** on the protection of animals used for scientific;
- Continue to strive to go **beyond what is legally required** and work to develop and validate systems leading to improved 3Rs, animal welfare and high-quality science and technologies in every day practice including focus on **tackling severe suffering**.

Refining and reducing animal use in potency testing of human combined DTaP* vaccines

* Diphtheria, Tetanus, acellular Pertussis

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Emmanuelle Coppens, Global Analytical Sciences

RSPCA – EFPIA webinar: *How the pharmaceutical industry is tackling 'severe' suffering in animals used in science - 26 January 2022*

Presentation Outline

1 Regulatory context and 3Rs status for DTaP potency assays

2 Single immunogenicity assay (SIA) vs current methods

3 The long journey

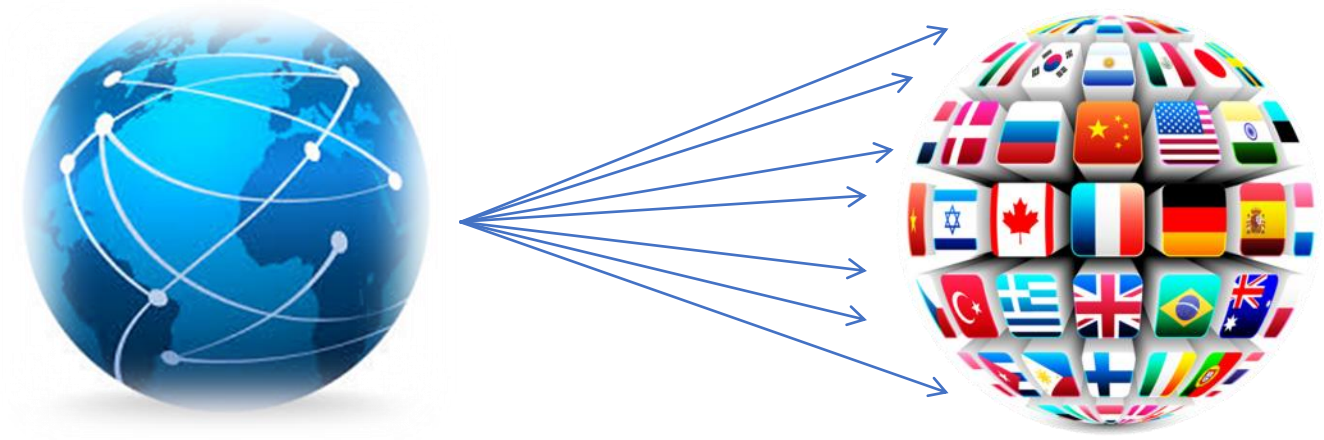
4 Conclusion

REGULATORY CONTEXT AND 3Rs STATUS FOR DTaP POTENCY ASSAYS

Testing Requirements for Medicinal Products : Specific National Batch Release Worlwide

Companies are globalized

Batch release requirements are nationalized*



*Note: or regionalized (e.g. EU)

1 product

Various and specific requirements for the same product

Regulatory assays for testing for DTaP potency

D &T Potency

Challenge tests

- Guinea pigs for D, mice and guinea pigs for T

  Multi-dilution assay (ED50)
  Ph. Eur.; WHO; JP; Chinese Ph.

  One-dilution assay (limit test)
  Ph. Eur.; WHO

  ***In vivo* toxin neutralisation test**
  US NIH (USPHS)

Immunogenicity tests

- ELISA or Vero cell assay (for D) / ToBI (for T)

  Guinea Pig model
  multi- or one-dilution assay
  Ph. Eur. , WHO

  Mouse model
  Chinese Ph. (vero cell assay for D), WHO (multi- or one-dilution assay)

Pertussis Potency

Intracerebral Challenge tests

- **Mouse model (MICA)**
  JP; Chinese Ph.

Immunogenicity tests (Mouse or Guinea Pig)

- **Relative potency**
  Ph. Eur.
- **GMU***
  WHO, US, Ph. Eur

Challenge assays not aligned with 3Rs principle but still mandatory for some countries

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*GMU : Geometric mean unitage

Application of 3Rs on Sanofi Pasteur analytical testing

Reduction

- **Minimize the number** of animals per experiment

Refinement

- **Minimize suffering** and improve animal **welfare**

Replacement

- **Avoid** or **replace** the use of animals

Refinement /Reduction : Intermediate Step

- Replacing challenge potency tests by **serological methods**
- Using **single-dilution** method design instead of multi-dilution design
- Use of **humane endpoint** for lethal or invasive assay

Replacement & Removal

- **Replacing** *in vivo* assays : Developing and implementing *in vitro* alternatives
- **Removing** unjustified tests : redundant, unnecessary, not required by regulations

3Rs approaches should allow to align testing profiles for all products and markets

SINGLE IMMUNIGENICITY ASSAY (SIA) versus CURRENT METHODS

Comparison of SIA versus Current Methods 1/1

- 2 non lethal challenge tests
- 1 Serological test

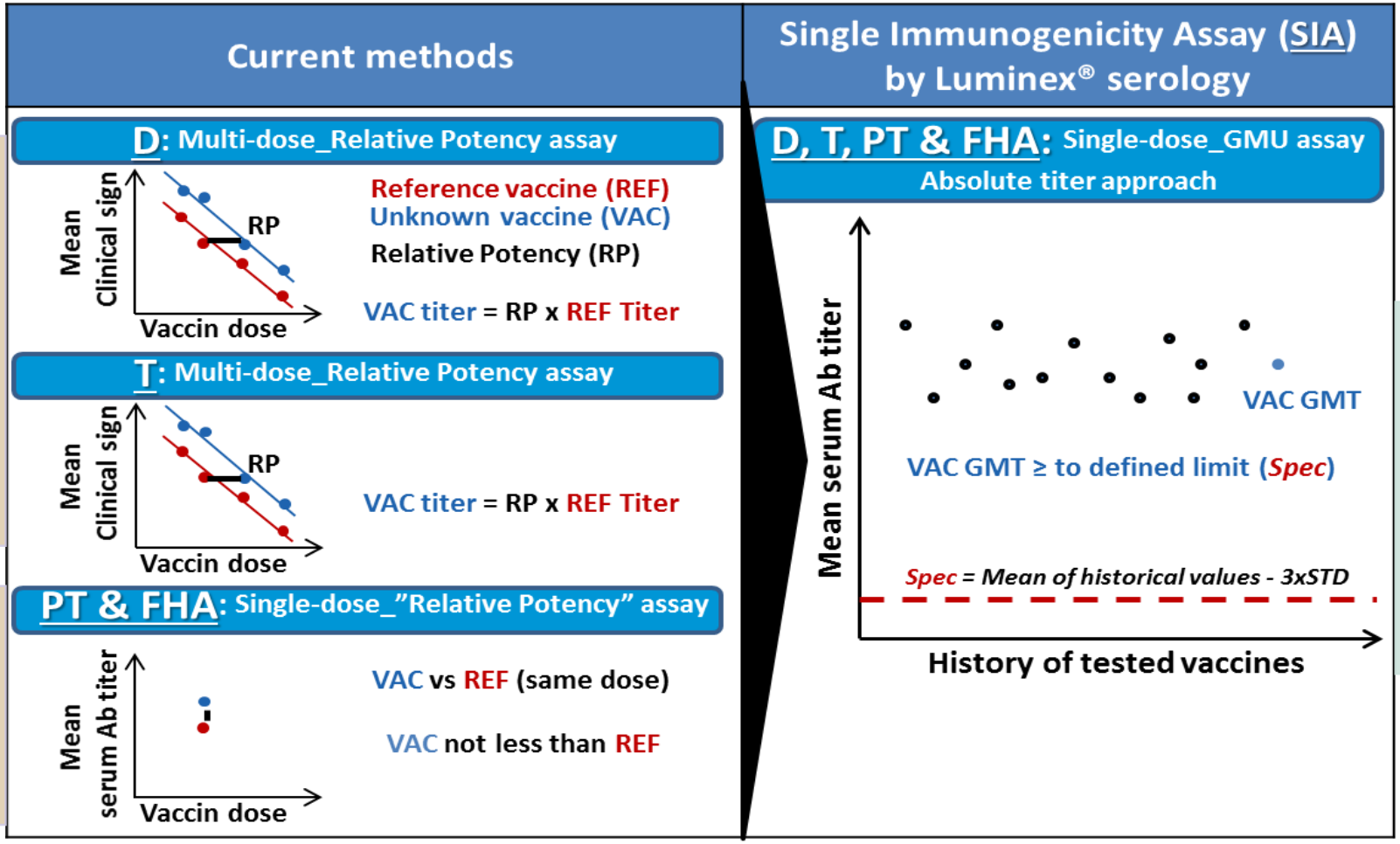
Current methods	Single Immunogenicity Assay (SIA) by Luminex® serology
D: EuPh 2.7.6 Method A **Intradermal reaction challenge test** Inhibition of diphtheria toxin-induced dermo-necrosis Guinea-pig (44 animals/vaccine lot) 	**D, T, PT & FHA:** **EuPh 2.7.6/2.7.8 Method C** **EuPh 2.7.16 Method B** **Guinea pig serology test** Simultaneous quantitation of anti-D, anti-T, anti-PT and anti-FHA antibodies in the same serum sample by using Luminex ®multiplex technology  Guinea-pig (16 animals/vaccine lot)
T: EuPh 2.7.8 Method B **Paralysis induction challenge test** Inhibition of tetanus toxin-induced paralysis Mouse (104 animals/vaccine lot) 	
PT & FHA: EuPh 2.7.16 Method A **Mouse serology test** Quantitation of anti-PT and anti-FHA antibodies in serum Mouse (16 animals/vaccine lot) 	

- 1 serological test

Comparison of SIA versus Current Methods 2/2

- Multidilution assays (1 group of animals per dilution)
- Potency based on assessing comparative vaccine/reference dose protecting 50% of animals against toxin challenge

- Single dilution serological assay
- Potency based on comparative vaccine/reference antibody titers

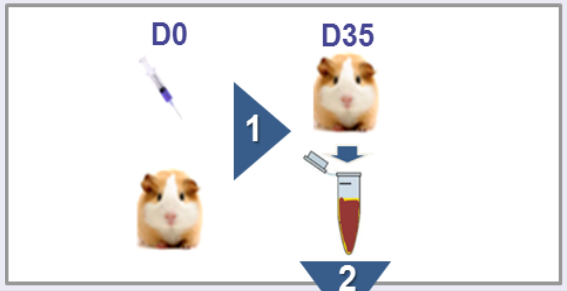


- Same single dilution for all antigens (1 single group of animals)
- Potency based on vaccine antibody titer

Description of SIA Analytical Method in 3 steps

STEP 1

Immunization and collection of sera

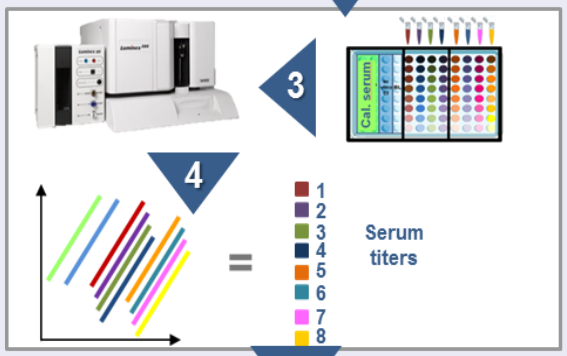


► **Reduction of preparations and animal injections**

→**Reduction of human handling**

STEP 2

Titration of sera



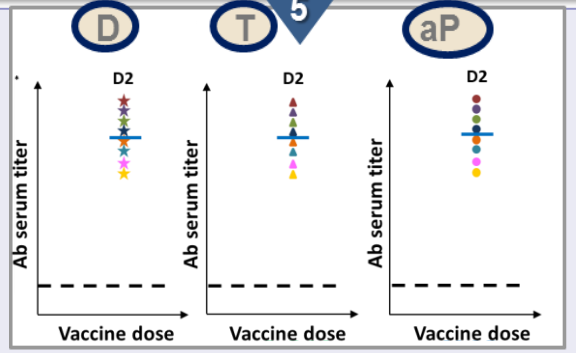
► **4 titrations in 1 run**

► **Simplified plate setup**

→ **Reduction of manual operations**
→ **Automation-friendly**

STEP 3

Vaccine titration



► **Automated analytical solution**

→ **Direct final result (vaccine potency values) from Luminex raw data**

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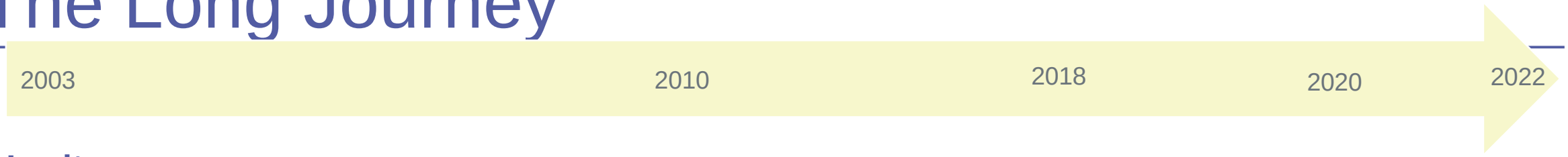
THE LONG JOURNEY

The Long Journey



- **In vitro**

Method Development & qualification

Method validation & Reagents qualification & Data analysis automation

Implementation

- **In vivo**

Immunization range definition
Sera generation

Sera for Suitability & Reagents qualification

- **Regulatory**

Scientific meetings with Health Authorities

Regulatory submissions & meetings with authorities

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CONCLUSION

Conclusion

- **Two severe challenge potency tests** in mice and guinea pigs have been **replaced** along with an immunogenicity test in mice by a **single test with mild severity** using a **serological approach** in guinea-pigs**.**

- In addition to the major refinement achievement this represents a **substantial reduction** of animals used for **potency evaluation** of pediatric vaccines.

Refinement

Reduction

That’s not all…..

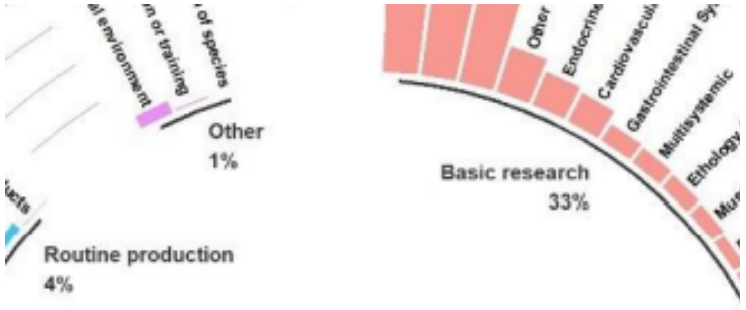
Conclusion

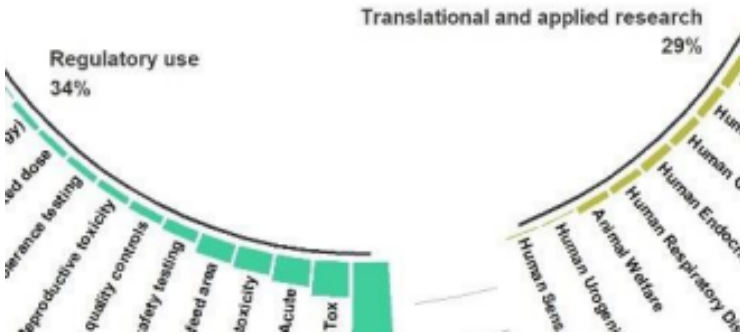
- It has taken more than 10 years of **development, validation** and has involved a **strong collaboration** between **R&D and Industrial Affairs** within the company**.**

- It implies also a **close collaboration with regulatory authorities** for its **acceptance worldwide** as an **innovative** testing approach.

- This big investment also benefits to people as it **simplifies and reduces technical operations** and allows for **automation** and leads to overall **reduction of QC testing time**.

THANK YOU





Reducing severe suffering at Novo Nordisk

RSPCA – EFPIA webinar: *How the pharmaceutical industry is tackling 'severe' suffering in animals used in science*

Thomas Bertelsen – Novo Nordisk

26 January 2022

Agenda

Our approach – using the RSPCA ‘Roadmap to end severe suffering’

Prospective assessment, - an example

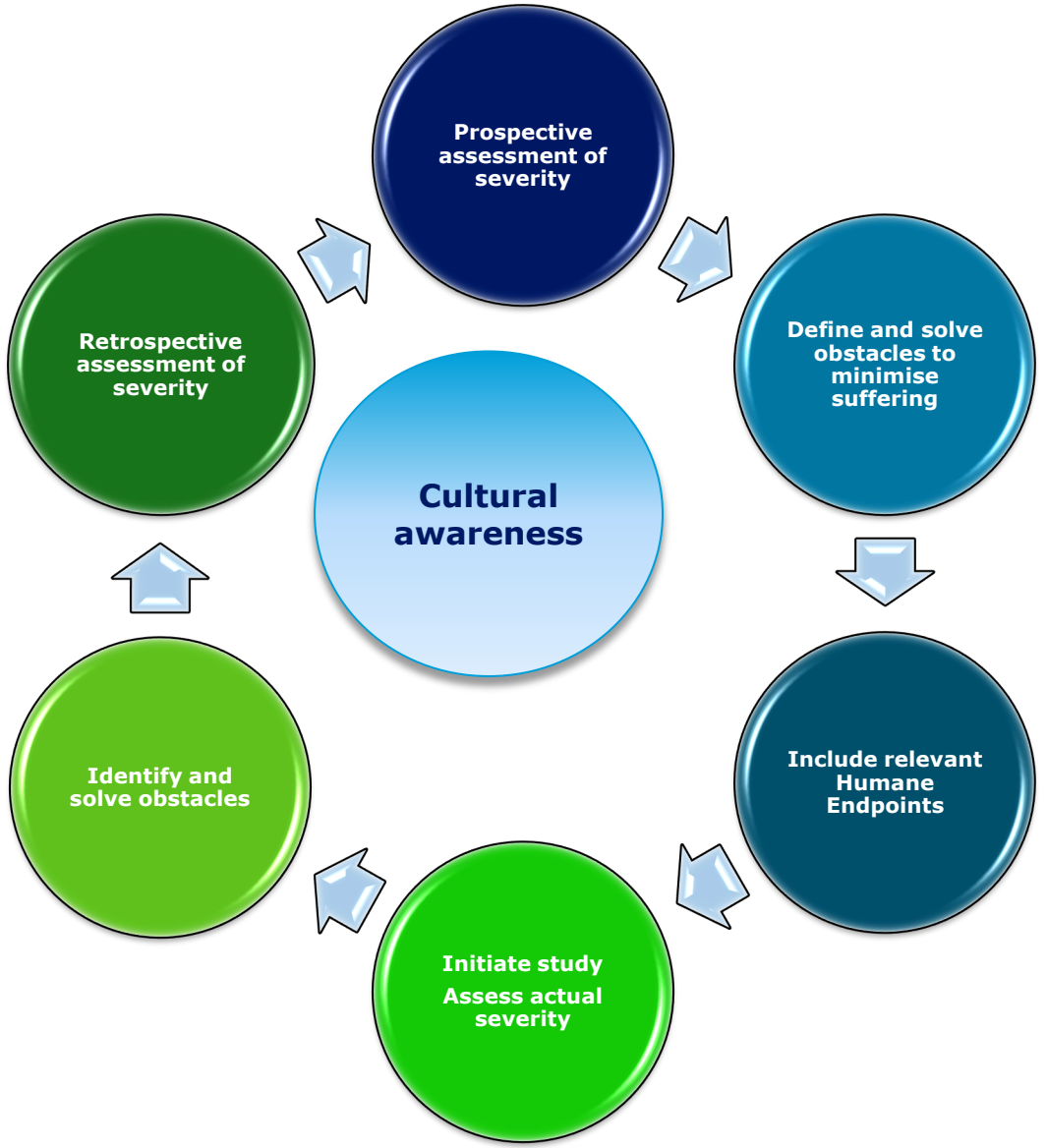
Retrospective follow-up, - why the approach is helpful

The RSPCA ‘Roadmap to end severe suffering’ as applied at Novo Nordisk

- Culture
  - A progressive, open minded and caring research culture
- Analysis
  - to what extent does severe suffering occur
- Evaluation
  - why severe suffering occurs
  - what current approaches are used to avoid it
- Define obstacles
  - Scientific, procedural, logistics, time
- Overcome obstacles
  - Re-frame the research question to avoid a severe mode
  - Refine all elements of the lifetime experience of the animal (include housing and care)
  - Use early Humane Endpoints

Systematic approach to minimise severe suffering

Study phase



Study planning

Inspired by Lilley et al. from RSPCA: A 'Road Map' toward ending severe suffering of animals used in research and testing. ATLA 42, 267-272, 2014.

Prospective assessment, - an example: Maximum Tolerated Dose (MTD)

- The MTD
  - To assess which doses are tolerated and which doses can be used in subsequent regulatory studies with animals

- The benefit of the MTD
  - Scientific:
    - Identify a dose level, which can demonstrate organ toxicity in the following pivotal tox studies
    - Identify possible side effects at high dose levels, which may be human relevant
    - Close projects early if severe toxicity of expected human relevance is observed
  - Animal welfare: de-risking ‘severe suffering’ in subsequent regulatory animal studies where many animals are used
    - Rodent studies: up to 264 animals (mouse study)
    - Non-rodent studies: up to 24-40 animals

Maximum Tolerated Dose (MTD) contd

- To what extent does severe suffering occur?
  - defining the level of tolerability unfortunately means also to know when the drug is intolerable
  - few animals (rodents max 12; non-rodents maximum 2-4) are expected to experience severe suffering

- Which current approaches are used to avoid severe suffering?
  - Ensure that as few animal as possible are subjected to an intolerable dose and that the duration for this is as short as possible
  - Knowledge about the drug's physical and chemical properties, its potency and mode of action has been investigated in non-animal methods prior to the studies, and this knowledge has been incorporated in the design of the study.
  - Groupwise dose-escalation. The dosing of the next group will not be initiated before the tolerability of the lower dose has been evaluated.

Maximum Tolerated Dose (MTD) contd

Overcome obstacles – study design

- Minimizing the number of animals:
  - Typical group size in a rodent MTD study is maximum 6 males and 6 females.

    3 dose groups treated with the test compound

  - Typical group size in a non-rodent MTD study is 1 male and 1 female

    one group is treated with escalating dose levels until the maximum tolerable dose is reached followed by

    one group of 1 male and 1 female dosed with the highest expected tolerable dose (without a dose escalating phase)

Maximum Tolerated Dose (MTD) contd

- Overcome obstacles
  - Intensified monitoring
  - Drug holiday
  - Stop dosing
  - Euthanasia when Humane Endpoints are reached

  - General HEs
  - Compound specific HEs per protocol (e.g., Hypoglycemia, drug related food intake)
  - Intrinsic harm in the housing conditions are addressed
  - Non-aversive handling to the extent possible
  - Blood sampling – only what is scientifically required (number and volumes)
  - Dosing – training and habituation to the extent possible

Retrospective follow-up - why the roadmap is helpful

- Animals that die ***unexpectedly*** due to the model or due to a harmful phenotype must be reported as ‘severe’
- Analysing data
- Dialogue with licence holders
  - Data check: Is the scoring as ‘severe’ for all animals correct?
  - Evaluation: Looking at why severe suffering occurs and what current approaches are used to avoid it.
  - Is the harm prospective or does severe suffering occur as an unforeseen event?
  - Define obstacles: Are the obstacles, - Scientific, Resource-based or Other
  - Overcome obstacles: Set out a plan to overcome issues and to end severe suffering
  - Action plan
  - Evaluate
- The RSPCA approach facilitates a **cooperative response** from licence holders, because:
  - Objective, data driven, systematic and no blame-game approach

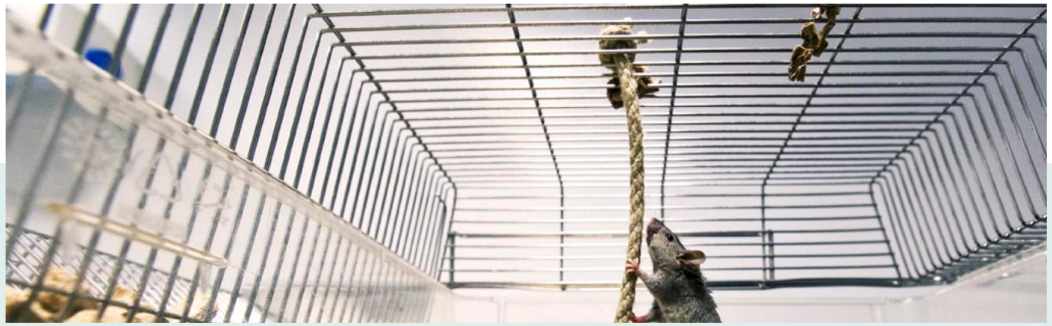
Thank you to my colleagues at Novo Nordisk - and thank you for your attention

- TSBT@novonordisk.com

- Novo Nordisk – the use of animals

Responsible use of animals

We recognise that not all research using animals can be replaced in the foreseeable future and consider it our responsibility to actively support the principles of the 3Rs (Reduce, Refine and Replace research using animals, Professor William Russell and Rex Burch, 1959) internally and externally.



Animal welfare is our

We have a centralised strategic department that contributes to internal awareness and education as well as ensure continued

Discussion

Challenges and progress towards avoiding and reducing severe suffering