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

# Reviewing animal use requirements in WHO biologics guidelines – opportunities for the 3Rs

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National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs)

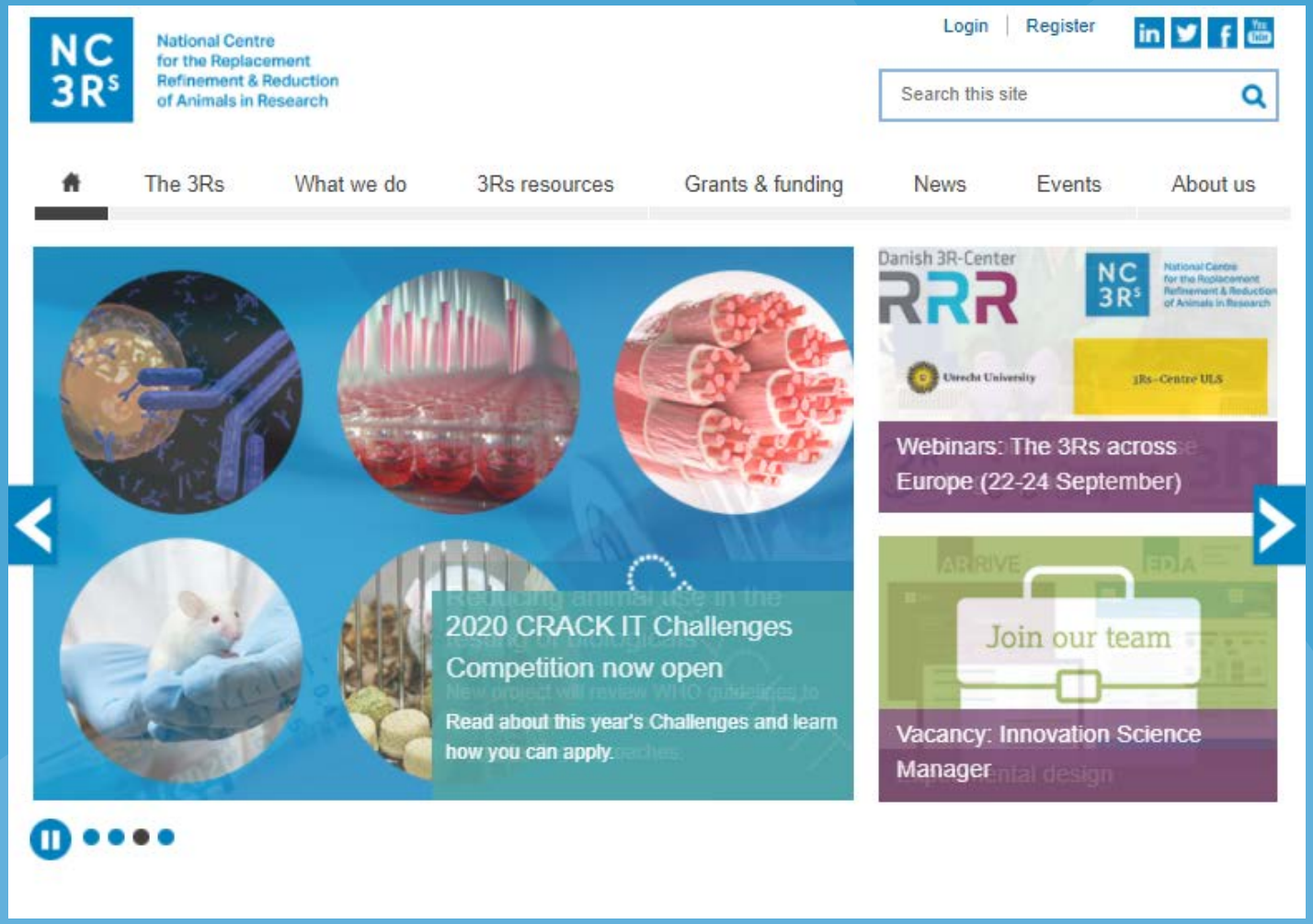
DCVMN webinar; 24 September 2020

**Pioneering Better Science**

# Agenda

1. Introduction to the NC3Rs
2. Project to review WHO biologics guidelines
3. Working with DCVMN members

# The NC3Rs




www.nc3rs.org.uk

# Who are we

- Established in 2004 by the UK Government
- Remit includes any area of animal use for research purposes
- 30 staff between London and our regional posts
- Reviewed every five years
- www.nc3rs.org.uk

NC3Rs 15th birthday celebrations, October 2019

# Role of the NC3Rs

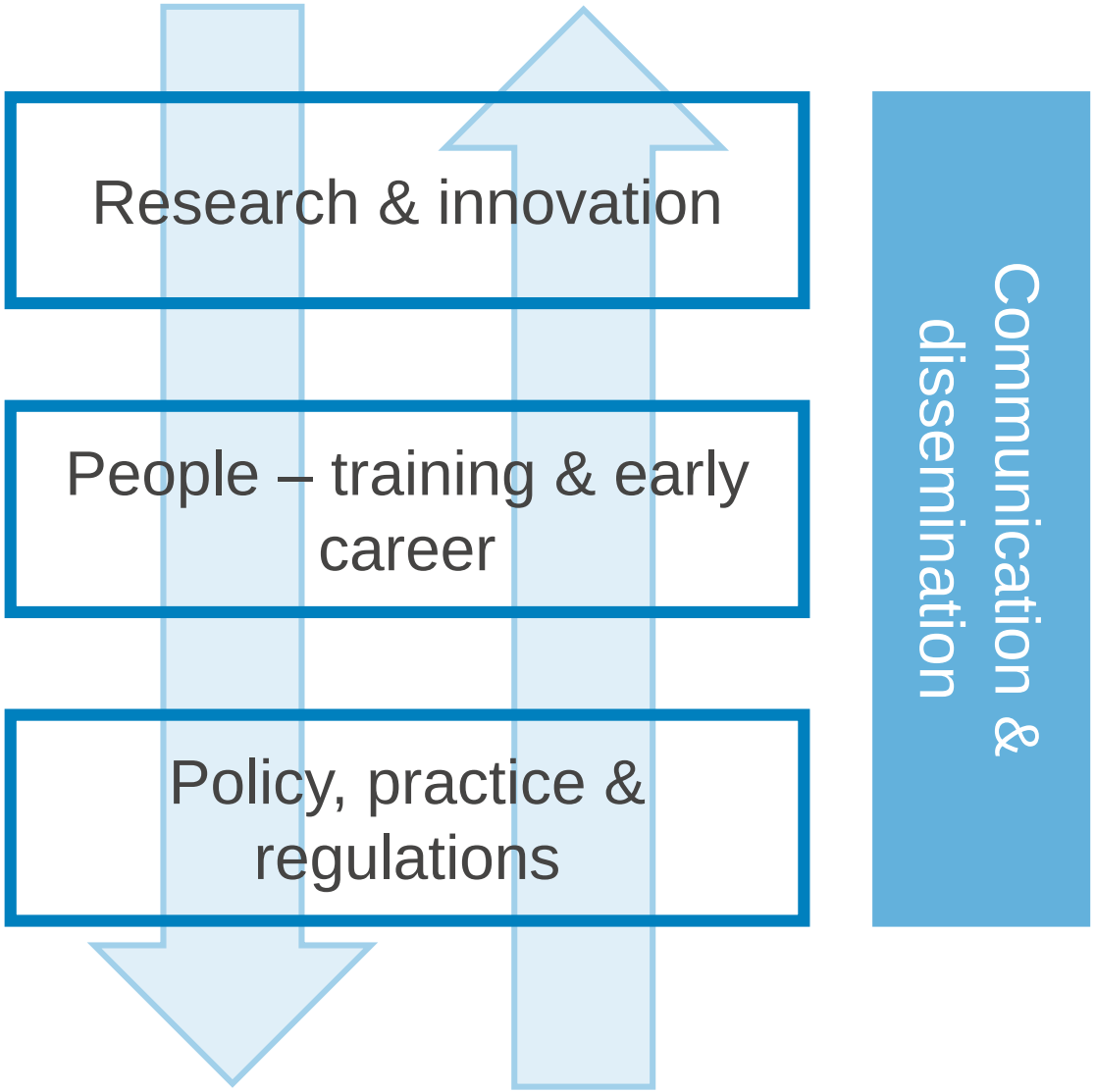
- Use the 3Rs as a framework to support science, innovation and animal welfare.
- Fund research and in-house programmes
- Work across the bioscience sector, with research funders, industry, regulators and academia.
- Budget of ~ £10 million per annum.

# A fresh look at the 3Rs

| | Standard | Contemporary |
|---|---|---|
| Replacement | Non-animal methods | Accelerating the development & use of human-relevant tools based on latest technologies |
| Reduction | Minimum number of animals consistent with scientific aims | Appropriately designed & considered animal experiments that are robust & reproducible |
| Refinement | Minimum pain, suffering, distress or lasting harm | New in vivo technologies that can benefit animal welfare & science |


50 years. . . . . .

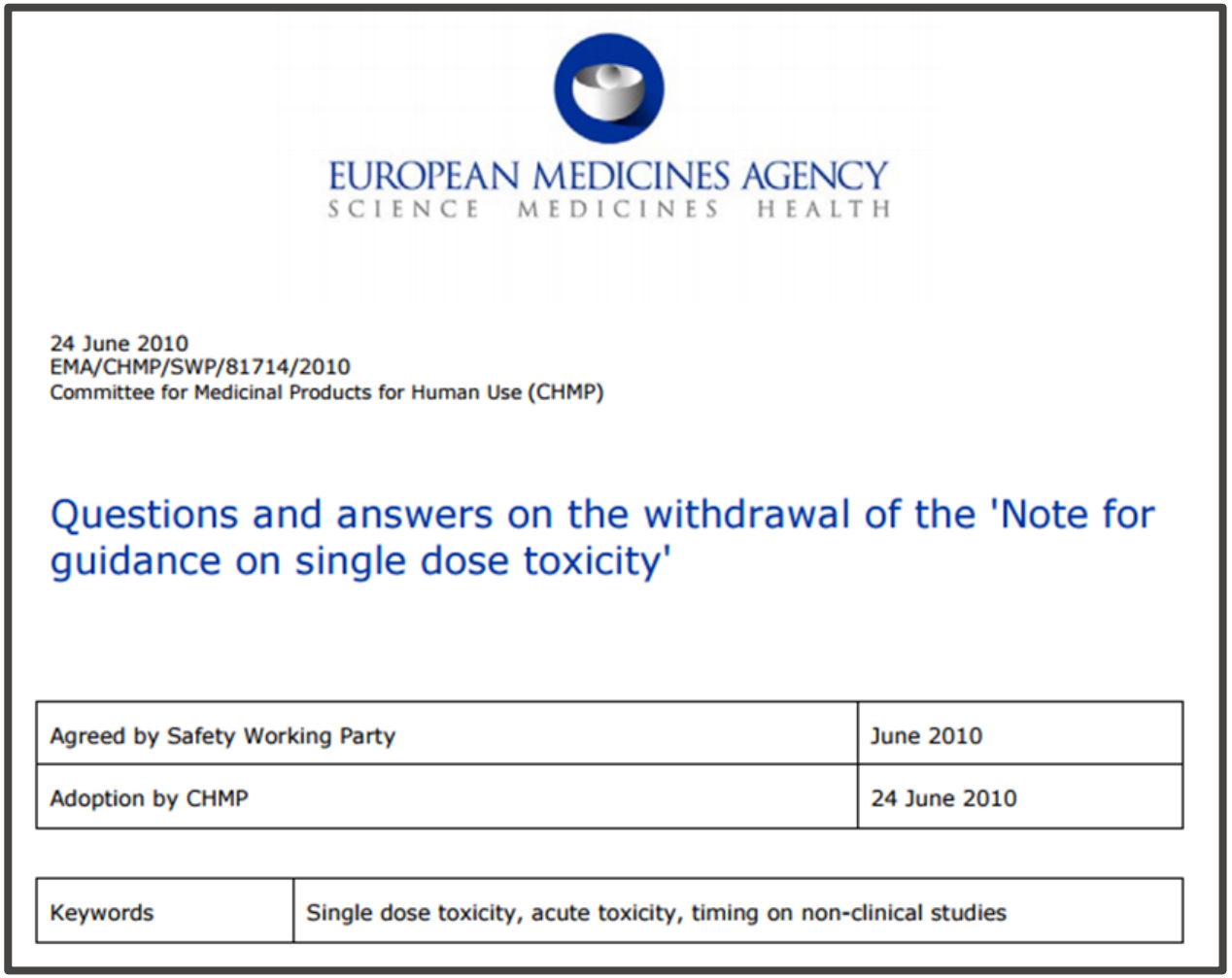
# Our strategy



# Forums for pre-competitive data-sharing

- Honest broker for cross-company and cross-sector data-sharing
- > 1000 non-publically available compounds
- 70 international companies across the pharmaceutical, chemical, contract research and consumer product sector
- 18 regulatory bodies (e.g. FDA, EPA, EMA)
- 21 working groups covering efficacy and disease models, safety pharmacology and toxicology
- Led to regulatory change

# Acute Toxicity: Animal tests do not always add value



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/SWP/81714/2010
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity'

| | |
|---|---|
| Agreed by Safety Working Party | June 2010 |
| Adoption by CHMP | 24 June 2010 |

| | |
|---|---|
| Keywords | Single dose toxicity, acute toxicity, timing on non-clinical studies |

# Acute toxicology studies

- Used in pharmaceutical and chemical development to identify a single acute dose causing lethality or severe toxicity.

| Regulatory framework | | |
|---|---|---|
| EEC | US | Japan |
| 2 Species[a] | 2 Species [b] | 2 Species[b] |
| 2 Routes, clinical route plus a route ensuring exposure[c] | 2 Routes (as EEC) | Clinical |
| 7–14-Day observation | 14-Day observation | 14-Day observation |

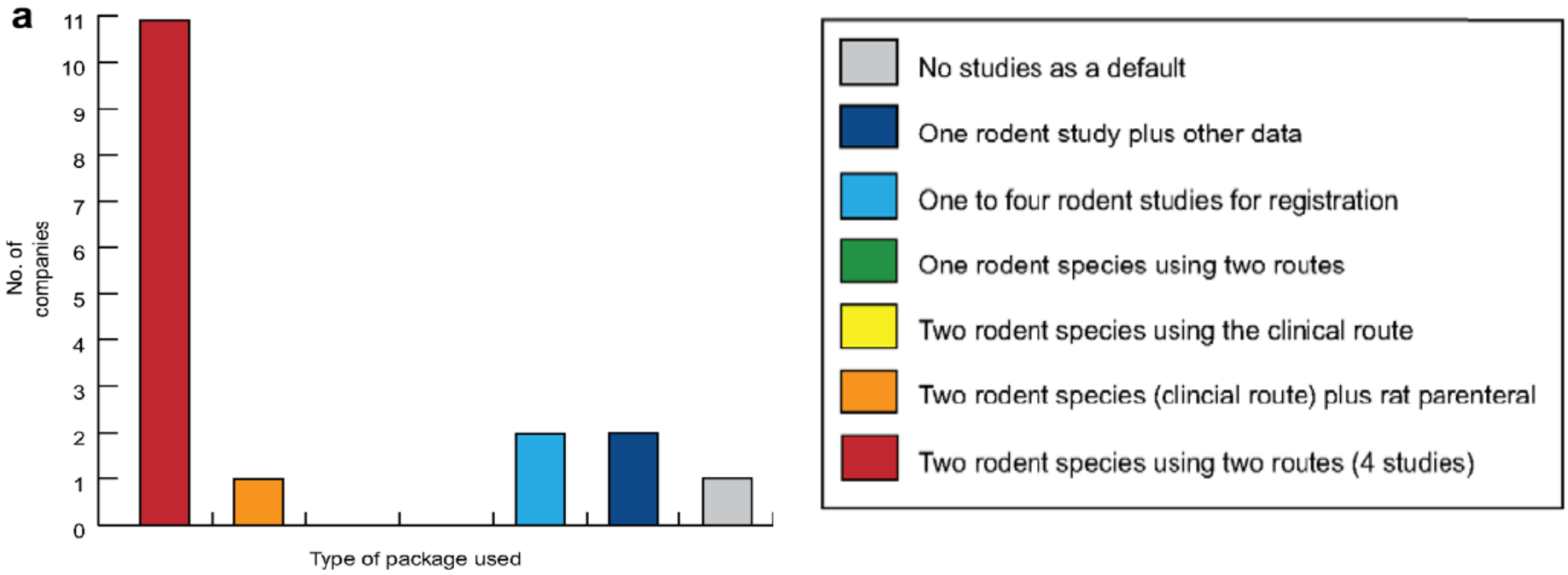
- Involved administration of a single high dose to rodents (up to 2000 mg/kg) and was the only test that used lethality as an end-point.

# Acute toxicology studies

- Used in pharmaceutical and chemical development to identify a single acute dose causing lethality or severe toxicity.
- Claimed scientific drivers:

# What studies are companies carrying out?

- Shared data from 18 companies, 70 compounds.

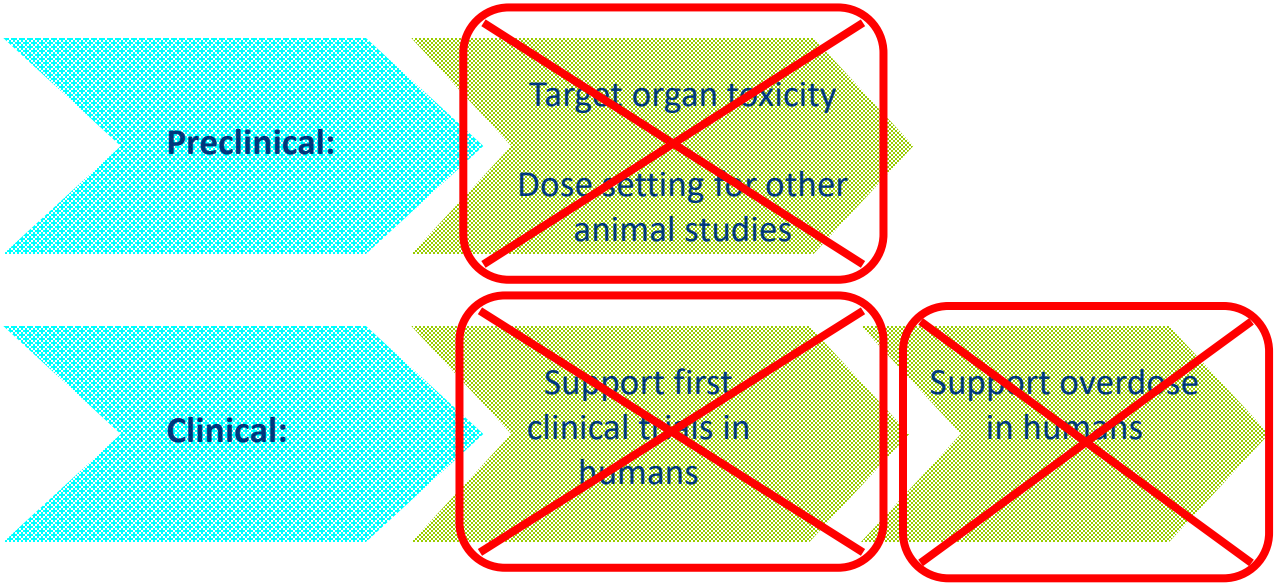



NC 3Rs

Johnson & Johnson Pharmaceutical Research & Development
Lilly
ALTANA
AstraZeneca
MDS Pharma Services
Pfizer
Roche
Boehringer Ingelheim
CHARLES RIVER LABORATORIES
sanofi aventis
SERVIER
COVANCE
gsk GlaxoSmithKline

# Acute toxicology studies

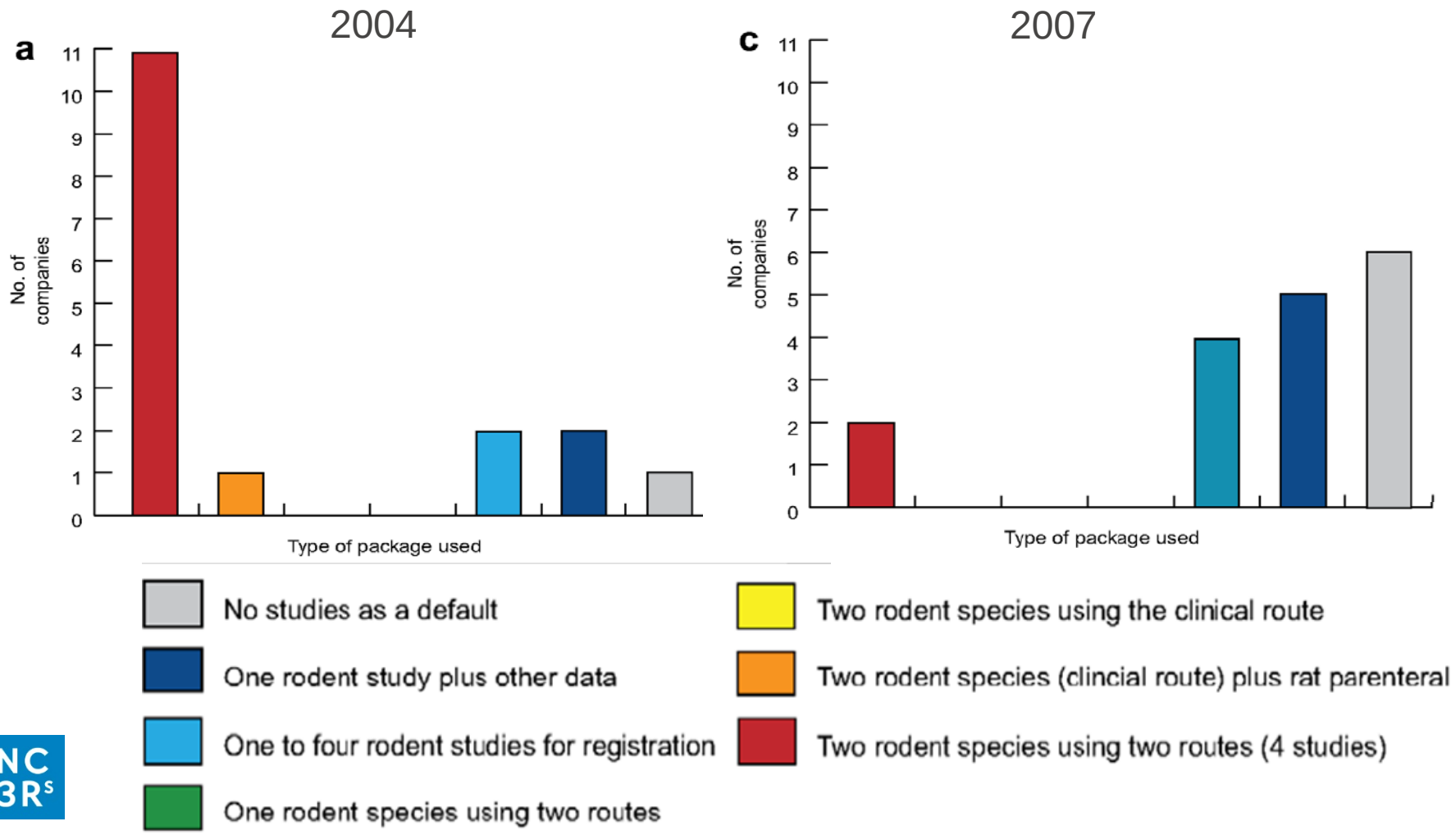
- After sharing data and experience on acute toxicity studies the value of rodent acute toxicity studies was questioned.
- Acute toxicity studies are not used for:




- BECAUSE…other studies routinely carried out in drug development (e.g., MTD) are more informative.

# Are single dose acute toxicity studies needed?

The same companies were re-surveyed in 2007 – and were already changing their practices…

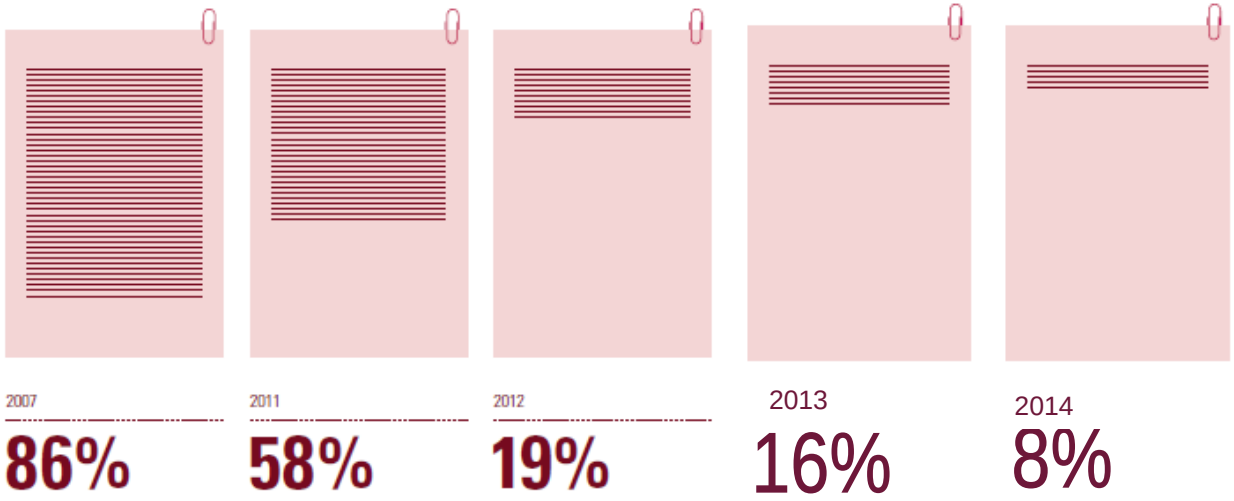


# Impact of working together in the 3Rs

Do acute toxicity studies add value in drug development?

- No for First In Man clinical trials.
- No for overdose.
- ICH M3 and Q&A changed.
- NC3Rs was a catalyst for change.


Proportion of clinical trial applications for drugs going into man for the first time in the UK which contain the results from single dose acute toxicity studies.




**Impact:**

- Regulatory change (ICH M3).
- In 2014 only 8% of clinical trial applications included acute toxicity data.

**Refs:**

1. Robinson, S., *et al.* (2008). Regul Toxicol Pharmacol *50*, 345-352; 2. Robinson, S., and Chapman, K. (2009). Regul Toxicol Pharmacol *55*, 110; 3. Chapman, K., et al (2010). Regul Toxicol Pharmacol *58*, 354-359.

# Our resources – supporting changes in practice

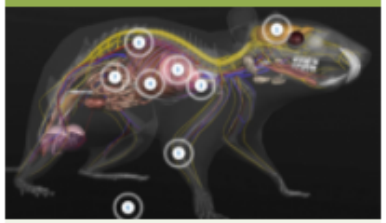
### Animal technician hub

Resources to help laboratory animal technicians implement the 3Rs.

### Blood sampling

Refining blood sampling from laboratory animals - advice on technique, route and volumes.

### E-learning resources

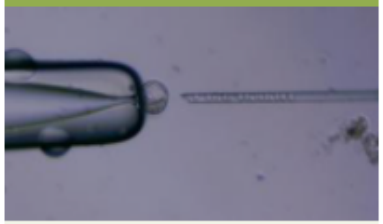


Online modules funded by the NC3Rs, which are freely available for training and continuing professional development.

### Experimental design


Resources to aid researchers improve the design and reporting of research using animals.

### Genetically altered mice



Information to help with the implementation of approaches to reduce and refine the use of GA mice.

### Grimace scales

Posters and other resources on the use of grimace scales to assess pain in laboratory animals.

### Housing and husbandry

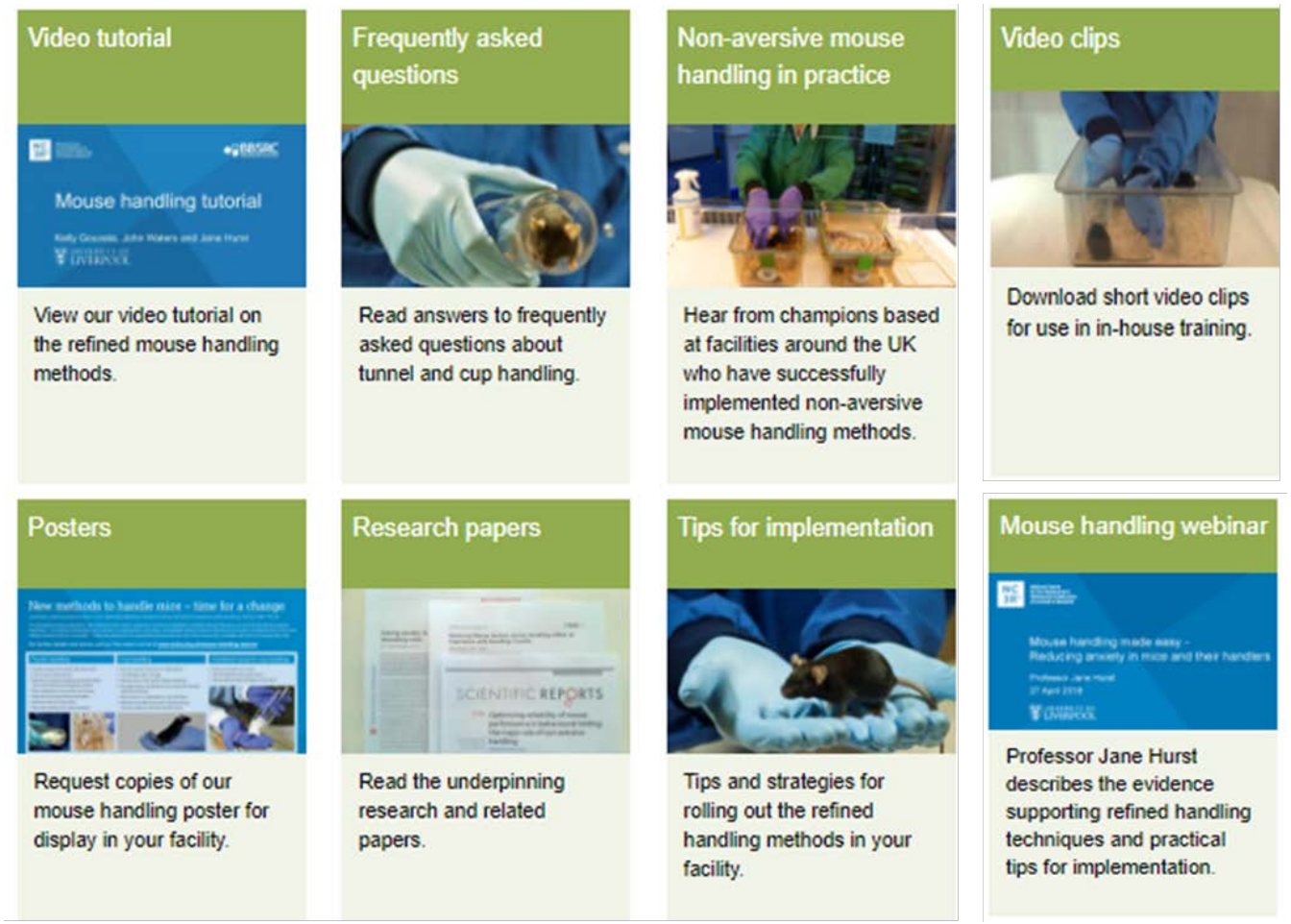
Refining the housing and husbandry of common laboratory animal species.

### How to pick up a mouse

Non-aversive methods for handling mice.

https://www.nc3rs.org.uk/3rs-resources

# Supporting adoption of non-aversive mouse handling




https://www.nc3rs.org.uk/how-to-pick-up-a-mouse

# Funding 3Rs model development & uptake

| Building capacity | Developing capacity | Furthering adoption | Commercialisation & uptake |
|---|---|---|---|
| Project grants | PhD studentships | Skills and Knowledge transfer grants | CRACK IT Challenges |
| | Training Fellowships | Technology to Tools awards | |

| | | | | |
|---|---|---|---|---|
| >400 major awards | >£95 million | 722 investigators | 164 students and fellows | 12 3Rs products / services |

NC 3Rs

https://www.nc3rs.org.uk/funding

# Our funding schemes



https://www.nc3rs.org.uk/our-reports-and-reviews

# Reviewing animal use requirements in WHO biologics guidance

# Aims and objectives of the project

- A scientifically-driven review of animal testing requirements described in WHO guidance documents for biologics and vaccines
- To identify evidence-based opportunities for the integration of the 3Rs
- To support vaccines manufacturers, regulators and control laboratories in applying the latest non-animal testing approaches and 3Rs strategies
- To support faster access to cheaper vaccines by the global communities who need them most urgently

# Animal use in biologics development and testing

- Animals are used extensively throughout the development life cycle of biologicals
- Vast majority of this is for quality control and batch release testing
- There are significant issues with this, including
  - Large numbers of animals are used
  - Potential to cause considerable pain and suffering
  - Expensive and labour intensive
  - Time consuming and a cause of significant delays
  - A high degree of variability and risk of failure of otherwise acceptable product batches
  - Often poor repeatability between manufacturer and control laboratories
  - Lack of harmonisation in assay requirements

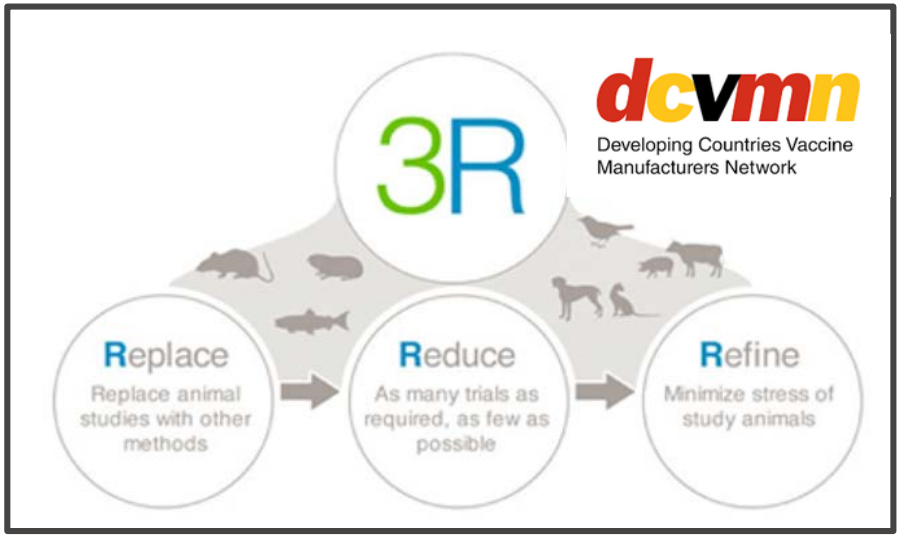
# A timely opportunity

- The WHO is mandated to "*establish and stimulate the establishment of international standards for biological, pharmaceutical and similar products*"
- A systematic review of established WHO guidelines for 3Rs purposes has never been done
- There is a global movement across sectors to embed the 3Rs in regulatory guidance and provide direction in implementing their integration
- Introduction of consistency approach means improved vaccines manufacturing
- Some progress has been made in biologics testing, but the process is slow and piecemeal

NC 3Rs

# Progress in the 3Rs

| Possible use of alternative methods | Ph. Eur. | Vaccine industry |
|---|---|---|
| **All vaccines**<br>Allow omission of abnormal toxicity test / general safety test | ☒ | ☒ partial |
| **Specific Toxicity test for Diphtheria vaccines**<br>Allow the use of a VERO cell-based method at DS*<br>Remove the test at DP** | <br>☒<br>☒ | <br>☒partial<br>☒partial |
| **Specific Toxicity test for Pertussis vaccines**<br>Allow CHO cell-based assay to replace HIST : at DS* at DP** stage | ☒ ongoing | ☒partial Devt |
| **Neurovirulence Test for Oral Polio Vaccine**<br>Allow switch from non-human primate to transgenic mice | ☒ | ☒ |
| **Inactivation test for inactivated Polio Vaccine**<br>Allow replacement of 1ry monkey kidney cells with L20B cell line | ☒ | ☒partial |
| **Test for adventitious agents**<br>Removal of GP & embryonated eggs for cell bank testing<br>Replace *in vivo* tests by broad molecular methods (HTS***) | <br>☒<br>☒ | <br>☒ongoing<br>☒Devt |
| **Potency tests for D and T vaccines**<br>• Allow using serology instead of lethal endpoints<br>• Allow introducing single-dilution assay | <br>☒<br>☒ | <br>☒partial<br>☒partial |
| **Potency test for inactivated Polio Vaccine**<br>Allow *in vitro* test | ☒ | ☒partial |
| **Potency test for inactivated Rabies Vaccine**<br>Allow *in vitro* test | ☒ | ☒Devt |
| **Potency test for inactivated Hepatitis A vaccine**<br>Allow *in vitro* test | ☒ | ☒ |
| **Potency test for inactivated Hepatitis B vaccine**<br>Allow *in vitro* test | ☒ | ☒ |
| **Potency test for Haemophilus influenzae vaccine**<br>Allow *in vitro* test | ☒ | ☒ |
| **Potency test for human Papilloma vaccine**<br>Allow *in vitro* test | ☒ | ☒ |



S. Urlich *et al.*, Alternatives to Animal Testing, pp. 76–82, 2019

# The project

- To review the animal testing requirements described in WHO guidance documents for biologics and vaccines to identify opportunities for the integration of the 3Rs.
    - What is the extent of animal testing included and are there alternative methods that should be included in the recommendations?
    - Would a WHO guideline for the adoption of 3Rs principles into the quality control and lot release of licensed vaccines be useful for harmonisation of non-animal methods and for guidance to WHO member states?
    - What are the barriers that are hindering the adoption of 3Rs principles?

# The project

## Stage 1 – NC3Rs

**Review & recommendations**

- Formation of an expert working group
- Review of WHO guidelines
- Recommendations for integration of 3Rs principles
- Identify barriers for adoption
- Stakeholder engagement workshops

**Estimated timeline: 3 years**

# The project

## Stage 1 – NC3Rs

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**Estimated timeline: 3 years**

## Stage 2 - WHO

**Drafting & implementation**

- WHO working group
- Drafting a response
- Putting the recommendations in to practice
- Implementation workshops

**Estimated timeline: 2-3 years**

Review is submitted to ECBS for their endorsement to proceed to Stage 2

# The project scope

## In scope

- Review of WHO written / physical standards relevant to biologics & vaccines regulation
- All 3Rs (not just replacement)
- Methods used in the post-licensure control of biologics and vaccines
- Identification of barriers towards adopting 3Rs strategies in the quality control and lot release of biologics and vaccines
- Development of scope and process for stage 2

## Out of scope

- Development or validation of 3Rs methods
- Documents not publicly accessible
- Animal methods not related to regulation of biologics or vaccines
- Non-constructive criticisms of WHO
- Ethical review of the use of animals
- Drafting of revisions to *in vivo* approaches in existing guidelines
- Animal testing or methods used in the development of biologics or vaccines

# Current status

- Proposal presented to ECBS and approved October 2019
- Gates funding awarded June 2020
- First meetings of the working group held June/July 2020
- Survey of the working group members August 2020

# Engaging relevant expertise

| National Regulatory Agencies | Manufacturers | National Control Laboratories | Others |
|---|---|---|---|
| MHRA | GSK | NIBSC, UK | WHO |
| FDA | Janssen | Paul Ehrlich Institute, Germany | Seoul National University, S. Korea |
| South Africa National Control Laboratory | Merck | National Institute of Infectious Diseases, Japan | Eur Commission Joint Research Centre |
| EDQM, France | Sanofi | National Institutes for Food & Drug Control, China | IABS |
| Health Canada | Serum Institute India | Ministry of Public Health, Thailand | Expert Committee on Biological Standardization |
| ANMAT, Argentina | IFPMA | RIVM, Netherlands | |
| | Finlay Institute, Cuba | National Control Laboratory Network | |

# Next steps

- Selection of WHO guidelines to focus on and establish sub-groups to begin the review
  - Expertise within the working group
  - Quick wins, are tests scientifically justified, are there significant welfare concerns?
  - Bacterial vs. viral, combination vs. single
- Survey of manufacturers and NRAs/NCLs
  - What 3Rs approaches are being explored/used
  - What are the barriers to adopting 3Rs testing strategies
  - What regional differences may affect uptake of 3Rs testing strategies

# Working with DCVMN members

# What are the challenges?

# Opportunities for engagement

- Contribute your expertise…join the working group or subgroups
- Distribute and complete the surveys
- Share your 3Rs approach experiences
- Help inform activities within DCVMN and your own organisations
- Where do you see the opportunities for having most impact regarding alternative 3Rs testing strategies – replacement and refinement
- Make sure your voice is heard in helping to shape the outcomes to meet your needs

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# Thank you!

## For more information


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## Keep in touch

Our monthly newsletter provides the latest updates from the NC3Rs, including funding calls and events
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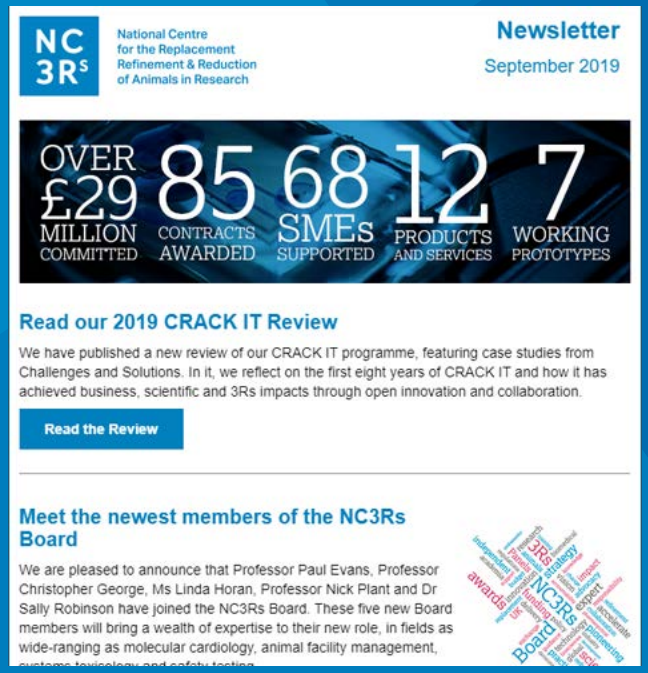


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