

RSPCA Meeting in Association with the Karolinska
Institutet

Refining Severe Disease Models and Procedures

August 25th 2022

labcorp
Drug Development

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Case Study: A New Group-Housing Approach for Nonhuman Primate Metabolism Studies



Primate Metabolism Studies (ADME) and Use of Metabolism Cages

Goal	How	Imperatives	Why
<ul style="list-style-type: none"> Determine the routes and rates of excretion of a novel pharmaceutical Investigate absorption and pharmacokinetics (how a novel pharmaceutical is metabolised) Evaluate metabolite profiles to assess safety profile of parent drug and metabolites compared to humans 	<ul style="list-style-type: none"> A radiolabelled marker is added to the novel pharmaceutical Animals are administered a measured amount of the novel radiolabelled pharmaceutical at non-toxic levels Urine and faeces (excreta) are collected over 168 hours after radiolabel administration – historically involves singly housed animals (n=3, mean data) Collection of blood and plasma samples for pharmacokinetics analysis 	<ul style="list-style-type: none"> For regulatory acceptance we must recover at least 90% of the radioactive material Animals must be housed in caging which does not absorb radioactivity, can be cleaned at specific time points and captures all excreta N=3 singly housed animals were deemed minimum number of animals to generate robust scientific data to illustrate variability in response to the drug tested 	<ul style="list-style-type: none"> Regulatory driven with data forming part of the submission dossier¹ Provide samples for profiling to enable metabolites in plasma and excreta to be identified as part of the safety assessment (MIST)² Provide data to qualify the species used in safety assessment studies for translation to humans

1. ICH Guidance M3(R2)

2. FDA Guidance on the Safety Testing of Drug Metabolites (2020)

What Are Stakeholder Drivers for a Different Approach to the Use of Single-Housing Metabolism Cages?

1

Colleagues at Novo Nordisk approached the Labcorp team to discuss the interpretation of severe suffering in EU/2010/63¹ and the use of metabolism cages.

2

UK Home Office Project Licence²
Authorization under A(SP)A³

3

Labcorp AWERB and
Novo Nordisk ERC⁴

L 276/76

EN

Official Journal of the European Union

20.10.2010

ANNEX VIII

SEVERITY CLASSIFICATION OF PROCEDURES

Severity classification: Moderate

(h) Use of metabolic cages involving moderate restriction of movement over a prolonged period (up to 5 days)

Severity classification: Severe

(i) Use of metabolic cages involving severe restriction of movement over a prolonged period

OFFICIAL - SENSITIVE

PPL number: PP4725046 | Granted: 01 Oct 21 | Expires: 01 Oct 26

Protocol 4

Metabolism studies in Primates

Severity: Moderate

Permission to confine in a metabolism cage..... up to a maximum of 15 days when singly housed



Novo Nordisk Global

Bioethics / Animal ethics

Harrogate Animal Welfare &
Ethical Review Body



Collective Aim: To evaluate & validate the approach of using a group housing study design to challenge the long-held paradigm of single housing of animals for safety assessment during these metabolism studies.

Engaging Stakeholders

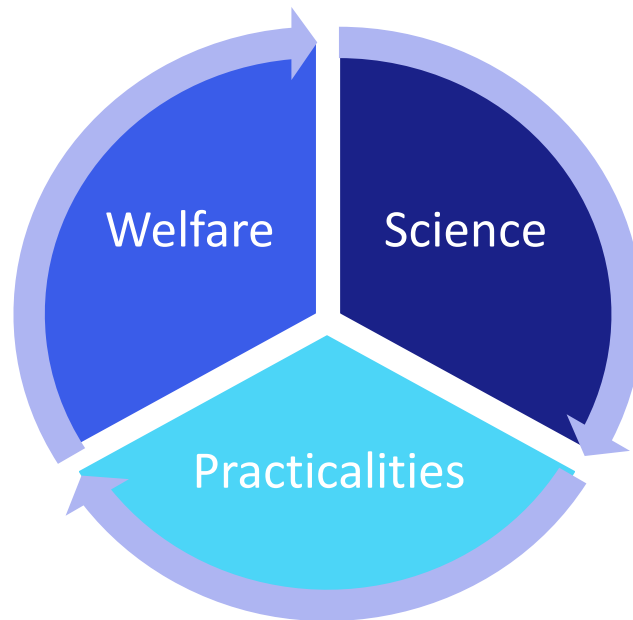
Initial 'problem statement' discussions occurred between Novo Nordisk welfare and science representatives and Labcorp Home Office PLH

Literature searches on alternative metabolism cages or approaches to obtaining regulatory approved ADME data were conducted

Current approach, ideal future state, benefits and willingness for both financial and in-kind contributions scoped out at high level

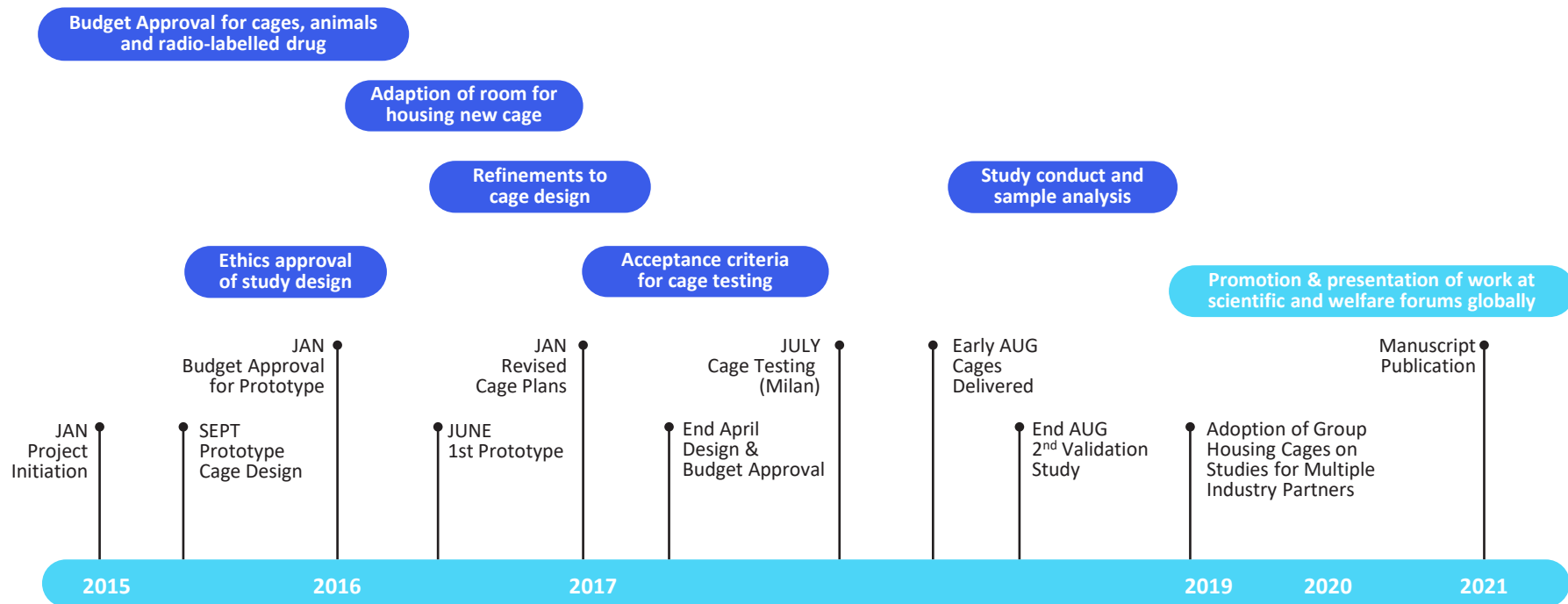
Wider stakeholder recruitment and engagement – with representatives from Animal welfare, Science and Operations brought together, along with an industry known metabolic cage manufacturer

Project Charter drawn up to define scope of initiative, with multiple TC and F2F meetings held to brainstorm a new cage design, its build, testing and implementation phases



Challenges Encountered	Solutions Agreed
<p>Stakeholder agreement on critical vs. 'nice to have' cage design improvements (balance between welfare, scientific endpoints and logistical conduct of the metabolism investigations)</p> <ul style="list-style-type: none">• Evident as the dimensions of the cage were evaluated, and potential compromise of the sample collection phase• Initial prototype build was tested and due to the internal shelving positioning and connection between the two halves of the cage, the cage was not water tight	<p>Compromise reached on some design elements that were likely to impact obtaining acceptable scientific outcomes, and impact regulatory acceptance</p>
<p>Initial cage manufacturer was unable to agree on timeline for production of the cage we have designed. An alternative cage manufacturer was engaged. This impacted timelines for an initial build.</p>	<p>Several alternative cage manufacturers were sought, via industry colleagues in the field of vivarium operational management and scientific study conduct.</p>
<p>Prototype build & transport from Italy meant in-situ cage assembly when at Labcorp. Limited options to test cage during build phase. Prototype cage was found to have a flaw that resulted in leakage.</p>	<p>Following unsuccessful testing of the prototype cage, a modified cage was commissioned, which required additional budget, time and resource allocated by sponsoring stakeholders, as well as delay to full cage validation of a revised design.</p>
<p>Regulatory approval</p>	<p>Challenging to obtain direct feedback on whether data would be accepted by regulatory authorities globally at the outset. Feedback received indicated data would be reviewed based upon scientific merit of the approach.</p>

Project Review





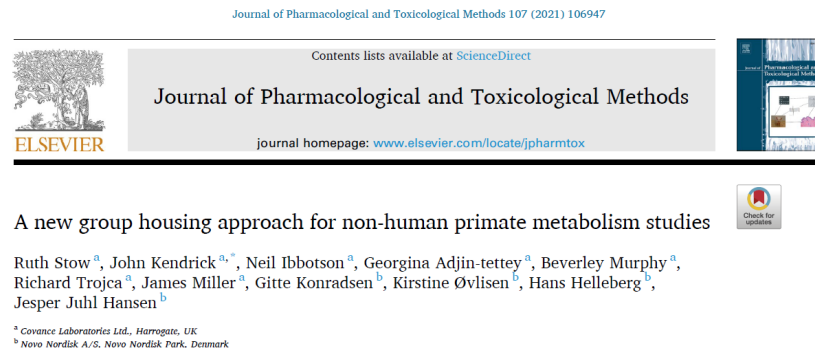
100 cm high x 60 cm deep x 110 cm wide



187.5 cm high x 118 cm deep x 200 cm wide
6.2 ft. high x 3,9 ft. deep x 6,6 ft. wide

Outcomes, Lessons Learnt and Future Perspectives

- Successful design, development, & validation of the metabolism cage with group housing of NHPs has been achieved
- Success was based upon openness to share ideas across organisations, willing contributions to allocate resource, time and budget, and desire to drive forward even when challenges were encountered
- Many processes took longer than anticipated due to a variety of approvals required
- Regulatory acceptance is assumed based upon scientific validity and robustness
- Wider adoption of group housing across Labcorp sites offering metabolism studies, other CROs and Pharma Industry is increasing, slowly
- Kudos and visible recognition has helped drive repeated behaviour and cultural change



Take Away Actions

- Please help publicise the work we have presented here to help engage colleagues, friends and collaborators in challenging long held paradigms of how animals are utilised in drug development.
- With this we can build momentum to influence regulatory perceptions, after all ***better welfare provides better models which provide better data.***
- Don't stop asking the questions, "Why are we using animals in this way, and what can we do differently?" at your local AW(ER)Bs.
- Reach out to CRO and Industry stakeholders directly, or via any platform (RSPCA, EFPIA, NC3R's, AAALAC, LASA, IAT etc) if there are collaborations that we could partner on to advance 3R's initiatives together, and, leverage local 'research or welfare hubs' and others with experience.

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