The A S C
Animals in Science Committee

NON-HUMAN PRIMATES USED IN SERVICE LICENCES

October 2024

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Abbreviations:

APC, Animal Procedures Committee; **ASC**, Animals in Science Committee; **ASPA,** Animals (Scientific Procedures) Act; **ASPeL**, Animals in Science Procedures e-Licensing; **ASRPU**, Animals in Science Regulation Policy Unit; **ASRU**, Animals in Science Regulation Unit; **AWERB**, Animal Welfare and Ethical Review Body; **HBA**, Harm Benefit Analysis; **ICH**, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **MHRA**, Medicines and Healthcare Products Regulatory Agency; **NC3Rs**, National Centre for the Replacement, Reduction and Refinement of Animals in Research; **NACWO**, Named Animal Care and Welfare Officer; **NHP**, Non-human primate; **NTS**, non-technical summary; **NVS**, Named Veterinary Surgeon; **WHO**, World Health Organisation

1. Introduction

In 2021, the Animals in Science Committee (ASC) established a Task and Finish Group for the Strategic Review of Project Licences. This was in response to a commissioning letter from the then Home Office Minister, Baroness Williams of Trafford (Home Office (UK), 2020a). The purpose of this group is to carry out reviews of selected project licences falling under a theme. The associated reports and advice, in the form of a series of recommendations to the Minister, are reviewed and agreed by the full ASC.

As part of its work, the ASC agreed with the Animals in Science Regulation Policy Unit (ASRPU) that it would undertake a review of current licences authorising the use of non-human primates (NHPs) in procedures that have been assigned a prospective severity category of either ‘unclassified’, ‘mild’ or ‘moderate’. For more information on the assignment of severity categories, see: Home Office (UK), 2014, Appendix G.

The ASC already routinely receives referrals for advice from the Animals in Science Regulation Unit (ASRU) for all applications proposing the use of NHPs in ‘severe’ procedures. In this current review, the Committee considered those licences involving the use of NHPs which are not normally seen by the ASC. As discussed in Section 3 of this report, the focus of the ASC’s review was further refined to focus on licences in which NHPs are used in multiple generic projects (usually referred to as ‘service licences’) in procedures aimed at assessing the safety or metabolism of potential new medicines, vaccines and other therapeutic substances, or for the supply of blood and tissues. For more information on the definition of 'multiple generic projects' see: Home Office (UK), 2014; Section 5.14.

The ASC and its predecessor, the Animal Procedures Committee (APC), have previously considered the subject of NHPs in service and regulatory licences in wider contexts. Four reports (Animal Procedures Committee, 2002; Animal Procedures Committee, 2003; Animals in Science Committee, 2017; Animals in Science Committee, 2020) include these committees’ views and recommendations on this type of licence. In this report, we note the previous recommendations and present a contemporary analysis of this specific type of project licence.

This report summarises our review of these licences as well as our consideration of the views and information submitted to us by stakeholders. It also makes recommendations to the Minister regarding future regulatory oversight.

2. Executive Summary

Our review focused on 11 project licences that use non-human primates (NHPs) in safety or metabolism testing, or for the supply of NHP blood and tissue. This type of use accounts for the majority of scientific procedures involving NHPs in the UK, most of which are required by regulatory authorities for use in their assessments of whether potential medicines and other therapeutics are to be considered safe for human use (Home Office (UK), 2022). All these licences used macaque monkeys: five specified only cynomolgus macaques, three specified cynomolgus and rhesus macaques and three specified ‘Old World monkeys, e.g. macaques’.

We sent a questionnaire to the holders of these licences and published a call for evidence from wider stakeholders. We found that, despite most of the project licence holders answering that robust internal systems are in place, many of the licences we reviewed

lacked detailed explanations as to why the use of NHPs is scientifically justified. This is important, as the legislation states that NHPs should only be used when no other species is suitable, and they should only be used for research into life-threatening or debilitating conditions (Home Office (UK), 2014).

More fundamentally, we found a systemic failure to link the animal test being performed with the identity or specific intended use of the substances being tested under these licences. The nature of these licences means that permission is granted ahead of knowing which substances will be tested. The 'benefit' is understood to be the provision of safety data for presenting to a medicines regulator, or the provision of blood and tissue for other research purposes, rather than, for example, the benefit or utility of the specific substance being tested. This is a matter of concern, as we believe there is a societal expectation that the potential benefit of the substance being tested should be taken into account in the harm benefit assessment (HBA). We make some recommendations as to how this issue might be addressed, noting that similar issues apply to all service licences (e.g. in the production of genetically altered (GA) animals it is not known at the time the licence is granted specifically which genotypes will be bred).

We note that the experimental design of these types of protocols differs from hypothesis driven research, but this should not mean that the licence application does not include a proper explanation of how the studies are designed to deliver the intended outcomes.

The licences we reviewed all had a mild or moderate severity categorisation. We noted that all the licences allowed for re-use of the animals, but details of what that re-use would involve were often lacking. The licences should include more information about the lifetime experience of the NHPs and how the cumulative severity is assessed.

A project licence application should also outline how the replacement, reduction and refinement of animals in research (the 3Rs) are to be applied. We were disappointed by the lack of detail in many of the licences we reviewed, especially since the survey of licence holders indicated that many of the organisations were active in 3Rs initiatives including some of the pharmaceutical industry projects facilitated by the National Centre for the Replacement, Reduction and Refinement of Animals in Research (NC3Rs).

The local Animal Welfare and Ethical Review Body (AWERB) has an important governance role to play in ensuring that any experiment using an NHP in this type of testing, or for the provision of blood and tissue, is scientifically and ethically justified, and, in the case of regulatory safety testing, required by regulators. With these licences, there is usually a commissioning organisation (sponsor) in addition to the designated establishment that is carrying out the work. In such cases, we would like to see more information on how the local AWERB has satisfied itself that the commissioned research being undertaken is justified and ethically valid.

We recognise that many of the licences we reviewed are multi-species with multiple potential experiments. One of our recommendations is that NHP use in this context should be confined to species-specific licences, with other species covered by separate licences. We hope that this would encourage applicants to include the level of detail we would expect to see.

We also looked at the non-technical summaries for the licences we reviewed. Although some gave appropriate explanations of the research in lay language, some did not, and we would like the public to be provided with better-written summaries of how and why NHPs are being

used in these types of studies, what is considered the justification for doing so, and the likely harms.

Our recommendations are intended to strengthen the project evaluation and authorisation process, improving the quality of this type of project licence and the accompanying non-technical summaries by including more detail on the scientific justification for using NHPs, the cumulative severity of what the animals experience, experimental design and the consideration of the 3Rs. We have also made some recommendations that we hope will encourage appropriate oversight of the scientific and ethical justification relating to each of the substances tested under these licences and address the embedded challenge of making an adequate HBA for these types of licences. For each of our recommendations, we have indicated the primary audience to whom they are addressed.

3. Our Methodology

In this report, the ASC seeks to provide independent, balanced and objective advice relating to the use of NHPs in scientific procedures, with a prospectively assigned severity classification other than 'severe', drawing on a review of relevant licences. Our findings are also informed by responses to our questionnaires completed by Project Licence Holders and by stakeholders.

The ASC review started with a qualitative review of 18 project licences granted by the Secretary of State between July 2018 and August 2022 and identified important themes. These licences were provided by the Home Office using the following search criteria; 'NHP (all species)', 'active licences' and 'permissible purpose'. From this selection, licences with a severity classification of mild or moderate were selected.

The licences authorised the use of NHPs for purposes including research into specific disease areas; for testing the safety or metabolism of potential new medicines, vaccines and other therapeutic substances; and for the supply of blood and tissues.

Following an initial reading of all 18 of the licences provided, the Committee decided to focus subsequent analysis on the 11 service licences that authorised the use of NHPs for safety or metabolism testing, or the supply of blood and tissues. These licences were chosen mainly because they provided a wide range of different examples, which would enable an appropriate level of insight and understanding of the type of information typically provided for those purposes of proposed NHP use. The other seven licences provided each focused on a specific disease research area, for example. As a consequence, there were too few licences in each category to be able to extract any general patterns or themes.

In addition to analysing each of the 11 licences, we also sought feedback from the Project Licence Holders via a questionnaire asking about internal governance processes within their establishments regarding consideration of the scientific, ethical and practical issues associated with a proposed use of NHPs, and for implementation of the 3Rs (Appendix 3).

Our review considered the information provided in project licence applications, particularly looking at:

- the justifications provided for the proposed use of NHPs (including for the specific species)

- the expected severity of the procedures, along with the steps to be taken to ensure that the 3Rs are fully implemented during the lifetime of the licence
- the factors to be considered in the carrying out of the Harm-Benefit Analysis
- the experimental design
- governance systems in place within designated establishments (including the role of the local AWERB)
- the information provided to the general public about the use of NHPs in these types of licences, via the publication on the gov.uk website of Non-Technical Summaries.

A call for evidence from stakeholders, published on the ASC website on 7 September 2023, also enabled the Committee to gather and understand a fuller range of perspectives on the use of NHPs in this type of research and testing (Appendix 4). The responses to these questionnaires have further informed our licence review. We would like to thank everyone who contributed to the review and acknowledge the breadth of opinions and information we received. We have collated the references supplied in response to the questionnaires (Appendix 5).

4. The current use of NHPs in multiple generic (service) projects

Multiple generic projects can be authorised if their purpose is to satisfy regulatory requirements or to use animals for production or diagnostic purposes with established methods. These are often referred to as service licences and this is the term we use throughout this report. In the context of the implementation of the Animals (Scientific Procedures) Act 1986 (as amended 2012) (ASPA), the term ‘Generic’ is best understood as either the breeding of genetically-altered mice, the production of antibodies, or the conduct of a safety evaluation test where the particular production process, experiment or study is the same irrespective of the actual genotype, specific antibody or substance concerned (Section 5.14, Guidance on the Operation of the Animals (Scientific Procedures) Act 1986). For more on the definition of 'multiple generic projects' see: Home Office (UK), 2014), Section 5.14.

4.i Safety or metabolism testing

Pharmaceutical Non-Clinical Safety Regulatory Requirements

The development and approval of new medicines is a global process. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of medicinal drug registration. The goal is to “*achieve greater harmonisation worldwide to ensure that safe, effective and high-quality medicines are developed and registered in the most resource-efficient manner*” (ICH (a)). The process of harmonisation involves scientific consensus between regulatory and industry experts. ICH regulators commit to implement the final Guidelines (ICH (a)).

In their answers to our questionnaire, some stakeholders pointed out that there is no formal legal requirement that mandates that animal testing should be done prior to clinical trials (UK Parliament, 2023). While there is no explicit UK legislation requiring this, the UK’s Medicines

and Healthcare products Regulatory Agency (MHRA) works to the ICH guidelines referred to above, which detail the animal models that are considered acceptable for use in pre-clinical toxicology studies. The guidelines allow both flexibility in approach based on scientific rationale and for the use of non-animal alternatives, where these exist. The ICH guideline (ICH, 2009) highlights: "*This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles and reduce the use of other drug development resources. Although not discussed in this guidance, consideration should be given to use of new in vitro alternative methods for safety evaluation. These methods, if validated and accepted by all ICH regulatory authorities, can be used to replace current standard methods. This guidance promotes safe, ethical development and availability of new pharmaceuticals*" (ICH, 2009).

It should be noted that any alternative methods are required to be accepted by all ICH regulatory authorities. At the point of writing this report there are no ICH agreed *in vitro* alternatives for general safety assessment of potential new medicines.

Safety assessment using mammalian species is generally expected to support clinical development and registration of potential new medicines. International regulatory guidelines outline recommendations for the number and type of species to be used (Prior et al., 2020). There is an established practice, based on the requirements of ICH, that potential risks to humans will typically be assessed in two species (i.e., a rodent and a non-rodent) (International Committee on Harmonization, (b); (c); 2009). Examples of non-rodent species include the dog, 'mini-pig' and NHP. It is widely understood that the most scientifically relevant species should be chosen for the development compound in question (Prior et al., 2020).

For biotechnology products, such as monoclonal antibodies, ICH (S6 (R1)) requires that *in vivo* studies need to be conducted in only one pharmacologically relevant species (International Committee on Harmonization (d)). As many of these products are highly selective, it may often be considered by those undertaking the tests and those authorising the use of the products in human trials that there is only one pharmacologically relevant species: i.e., an NHP (Chapman et al., 2009; Chapman et al., 2013a).

Another guideline (International Committee on Harmonization (e)) outlines the requirements for the assessment of QT prolongation (an abnormal heart rhythm that can be seen on an electrocardiogram), which can be a side-effect of some drug treatments. The guideline specifically states that the use of mice and rats is not considered appropriate because the ionic mechanisms of repolarisation of heart muscle differ from humans (International Committee on Harmonization (e)). Therefore, this guideline (S7 B) highlights the animal species that may be used for *in vivo* electrophysiology studies as: dog, NHP, 'mini-pig', rabbit, ferret and guinea pig. The data required for species selection will be similar to that outlined for the selection of the non-rodent species for general assessment of safety; the data already available on the compound in that species will aid study design (International Committee on Harmonization (f)). Therefore, the non-rodent species used for the assessment of QT prolongation may be the same as the species selected for general safety assessment: e.g., dog, NHP or 'mini-pig'.

Several stakeholder responses outlined appreciable criticisms of the current regulatory requirements for safety or metabolism testing, including the specific value of obtaining data from a 'second species' for the assessment process undertaken by regulators. These

responses highlighted the need for the further development and uptake of approaches not involving the use of animals.

While these critiques lie outside the scope of this review, they are important in several respects: e.g. by raising questions concerning the wider (often internationally determined and applied) regulatory framework for new medicines; the scientific validity of using animals for this purpose; the current status of 'alternatives' in this field; and the ethics of using NHPs or animals more generally in research and testing. The UK government has announced that it will publish a plan to accelerate the development, validation and uptake of technologies and methods to reduce reliance on the use of animals in science (UK Parliament, 2024).

We are aware that the UK NC3Rs has brought together pharmaceutical companies to facilitate cross-company data sharing, which includes the collation and analysis of information on hundreds of compounds and/or sharing study designs, in order to try to find new opportunities for applying the 3Rs across the drug development process. Using this evidence-based approach and involving regulators where appropriate has led to changes in company practice and in some cases regulatory guidelines. The NC3Rs has facilitated a number of areas for implementation of the 3Rs in the use of NHPs in drug development. For further information on advances in 3Rs in the use of NHPs in drug development see Section 5.ii below and, for example, the NC3Rs resource (NC3Rs, 2022).

4.ii Sources of blood and tissue

The second type of service licence we reviewed comprised those that involved the provision of NHP blood or tissue. Their purpose was primarily to support non-regulatory requirements although there may be some use in specific regulatory tests. Scientists state that they require NHP blood for several purposes. Examples include: the development of laboratory tests that support medical research, generally; as a cross-species pre-screen to determine whether cynomolgus macaques are appropriate to use in pre-clinical trials; to support validation of data from NHP work conducted under other licences; and to calibrate equipment for use with NHP blood. NHP blood is also used to test for contaminating organisms in the manufacture of the pharmaceuticals known as 'biologicals'; this is a regulatory requirement. For more information on biologicals and what distinguishes them from other medicines, see World Health Organisation, (webpage accessed 03/05/2024).

4.iii Regulation of the use of NHPs in the UK

ASPA (as amended in 2012) and its associated guidance (Guidance to the Operation of ASPA) outline specific and additional conditions that must be met for the granting of certain types of project licence (Home Office (UK), 2014). This guidance describes NHPs as "*specially protected species"* alongside dogs, cats and equidae (Home Office (UK), 2014). Authorisation for the use of non-endangered NHPs may be given only when the work is being carried out for:

- basic research
- translational or applied research
- research aimed at preserving the species of primate being used

Furthermore, translational or applied research using NHPs "*must be for the avoidance, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical*

conditions or their effects in humans, or the development, manufacture or testing of the quality, effectiveness and safety of drugs for the same purposes" (Home Office (UK), 2014).

In addition, there must be *"scientific justification to the effect that the purpose of the programme of work to be specified in the licence cannot be achieved by the use of animals which are not primates"* (Home Office (UK), 2014).

5. Findings

5.i Justifications provided for using NHPs

A robust assessment of the justification for the use of any animal in scientific procedures is a fundamental component of the HBA (Animals in Science Regulation Unit, 2015).

The licences reviewed for this report included projects that were authorised to evaluate the safety or metabolism of new medicines in relevant species (including NHPs) and licences that were authorised for the supply of blood and tissue from NHPs. These types of licence can fall under the category of a service licence (see Section 4, above).

Whatever the purpose of the studies to be authorised by any licence, ASPA requires the most appropriate species to be used on scientific grounds.

Safety or metabolism of new medicines

For the licences we reviewed that authorised the use of NHPs to test the safety or metabolism of potential new medicines, a general requirement for the use of two species (rodent and non-rodent) was provided within the text of the project licence application as 'justification' for the use of the NHP (see Section 4.i, above).

However, there was inconsistency in the provision of scientific justification for the specific use of NHPs (and the other non-rodent species in multi-species licences). Some (but not all) licences did provide a description of the process used to assess the scientific justification for the need to use an NHP. For example, this included the requirement for information and/or confirmation from the sponsor in a number of areas:

- That NHPs will be used in the testing of pharmaceuticals only for use in 'life threatening' or 'debilitating' clinical conditions in humans
- The work will not generate data that are already available
- The class of compound to be tested
- Details of the clinical development plan
- Target receptor specificity compared with other species
- Pharmacodynamic response
- Metabolic profile compared with other species
- Whether the compound is one that is more likely to provoke an inappropriate immune response in species other than NHPs

Those licences that described such a process for approval of animal use for each substance indicated that the AWERB or a subgroup of the AWERB (with or without input from the Project Licence Holder) was responsible for assessing the information provided.

As noted above, not all the licences mentioned a process to assess the scientific justification for the use of NHPs. However, the responses we received to our survey of project licence holders highlighted processes that are used to assess the information that is provided by sponsors ahead of the initiation of any studies using NHPs. These included requesting that the sponsor supply information similar to that outlined above. However, without this information being specified within the actual licence applications, it is difficult to understand how the Animals in Science Regulation Unit (ASRU) can conduct an adequate HBA, other than noting that the studies are needed to comply with legal requirements that are governed by other regulatory bodies (for more on this, see: Section 5. iv, below (The Harm-Benefit Analysis).

One licence stated: "*pigs or dogs will be used unless the target of the drug is not expressed in those species*". While to some it may appear a refinement to use 'mini-pigs' or dogs instead of NHPs, there is an absence of scientific evidence to suggest that dogs or 'mini-pigs' can 'suffer less' than NHPs and in any case, such a substitution would be neither scientifically valid nor ethical unless other criteria (e.g., metabolism, disposition or pharmacokinetics) were also appropriate in these species. Of relevance, it was also noted from the stakeholders' responses that the scope of animal sentience is currently a topic of considerable interest and discussion, and the assumption of a hierarchy of neurophysiological sensitivity in non-human animals, with NHPs being at the top, is the subject of increasing debate.

Species choice can often be a balancing act between scientific, practical, welfare and ethical considerations when there is more than one species that is scientifically justified. However, when it comes to the choice of an NHP, in accordance with ASPA, the law dictates that it must be deemed that no other species can be used as an alternative.

Provision of blood and tissue

For the licences involving the provision of blood and tissue from NHPs there was inconsistency in the justifications provided. In some cases, no specific justification was provided. In others, the licence included generic descriptions such as: "*to enable the provision of non-human primate blood to support a wide range of research programmes, diagnostic tests or to support the development of novel in vitro tests that inform the conduct of scientific studies involving non-human primates*". From the survey responses submitted by Project Licence Holders it would appear that, in some establishments at least, processes used to assess the need for NHP blood or tissue are in place. For example, the requirement to complete a 'procedure request form' that asks for answers in relation to areas such as: the purpose for the blood or tissue; justification for the need for this blood or tissue to be provided from NHPs; and the steps they take to implement the 3Rs. Completed forms can be discussed by the project licence holder and the named persons team or by the full AWERB. However, as these processes are not always described in the licences, it is again difficult to see how ASRU can conduct an appropriate HBA.

Multi-species safety and metabolism studies

Several of the licences we reviewed included authorisations for the use of a range of species in safety and metabolism studies, including rodents (typically rats and mice), dogs and 'mini-

pigs'. The broad scope of species covered often meant the justification provided for the species to be used was usually superficial and/or general. In addition, housing, husbandry, handling and refinements are species-specific but, in multi-species licences, the level of detail provided was often limited: for example, there were few references to publications from the NC3Rs or others on reducing the use of NHPs in toxicology studies in the licences reviewed.

However, despite the lack of specific details in the licences reviewed, the licence holders' survey indicated that several organisations focused on 3Rs improvements. Examples included: having 3Rs programmes in place; working with sponsors; sharing good practice across sites; and/or being involved in NC3Rs projects, and several specific examples of 3Rs improvements were detailed.

Recommendation 1: In accordance with ASPA, all licences involving the use of NHPs must provide a clear justification for the requirement to use NHPs and the type of NHP to be used, and explain why no other species is appropriate.

Recommendation 2: If the licences are providing a service, they should include a description of what information the applicant obtains from the sponsor and how that information is assessed.

Recommendation 3: ASRU should consider limiting safety assessment licences to cover a smaller number of species, and licences involving the use of NHPs should be confined to that species only. This would encourage more specific justification for the use of NHPs, more specific details on experimental design and more focused and detailed consideration of 3Rs initiatives that are in place. This consideration could also apply to other non-rodent animals that are used as a second species in safety and metabolism testing.

5.ii The 3Rs

We felt that the application of the 3Rs was rarely adequately described in the service licences we reviewed, and, for example, we found limited reference to NC3Rs resources that are relevant to NHP use. We found this disappointing given that the NC3Rs (UK) has worked with pharmaceutical companies over many years to propose ways to minimise the use of NHPs in drug development (e.g. see (NC3Rs, 2022).

When NHPs are used in the development of new medicines and therapeutics, this is usually preceded by, or in conjunction with, *in vitro*, *ex vivo* and *in silico* approaches, as well as assessments in other species. When there is a regulatory requirement for an *in vivo* study and replacement by an *in vitro* alternative is not considered feasible, the licence applications should explain the testing cascade. This should not only explain the information from non-animal methods that has been used to identify the most appropriate non-rodent species, but also explain the rationale for deselecting compounds for progression into *in vivo* studies. This ensures that when NHPs are used, only compounds that have the best chance of success are tested.

Experimental design (described in more detail in Section 5.v) should explain why the number of groups within a study, as well as why the number of NHPs per group, are the minimum necessary to achieve the intended outcome. When technologies can be used to reduce animal numbers (for example by combining study assessments) these should also be described. There are several publications that outline ways to reduce the number of NHPs used or streamline the medicines' development programme. For example, in development of

monoclonal antibodies the NC3Rs has facilitated published approaches that include re-evaluating the duration of chronic studies, the need for recovery assessments and study designs (including number of groups studied and number of NHPs per group). There are also publications on species selection and the use of one species in safety assessment programmes (e.g. NC3Rs, 2022).

Specific consideration should be given in the licence applications to describing all efforts to minimise cumulative suffering of NHPs (e.g., housing, habituation and handling) as well as ensuring that humane endpoints are as refined as possible. For example, body weight loss is one of the objective indicators of ill health in animals. The NC3Rs has published information on refining the use of body weight loss in short-term studies including those using NHPs (Chapman et al., 2013b). The ASC noted that there is useful information on the NC3Rs website on various aspects of refining NHP use (e.g. NC3Rs(b). Consideration of how dose levels are selected and the sequence of testing (e.g. in early short-term studies rodent studies preceding non-rodent studies) are also important considerations in reducing harms (Laboratory Animal Science Association, 2009).

Recommendation 4: Licence applications should consider and reference (as a minimum) the resources available on the NC3Rs (UK) website and clearly outline how all aspects of the 3Rs will be incorporated into the programme of work.

5.iii Severity/life experience of the animals

Of the 11 licences we reviewed, three had a maximum severity of mild and comprised the provision of blood and tissue samples.

Eight of the 11 service licences contained protocols with a maximum permitted severity of moderate. Protocols authorised by these licences typically comprised administration of test substances, restraint, observations, blood sampling, and on occasions depending upon the purpose of the study other procedures such as surgeries to implant telemetry devices, osmotic pumps or catheters, food and/or fluid control, use of jackets and single housing in metabolism cages.

It is not expected that NHPs would undergo all these procedures within a given study. In some licences this was explained well, and these tended to be the more focused NHP- or area- (e.g. inhalation dosing, metabolism) specific licences. Other licences were much more limited in the information provided and it was difficult to gauge the expected typical or worst-case life experience of the NHPs. These tended to be the multi-species and broader service licences that covered many study types. Humane endpoints in the case of adverse events, for example weight-loss (between 15 and 20%), were provided and in general were appropriate for the severity limit. Nevertheless, the licences as granted have scope to cover a range of different studies within the moderate limit. It is therefore possible that some studies may fall at the upper end of the moderate limit, and this should be taken into consideration when harm-benefit assessments are made.

Of note, all the licences authorised re-use. Re-use can be one method of reducing the numbers of NHPs (or other species) used in procedures where it does not detract from the scientific objective. Killing the animal at the end of its use in a study is often necessary to achieve the scientific objective (e.g., pathology or other tissue analysis needed) but this is not always the case. For example, blood sampling for pharmacokinetic studies (or for supply of blood for other purposes) is a mild procedure and does not require the NHP to be killed at the end of the study. Reuse must strike a balance between avoiding the use of a naïve

animal vs consideration of the cumulative severity of repeated procedures and this should be controlled to limit suffering.

We are aware that in the new ASPeL project licence application form the applicant is required to address ‘why they intend to reuse animals’ and ‘what the limitations are’. However, the information supplied is not included in the approved licence. The absence of this information in the approved licence means that reuse is often not explicitly explained or covered in the description of the animals’ experience. For this licence review the absence of such information made it impossible for us to assess the adequacy of the process for justifying reuse. In addition, the absence of this information in the protocol makes it difficult for those conducting procedures on animals under these licences to understand what has been authorised.

As a general observation, those licences written on the previous electronic licence application form were generally clearer and contained justification for reuse and there were criteria outlined. Those written in the new licence application form generally cited the Section 14 of ASPA 1986. However, in these licences there was little or no explicit justification for reuse or consideration of the cumulative severity of procedures (as per the advice note of re-use of animals under ASPA (Animals (Scientific Procedures) Act (1986), 2015). All procedures have the potential for cumulative suffering if repeated multiple times for long experimental durations. This approach is at odds with licences that outline hypothesis driven research that fall under a severe limit where scrutiny is given to cumulative severity.

From our review, it is not clear how the cumulative experience of animals is considered when assessing the re-use of an animal multiple times within these licences using the current application form. Only some of the licences described and justified the limits on the number of procedures or duration for which an animal could be used but these were generally licences written on the previous application form. In addition, we believe the absence of such information in the approved licence may also make it more difficult for those working under the licence to be aware of the limits.

Recommendation 5: Scientific and ethical justifications for re-use, and the humane endpoints to be used to ensure that overall cumulative severity remains within a moderate severity, should be clearly stated, considered as part of the evaluation process, and included in a final authorised licence as well as the non-technical summary.

5.iv The Harm-Benefit Analysis

The undertaking of the HBA is a legal requirement for all licence applications under ASPA. This process is frequently referred to as ‘the cornerstone’ of the legislation. As described by a former Home Office Minister, the purpose is to *“ensure that any harm that may be caused to the animals is justified by the expected benefits for humans, animals or the environment*” (UK Parliament, 2020).

Expectations and explanations for how the HBA is carried out appear in the current Guidance on the Operation of the ASPA (1986) (Appendix I), which refers to the HBA judgement as being “*fundamental to the recommendation provided to the Secretary of State with regard to granting or rejection of the application and reflects the scale and significance of the proposed harms and benefits*” (See also: (Animals in Science Regulation Unit, 2015).

The HBA of a proposed project of animal research is a formal requirement that is performed by the ASRU as part of its statutory responsibility for project evaluation and authorisation,

and it advises the Secretary of State accordingly. But in the process of preparing a licence application, the applicant, named persons and AWERBs engage in a wider process of ethical review which includes ensuring that the potential harms and benefits involved have been identified and considered from a local perspective, and that all proposed animal use is appropriately justified (ASPA, 1986).

The application of the Harm-Benefit Analysis to service licences

ASRU currently authorises projects seeking to use animals - including NHPs - to generate data on the safety or efficacy of different substances (such as potential new medicines) for submission to other regulators. However, at the time of formal project evaluation and authorisation, the specific substances to be tested under that licence over the period that it will be in force, are generally not known. This poses particular challenges in the application of the HBA, which are well acknowledged and have been reflected on - by both the current ASC and its predecessor, the APC - in broader reviews of the HBA (e.g., Animal Procedures Committee, 2003; Animals in Science Committee, 2017), as well as the licensing process more generally (Animals In Science Committee, 2020) and, specifically, the use of NHPs (Animal Procedures Committee, 2002).

In our recent Licence Analysis Report (Animals in Science Committee, 2020), the ASC recommended: *"While acknowledging that ASRU is aware of these above difficulties, the ASC should review whether it is appropriate for generic service licences (including those for breeding and antibody production) to use the same harm-benefit framework as research licences, in cases where the eventual use of the substance is not considered."*

What is the expected 'benefit'?

A key aspect of difference between the administration of the HBA for service licences compared with other types of licences is the nature of the assessed expected benefit. In many other licences, the proposed 'benefit' considered when undertaking the HBA might, for example, be increased knowledge or insight, or the discovery and development of a new treatment. But, in the types of licences reviewed in this report, the expected benefit that is considered by project evaluators and authorisers fell into two broad categories. One was the generation of data to satisfy the requirements set by regulatory bodies to enable them to make an informed assessment of the risk of a substance to humans, other animals or the environment, were that substance to be approved for use. The second category was the provision of blood and tissue for subsequent use, as described in Section 4.ii above.

As the ASC commented in 2020 *"various international regulatory frameworks require the evaluation of data from tests on substances in order to assess the risk of harmful effects to humans or the environment. In a licence application within ASPA from a contract research organisation, the identity of any individual compounds to be tested for regulatory purposes generally remains unknown. This means that the benefit of the eventual use of the specific substance to humans, animals or the environment – that would normally justify the harms to the animals involved in performing the test – is not currently considered under ASPA. Within ASPA, the only benefit against which to set the harm to the animals is the benefit of knowing whether a harmful effect is demonstrated by compounds under test or not. Hence the harm benefit analysis is limited to the test procedure itself, not the potential benefits to society of the substance which is tested using animals."* (ASC, 2020)

The APC had also noted that under Home Office implementation of ASPA for these types of licences *"there is no requirement to include consideration of the* ***nature and strength of the***

***likely benefits of, or need for, the substances themselves**. On these grounds, project licences may permit the use of animals in testing a wide range of different kinds of substance, defined only in general terms in the licence"* (our emphasis).

But, as the ASC has previously highlighted, *"animal tests are used to assess the safety of substances that have differing kinds of human benefit and levels of societal support (for example, medicines, chemicals, pesticides and food additives) […], however, [the licensing process] does not include consideration of the value to society of the substance being tested"* (Animals in Science Committee, 2017). We recognise that the use of NHPs (or their blood or tissues) in the UK is likely to be associated with the development or testing of potential medical interventions for humans (see section 4.iii above). Even within a medical context, however, the 'value to society' of a substance depends on the ethical worth, which might be attributed to its primary use. For example, one stakeholder compared the use of NHPs to test a product aimed at combating the effects of jetlag with a potential treatment for Parkinson's disease. It is worth noting that Schedule 2B(2) of ASPA requires that, when NHPs are being used for 'the development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feed-stuffs or any other substances or products', the purpose must be for "*the avoidance, prevention, diagnosis or treatment of **debilitating or potentially life-threatening clinical conditions** in man"* (our emphasis).

A number of stakeholders, with differing perspectives regarding the use of animals in research and testing, described how, in the case of these licences, potential 'benefit' depends eventually on how effectively the findings are translated to humans, and reflected on the importance of a governance system that incorporates a robust review and assessment of this. The value of the expected benefits[1] is also affected by factors such as whether the potential medicine being tested is a novel treatment or a treatment that is similar to something already available on the market but with some additional benefit.

With regard to all the points above, the ASC is not clear on who currently makes these assessments on a substance-by-substance basis, what criteria are being used, or the extent to which officials working on behalf of the Secretary of State contribute to this process.

We consider that the absence of routine effective scrutiny of the wider potential value and utility of <u>each substance</u> being tested remains an important gap within the regulatory oversight of these licences in the UK. While the actual number of these types of licences is small compared with the overall number authorised, the numbers of NHPs involved in these types of licences is, relatively, very high. Indeed, the vast majority of NHP use in the UK takes place under such licences. We seek clarity and assurance that current operational practices enable the Secretary of State to discharge their required responsibilities effectively under Section 5B(3)(d) of ASPA.

[1] While many of the substances being tested may go on to have significant 'commercial' value to the client or sponsor, the APC concluded that 'economic benefit' cannot itself form a legitimate part of the [harm]-benefit assessment (Animal Procedures Committee, 2003). Similarly, the Home Office has previously stated a position that the profitability of a company plays no part in the assessment of 'benefit'. However, a goal of improved access to healthcare for all could be a legitimate reason for using animals because of the effects on health, (Animal Procedures Committee,2003), including overall economic benefits. We acknowledge this position but recognise that this aspiration may not be what is achieved in practice. At least one establishment holding project licences authorising this type of animal use described how the defined criteria used by their internal review system to assess the justification for NHP use did not include the 'commercial desirability' of the substance to be tested.

Assessing justification

The approach for evaluating and authorising these types of licences has created long-standing concern among a number of stakeholders as to the extent to which there is *"adequate assessment of the harms, benefits and justification for primate use, and for monitoring primate use".* (Animal Procedures Committee, 2002)

A range of factors must be considered when identifying the potential harms and benefits of proposed animal use, and assessing how these balance to determine whether the proposed use of animals can be justified. It is worth reiterating that "*a regulatory requirement is not, in itself, sufficient to justify particular animal tests*" (Animal Procedures Committee, 2003) and should not lead to an 'automatic' positive outcome in an HBA.

As well as the factors already highlighted in the previous sections, the ASC has stated elsewhere that there is also *"ongoing debate about the scientific validity and recognition of the limitations of animal tests. Considerable efforts are being made to replace animals in regulatory procedures. Some specific animal tests have been and/or are being challenged with respect to necessity, for example, acute toxicity studies in the development of new medicines. These issues around the scientific validity of animal research and testing are not unique to regulatory science, but given animal tests are mandated by regulators as part of safety protocols they do require continuing challenge and review."* Furthermore, *"Many regulatory toxicology tests were introduced 30 or 40 years ago. The pharmaceutical industry has changed considerably since with new drug targets, new types of compounds and new in vitro and in silico technologies available to evaluate safety. This challenge to requirements laid out in the regulations is an important part of ongoing HBAs."* (Animals in Science Committee, 2017).

Since the publication of the ASC's report (Animals in Science Committee, 2017), the NC3Rs has continued to work with the pharmaceutical industry and others to apply the 3Rs principles to safety and metabolism tests using NHPs (NC3Rs, 2022). We would like to see the results of this work applied more widely.

Because of the range of factors that should be robustly scrutinised before any animal use takes place, we believe that there must be an effective forum and process for challenging the need for performing a test using animals, for considering the societal value of the substance being tested, and for ensuring that all opportunities for avoiding, replacing, reducing and refining animal use are taken, as discussed in the next section.

A role for ASRU and/or for AWERBs in the Harm Benefit Analysis?

Various potential mechanisms and opportunities have been looked at with the aim of increasing the robustness of governance within the ethical review process and licensing system.

One option, proposed by some stakeholders who responded to our survey, is for ASRU project evaluators to have a role in the prospective consideration of the individual substances to be tested once this is known. This could increase regulatory oversight for these types of licence, given that the responsibility under ASPA for carrying out of the HBA falls to ASRU, on behalf of the Secretary of State. In practice, we recognise that this would increase the amount of regulator resource that would be needed and would also require multiple additional communications between the establishment or project licence holder and the regulator.

Another option is that, as part of the Retrospective Assessment process required by Section 5B(7)(a) of ASPA, the licensee would provide comprehensive information regarding the individual substances that have been tested under the licence, including exactly how the data from those studies were used. This is particularly pertinent given that the studies involved usually appear in successive licence applications covering similar plans of work. This would enable better tracking and review and could thereby inform evaluation and authorisation of decisions on subsequent licence applications. Overall, we believe that serious consideration should be given to both the added value and the practicalities of introducing either or both measures.

Among other options, we note in particular that the ASC has previously recommended that *"local AWERBs of establishments engaged in regulatory toxicology testing should ensure that their mechanisms for weighing harms and benefits consider the context of the types and utility of substances/products being tested, the opportunities for data sharing and the contribution to ongoing HBA review in this area of work"* (Animals in Science Committee, 2017). This recommendation was accepted by the then Home Office Minister (Home Office (UK), 2020b).

In a subsequent report we elaborated on this point by recommending that "*Where a project licence covers a broad category of substances (e.g. potential medicines or pesticides), but the specifics of the substance to be tested are not known (e.g. its disease indication or chemical series), consideration should be given to the development of a system which provides local oversight of the justification for the specific substances being tested, and which allows the opportunity for ASRU to review this"* (ASC, 2020).

We noted at that time that some individual establishments have already set up such an internal process of governance. The responses to our survey of establishments holding these licences confirms this, but our understanding is that this is by no means commonly done.

Recommendation 6: ASRU should review its operational practices, especially the audit process, to ensure that all relevant establishments are empowering their local AWERBs (or have an equivalent process) to challenge the need to use animals, prospectively. This would include:

- an assessment of ethical justification on a substance-by-substance basis, which includes consideration of the societal value and utility of each substance to be tested, and
- ensuring that all opportunities for avoiding, replacing, reducing and refining animal use are being taken and shared.

The ASC would be happy to work with ASRU and ASRPU to develop guidance for establishments on this matter.

5.v Experimental Design

Good experimental design is a fundamental requirement in animal research that facilitates the quality and reliability of the information obtained while minimising the use of animals.

In hypothesis driven research, each study should detail the experimental design principles that will underpin the hypothesis being evaluated. This includes the consideration of outputs, the choice of control groups and details of how the group sizes will be determined with

adequate statistical power. Typically, such justification will include sample size calculations using information on variability and a biologically relevant effect-size derived from prior experiments or literature. However, when this information is not available, pilot studies should be conducted to gather this information. When applying for a licence, an estimation of the number of planned studies and the groups/group sizes required for each one are then used to determine the total number of animals requested for the whole licence.

In the course of our review, we considered two types of service licence involving the use of NHPs (regulatory testing, and the supply of blood and tissue); these fall under the umbrella of non-hypothesis driven research and therefore some aspects of experimental design such as power analysis are not generally applicable. For example, in regulatory safety testing the purpose of the study is to assess potential safety effects and risks that may either support progression of the compound to clinical trials or stop further development of the compound (International Committee on Harmonisation, 2009), and Roberts et al., 2014). Given the number of unknown functional and pathological effects that might occur, standard power analysis is not possible (Sparrow et al., 2011). Such studies are conducted in accordance with international guidelines (Sparrow et al., 2011). Pilot studies (often referred to as maximum tolerated dose or dose-range finding studies) are conducted using a smaller number of animals to explore tolerability, kinetics and potential adverse effects so that appropriate dose levels can be set for further regulatory studies of longer duration, using more animals. Some regulatory studies do use the hypothesis driven approach where a specific function is being investigated, for example QT prolongation, (Sivarajah A et al., 2010).

For the safety assessment licences we reviewed, details on study design (number of groups, animals per group etc) were limited or absent. Generally, there was no explanation of how the studies proposed were designed to give robust and reliable data. While power analysis might not be appropriate in such studies, it is expected that typical study designs should be described, and a rationale included that explains how these are appropriate to deliver the outcome required. Many of these studies are conducted in compliance with Good Laboratory Practice and have several quality criteria that must be met before studies are started, but these were not described. Some licences contained statements regarding group size: i.e., where 3-4 groups of 4-6 animals is outlined on a protocol for 24 or 36 NHPs. Yet, these were often difficult to reconcile with a described study design. For example, there was no explanation of why 24 NHPs might be used in some cases versus 36 in others (even when there could be good reasons, such as the inclusion of recovery groups).

We also noted that within the current licence application template provided by ASRU there is a question: "*Will your experimental design be determined by a regulatory guideline*" If the answer is 'yes', there are no further questions about the experimental design. Appendix 1 illustrates the questions within the Animals in Science Procedures e-Licensing (ASPeL) template for regulatory testing versus basic research with the latter being much more robust. Some licences refer to regulatory guidelines to justify the study design without further rationale. It is worth noting that many regulatory guidelines do not include the numbers of animals to be used thus allowing for flexibility in design. Where these are cited in licence applications, they cannot always be used as a justification for individual study designs.

In our view the template questions for regulatory testing drive the lack of information on study design in the licences we saw. Most pharmaceutical guidelines outline principles and the types of preclinical programme required to support different types of clinical trial and the

numbers of animals required in individual experiments (e.g. International Committee on Harmonisation, 2009). Therefore, it is critical that a project licence application template should require full details of the experimental design and numbers of animals to be used even in studies for regulatory testing.

We also observed that some of the safety licences covered a wide range of study types and species (e.g., rodents and non-rodents including NHPs). This approach is not focused and makes it difficult to provide the detailed information on study design that is relevant to each species and study type without the licence becoming overly complex and unwieldy.

A smaller number of licences were authorising the supply of blood and tissue. One of the licences mentioned a standard form for requesting samples that is used to assess the justification for requesting blood or tissue, which was reviewed by the senior management team, Named Animal Care and Welfare Officer (NACWO), Named Veterinary Surgeon (NVS) as well as reviewed regularly by a sub-committee of the AWERB.

In general, these licences mentioned maximising the use of samples and minimising procedures. Tissue provision is co-ordinated to maximise the use of tissues taken from NHPs already scheduled to be humanely killed. One licence mentioned statistical input was sought into the number of NHPs to be sampled for specific assays. Much of the data generated from the supply of NHP blood or tissue is not quantitative data. The current ASPeL project licence template does not request further experimental design rationale if the applicant answers 'no' to the question "*Does this protocol generate quantitative data?"*. There are other questions in the application that request information about how requests are accepted or rejected and how supply matches demand. However, these are outlined specifically for producing genetically-altered or surgically prepared animals/animal products using standardised protocol frameworks and for manufacturing vaccines and medicines for medical or veterinary use (Appendix 2) and do not address the justification for the numbers of animals to be used.

With the absence of information on experimental design in both types of licence we reviewed and the lack of focus on experimental design in the safety licences, it is unclear how a HBA can be conducted to authorise the use of the animals within such licences. This is a particular source of concern given the large numbers of NHPs and other species that are proposed to be uses within the lifetime of these licences.

Recommendation 7: All licence applications (including for service licences) should detail the experimental design processes that are being used to justify the number of animals required by species. Within licences that include regulatory testing this does not necessarily have to include power analysis.

Recommendation 8: For the provision of blood and tissue, adequate justification should be provided in project licence applications for the number of samples taken and the oversight processes associated with supplying blood or tissue.

Recommendation 9: The ASPeL project licence application template should be reviewed and updated to include questions to the applicant about how they determine that the experimental design and group sizes are appropriate for delivery of the required experimental outcome. This should be updated for studies that are conducted for regulatory purposes as well as for those that do not generate quantitative data.

5.vi Governance

Responding to our surveys, Project Licence Holders and other stakeholders emphasised the central role of an appropriately constituted and effective AWERB in governance, in reviewing the ethical and legal aspects of research plans for funding, and the subsequent project licence applications. From examination of these 11 project licences, the smooth articulation of these two distinct phases is most easily achieved within a single institution. The governance of animal use is more complex, however, when it involves a commissioning organisation, or sponsor, in addition to the service provider, which holds NHPs and has the appropriate licence(s) and expertise to conduct the research.

Project Licence Holders of service licences told us that they require confirmation from commissioning organisations that the appropriateness of and necessity for using NHPs have been considered and various 'NHP justification forms' have been developed by different service providers for this purpose. This information, in addition to the details of the animal-related research required, is considered by the service provider in its decision on whether to accept the commission. This key scrutiny may be undertaken by the AWERB, or a subgroup, or (as in one organisation) a separate group of different professionals with expertise in working with NHPs.

Some service providers emphasise the responsibility of the commissioning organisation to conduct an ethical review of their own, and our stakeholder responses described some examples of good practice in respect of this process within large pharmaceutical companies. However, good practice within the service provider, as garnered from licence applications, involves: evaluation (among other criteria) of whether the work is ethically and scientifically justified; whether their licence authority allows them to conduct the work; and whether a more refined approach can be identified. Further details will be sought from the commissioning organisation if information that is needed to satisfy any criterion is lacking. If any of the service provider's criteria for acceptance cannot be met, the commission will be rejected. If accepted, the work will be undertaken with due regard to advice from the AWERB and the named professionals in the service provider appointed for supervision of research work.

Some stakeholders said that they are concerned about two perceived governance "*weaknesses*" in this system. The first relates to the AWERBs' role in considering alternatives and refinements. We recognise that this may be due in part to the more prescriptive nature of regulatory studies. The second is the lack of external oversight of each of these separate studies, given that the authorisation of a project licence for a service will support multiple individual studies, testing different agents, for different commissioning organisations. These stakeholders would welcome formal consideration of alternative refined and non-animal methods in the governance process, before work proceeds, and clearer, separate ethical consideration of each individual piece of commissioned work.

Discussion of whether non-animal alternative approaches could be used is an AWERB task that is considered to receive less attention and to be less effectively carried out across AWERBs (Rawle, 2023). It is recommended that consideration is given to how this could be best facilitated, in view of the common problem that AWERBs might have insufficient expertise to propose further possibilities for replacement. However, with the division of responsibility between the commissioning organisation and the service provider, and the need for individuals with up-to-date knowledge of and expertise in replacement of NHPs used in these service licences, it is unclear where this review would be best located. Further,

it is recommended that, in addition to the ethical review undertaken by the service provider before acceptance of a commission, they (the service provider) receive formal confirmation that the ethics and regulatory necessity of the proposed work have been fully considered by the commissioning organisation through a robust, internal system. Finally, it is recommended, in the interests of disseminating best practice, that a common pro-forma is developed for the collection of all the necessary preliminary information from the commissioning organisation, to ensure that all this detail will be considered (see also Section 5.iii above and ASC, 2020).

Recommendation 10: Before proceeding with their own ethical review, service providers should receive formal confirmation that the regulatory necessity of the proposed work and its ethical justification have been fully considered by the commissioning organisation through a robust internal system.

Recommendation 11: A common pro-forma should be developed for the collection of all the necessary preliminary information from a commissioning organisation, including formal confirmation that their own ethical review has been completed.

5.vii Non-Technical Summaries (NTSs)

The non-technical summaries of these licences vary widely in both the accessibility of the language used, and in how well they summarise the project of work as ASPA requires. The ASC notes that guidance on drafting of NTSs has recently been published by ASRU (Animals in Science Regulation Unit, 2024).

Non-technical language

Some used appropriate non-technical language and were considered likely to be understandable to a lay person. However, some were written so technically that they should never have been accepted by the AWERB or ASRU as fulfilling the ASPA requirement for non-technical language. Most were a mixture, with parts of the work that are well explained, but also containing sections that are far too technical for a lay person to understand.

In several of the licences, the harms and 3Rs sections of the NTS were not proper summaries for a lay person, but contained an inappropriate degree of detail and technicality, or information on the benefits that might be suitable for funding applications but unnecessary in a brief lay summary of the project of work.

Justification for NHPs

In some licences, appropriate explanation was provided as to why the use of NHPs was being sought, but in many the NTS did not make this clear enough. In two cases, the NTS did not even make reference to the use of primates. In several licences, the description of the uses was so broad that “any new medicinal product” in which NHP testing was required could be justified regardless of the end application, or else was described in such technical terms as to be incomprehensible to a lay person. Two very similar NTSs left blank the question of what animal species or numbers were to be used, which is one of the specific requirements for the NTS in Article 5A of ASPA.

Despite the legal requirement that studies using NHPs involved in translational or applied research must be for the “*avoidance, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical conditions or their effects in humans, or the development, manufacture or testing of the quality, effectiveness and safety of drugs for the same*

purposes", the NTSs did not include such confirmation. It would be important to state this, and to indicate the process the establishment has in place to assess this, and also the consideration of alternatives to animals.

Recommendation 12: There is a need for greater oversight on the part of both the AWERB and ASRU on the readability and quality of non-technical project summaries. It is recommended that establishments have processes in place to assist the applicant with the help of lay members or non-technical staff.

6. Summary of recommendations

Recommendation 1: In accordance with ASPA, all licences involving the use of NHPs must provide a clear justification for the requirement to use NHPs and the type of NHP to be used, and explain why no other species is appropriate. (PPL Applicant)

Recommendation 2: If the licences are providing a service, they should include a description of what information the applicant obtains from the sponsor and how that information is assessed. (PPL Applicant)

Recommendation 3: ASRU should consider limiting safety assessment licences to cover a smaller number of species, and licences involving the use of NHPs should be confined to that species only. This would encourage more specific justification for the use of NHPs, more specific details on experimental design and more focused and detailed consideration of 3Rs initiatives that are in place. This consideration could also apply to other non-rodent animals that are used as a second species in safety and metabolism testing. (ASRU)

Recommendation 4: Licence applications should consider and reference (as a minimum) the resources available on the NC3Rs (UK) website and clearly outline how all aspects of the 3Rs will be incorporated into the programme of work. (PPL Applicant)

Recommendation 5: Scientific and ethical justifications for re-use, and the humane endpoints to be used to ensure that overall cumulative severity remains within a moderate severity, should be clearly stated, considered as part of the evaluation process, and included in a final authorised licence as well as the non-technical summary. (PPL Applicant)

Recommendation 6: ASRU should review its operational practices, especially the audit process, to ensure that all relevant establishments are empowering their local AWERBs (or have an equivalent process) to challenge the need to use animals, prospectively. This would include:

- an assessment of ethical justification on a substance-by-substance basis, which includes consideration of the societal value and utility of each substance to be tested, and
- ensuring that all opportunities for avoiding, replacing, reducing and refining animal use are being taken and shared.

Recommendation 7: All licence applications (including for service licences) should detail the experimental design processes that are being used to justify the number of animals required by species. Within licences that include regulatory testing this does not necessarily have to include power analysis. (PPL applicant)

Recommendation 8: For the provision of blood and tissue, adequate justification should be provided in project licence applications for the number of samples taken and the oversight processes associated with supplying blood or tissue. (PPL applicant)

Recommendation 9: The ASPeL project licence template should be reviewed and updated to include questions to the applicant about how they determine that the experimental design and group sizes are appropriate for delivery of the required experimental outcome. This should be updated for studies that are conducted for regulatory purposes as well as for those that do not generate quantitative data. (ASRU)

Recommendation 10: Before proceeding with their own ethical review, service providers should receive formal confirmation that the regulatory necessity of the proposed work and its ethical justification have been fully considered by the commissioning organisation through a robust internal system. (Service provider / Commissioning organisation)

Recommendation 11: A common pro-forma should be developed for the collection of all the necessary preliminary information from a commissioning organisation, including formal confirmation that their own ethical review has been completed. (Service provider / PPL holder)

Recommendation 12: There is a need for greater oversight on the part of both the AWERB and ASRU on the readability and quality of non-technical project summaries. It is recommended that establishments have processes in place to assist the applicant with the help of lay members or non-technical staff. (AWERB / ASRU)

7. References

Animal Procedures Committee (2002) The use of primates under the Animals (Scientific Procedures) Act 1986 - Analysis of current trends with particular reference to regulatory toxicology. <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/118994/primates.pdf>

Animal Procedures Committee (2003) Review of cost-benefit assessment in the use of animals in research. <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/119027/cost-benefit-assessment.pdf>

Animals in Science Committee (2017) Review of the harm-benefit analysis in the use of animals in research. <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/675002/Review_of_harm_benefit_analysis_in_use_of_animals_18Jan18.pdf>

Animals in Science Committee (2020) Licence analysis review. <https://www.gov.uk/government/publications/licence-analysis-review-report-by-the-animals-in-science-committee>

Animals in Science Regulation Unit (2015) Harm Benefit Analysis Process. New Project Licence Applications. Advice Note 05/2015. Harm_Benefit_Analysis__2_.pdf (publishing.service.gov.uk). < https://assets.publishing.service.gov.uk/media/5a759e39e5274a545822ce88/Harm_Benefit_Analysis__2_.pdf>

Animals in Science Regulation Unit (2024) Non-Technical Summaries. Animal Testing and Research: Guidance for the Regulated Community. <https://www.gov.uk/government/collections/animals-in-science-regulation-unit#non-technical-summaries>

Animals (Scientific Procedures) Act (1986) (2013) Schedule 2B Additional Conditions for the Grant of Certain Project Licences. Section 2.4. <https://www.legislation.gov.uk/ukpga/1986/14/schedule/2B>

Animals (Scientific Procedures) Act (1986) (2015) Use, Keeping Alive and Re-use. Advice Note (02/2015) <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470008/Use__Keeping_Alive_and_Re-use_Advice_Note.pdf>

Chapman K, Pullen N, Coney L, Dempster M, Andrews L, Bajramovic J, Baldrick P, Buckley L, Jacobs A, Hale G, Green C, Ragan I, Robinson V (2009) Preclinical development of monoclonal antibodies, mAbs, 1:5, 505-516, doi: 10.4161/mabs.1.5.9676

Chapman K, Holzgrefe H, Black L, Brown M, Chellman G, Copeman C, Couch J, Creton S, Gehen S, Hoberman A, Kinter L, Madden S, Mattis C, Stemple H, Wilson S (2013a) Pharmaceutical toxicology: Designing studies to reduce animal use, while maximizing human translation, Regulatory Toxicology and Pharmacology. 66(1):88-103. doi: 10.1016/j.yrtph.2013.03.001

Chapman K, Sewell F, Allais L, Delongeas J, Donald E, Festag M, Kervyn S, Ockert D, Nogues V, Palmer H, Popovic M, Roosen W, Schoenmakers A, Somers K, Stark C, Stei P, Robinson S (2013b) A global pharmaceutical company initiative: An evidence-based approach to define the upper limit of body weight loss in short term toxicity studies, Regulatory Toxicology and Pharmacology, 67(1): 27-38. doi: 10.1016/j.yrtph.2013.04.003

Home Office (UK) (2014) Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 (amended 2023). <https://www.gov.uk/guidance/guidance-on-the-operation-of-the-animals-scientific-procedures-act-1986>

Home Office (2020a) Letter from Baroness Williams to the Chair of the Animals in Science Committee (August 2020). <https://www.gov.uk/government/publications/ministerial-commission-of-work-for-the-animals-in-science-committee-2020-to-2021>

Home Office (UK) (2020b) Harm-benefit analysis review: minister's reply to the ASC's recommendations (May 2020). < https://www.gov.uk/government/publications/harm-benefit-analysis-review-ministers-reply-to-the-ascs-recommendations>

Home Office (UK) (2022). Statistics of scientific procedures on living animals, Great Britain: 2022. Updated 13 July 2023. Accessed 30 May 2024. https://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on- living-animals-great-britain-2022.

International Committee on Harmonisation (2009) Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. In: International Conference on Harmonisation (ICH) R2. <https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf>

International Committee on Harmonisation (a).(Accessed 03/05/2024) Mission: harmonisation for better health. <https://www.ich.org/page/mission>

International Committee on Harmonisation (b). Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing) -Scientific guideline (ICH S4). (Implemented in Europe in 2009). < ICH Official web site : ICH>

International Committee on Harmonisation (c). Non-clinical evaluation for anticancer pharmaceuticals - Scientific guideline (ICH S9). (Implemented in Europe in 2009). < ICH Official web site : ICH>

International Committee on Harmonization (d). Preclinical safety evaluation of biotechnology-derived pharmaceuticals - Scientific guideline (S6 R1). (Implemented in Europe in 1998). < ICH Official web site : ICH>

International Committee on Harmonization (e) Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals - Scientific guideline (S7 B). (Implemented in Europe in 2005). < ICH Official web site : ICH>

International Committee on Harmonization (f). Safety pharmacology studies for human pharmaceuticals - Scientific guideline (S7 A). (Implemented in Europe in 2005). < ICH Official web site : ICH>

Laboratory Animal Science Association (2009) Guidance on dose level selection for regulatory general toxicology studies for pharmacology. Accessed 6th May 2024. <https://www.lasa.co.uk/PDF/LASA-NC3RsDoseLevelSelection.pdf>

NC3Rs (2022) Guidance: Minimising non-human primate use in drug development. <https://nc3rs.org.uk/minimising-NHP-use>

NC3Rs (a) (Accessed 03/05/2024) Refining MTD studies. NC3Rs.) <https://www.nc3rs.org.uk/our-portfolio/refining-mtd-studies >

NC3Rs (b) (Accessed 03/05/2024) Training using positive enforcement. <https://www.nc3rs.org.uk/our-portfolio/training-using-positive-reinforcement>

Prior H, Haworth R, Labram B, Roberts R, Wolfreys A, Sewell F (2020) Justification for species selection for pharmaceutical toxicity studies, Toxicology Research 9:758-770. doi: 10.1093/toxres/tfaa081

Rawle F (2023) The role of review and regulatory approvals processes for animal research in supporting implementation of the 3Rs. <https://nc3rs.org.uk/role-review-and-regulatory-approvals-processes-animal-research-supporting-implementation-3rs-2023>

Roberts R, Kavanagh S, Mellor H, Pollard C, Robinson S, Platz S (2014) Reducing attrition in drug development: smart loading preclinical safety assessment. Drug Discovery Today. 19(3)341-347. doi: 10.1016/j.drudis.2013.11.014

Sivarajah A, Collins S, Sutton M, Regan N, West H, Holbrook M, Edmunds N (2010) Cardiovascular safety assessments in the conscious telemetered dog: Utilisation of super-intervals to enhance statistical power. Journal of Pharmacological and Toxicological Methods, 62(1): 12-19. doi: 10.1016/j.vascn.2010.05.011

Sparrow S, Robinson S, Bolam S, Bruce C, Danks A, Everett D, Fulcher S, Hill R, Palmer H, Scott E, Chapman K (2011) Opportunities to minimise animal use in pharmaceutical regulatory general toxicology: A cross-company review, Regulatory Toxicology and Pharmacology, 61(2):222-229. doi: 10.1016/j.yrtph.2011.08.001

UK Parliament (2020) Animal experiments: Home Office Written Question, answered in Parliament 14 October 2020. <https://questions-statements.parliament.uk/written-questions/detail/2020-10-09/101318>

UK Parliament (2023) Written questions answers and statements. Clinical trials: question for the Department of Health and Social Care: < https://questions-statements.parliament.uk/written-questions/detail/2023-09-19/200502>

UK Parliament (2024) Animal testing. Hansard. 745(debated 19th February 2024). <https://hansard.parliament.uk/Commons/2024-02-19/debates/0C64E6BD-AE31-4DD7-80BB-3CEDC6272C2E/a>

World Health Organisation (Accessed 03/05/2024) Biologicals. <https://www.who.int/health-topics/biologicals#tab=tab_1>

8. Appendices

Appendix 1: ASPeL Experimental Design Questions for Regulatory Testing versus Basic Research

- **Journey 1 (regulatory testing)**

Will this protocol generate quantitative data?

Answer YES

Will your experimental design be determined by a regulatory guideline?

Answer YES

How will you ensure that you are using the most refined methodology?

- **Journey 2 (non-regulatory testing e.g. basic research)**

Will this protocol generate quantitative data?

Answer YES

Will your experimental design be determined by a regulatory guideline?

Answer NO

Where relevant, explain how and when pilot studies will be used.

How will you choose different experimental groups?

For example, controls, dose levels, satellites etc.

How will you choose control groups?

Provide a robust scientific justification for controls with significant suffering such as sham surgery controls or untreated infected controls.

How will experiments and data analysis be randomised and blinded?

How will you minimise variables to ensure reproducibility?

How will you determine group sizes?

You should reference POWER calculations you have made, if relevant.

How will you maximise the data output from the animals you use on this protocol?

Appendix 2: Questions within the ASPeL template that address product quality, processes for accepting/rejecting requests

In the Action Plan:

- **Will you be producing genetically altered or surgically prepared animals/animal products using standardised protocol frameworks?**

If yes:

How do you assure the quality of the products?

How will you match the supply of your products with demand?

Will these products be offered as a service to others?

If yes:

What is your process for accepting or rejecting work?

What specific criteria will you use to decide whether to accept or reject work?

Will others help you make decisions about accepting or rejecting work?

Similarly, for:

- **Will you be manufacturing vaccines and medicines for medical or veterinary use?**

If yes:

Will all manufacturing be conducted in compliance with Good Manufacturing Practice (GMP) standards?

If not, explain why this is not required.

Describe how animals are used throughout the manufacturing process.

What animal-based tests do you need to undertake on your products, and for which regulator?

How do you assure the quality of your products?

How will you match the supply of your products with demand?

Will you use animals to develop and validate more refined methods or non-animal alternatives?

Explain the type of work you will do, and indicate which steps in the manufacturing process this relates to.

Appendix 3: PPL holders' questionnaire

1. Please describe your criteria for species selection, focusing on the selection of NHPs as opposed to another species.

2. What types of products will be tested using NHPs in your licence?

   2a Please describe how decisions are taken within your establishment as to whether the use of NHPs is required and justified for each study.

   2b Describe the process for selection of the specific species.

   2c Describe how the number of animals to be used is reviewed and determined (please reference specific regulatory guidelines if you use these for justifying numbers).

   2d If relevant, to what extent is there potential for flexibility in the experimental and study designs you use?

3. For what purposes are you supplying NHP blood/tissue in your licence?

   3a Please describe how decisions are taken within your establishment as to whether the use of NHPs is required and justified for each study

   3b Describe the process for selection of the specific species

   3c Describe how the number of animals to be used is reviewed and determined (please reference specific regulatory guidelines if you use these for justifying numbers)

   3d If relevant, to what extent is there potential for flexibility in the experimental and study designs you use?

4. Have there been any instances where proposed studies (or supply of blood/tissue) have not been approved, or only approved after significant amendments to the proposal?

5. Do your governance processes include a local mechanism for assessing the likely benefits or value (economic, wider societal etc) of each of the substances you are testing? (or if supplying blood/tissue the purposes for which these will be used) How are decisions made? Does your AWERB have a role in this?

6. Please describe how your establishment seeks to ensure it is using the most up-to-date good practices for reducing potential adverse impacts on animals, e.g. habituating/training animals; improving handling, housing and care; welfare monitoring and assessment etc.

7. Which areas of refinement do you feel are the most challenging given the nature of the studies you undertake?

8. Can you provide any examples of when you have been able to share good practices with other organisations working in the sector using similar study protocols?

   8a What might help facilitate this process in the future?

   8b Are there any issues concerning commercial sensitivity that could provide an obstacle to the sharing of such information and expertise?

   8c If you supply NHP blood or tissue, do you work collaboratively with other organisations to maximise the use of animals e.g. tissue sharing networks etc.

9. Is there anything else that you would like to share with the ASC regarding the processes in place, and efforts made, within your organisation to ensure that each use of NHPs is ethically and scientifically justified and is undertaken in line with the aim of ensuring the optimal implementation of the 3Rs?

Appendix 4: Stakeholder questionnaire

1. Name of organisation

2. Please provide your views and comments on the most important roles and responsibilities of the designated establishment, particularly the project licence holder and the local Animal Welfare and Ethical Review Body, in ensuring that each use of animals in projects relating to the safety testing of potential new medicines and other substances has been adequately justified, both scientifically and ethically.

3. Please provide your views and comments on the most important roles and responsibilities of the regulator, the Animals in Science Regulation Unit, in ensuring that each use of animals in projects relating to the safety testing of potential new medicines and other substances has been adequately justified, both scientifically and ethically.

4. Please provide your views and comments on how you think the Harm-Benefit Analysis should be applied and undertaken for project applications under the Animals (Scientific Procedures) Act 1986 (as amended) in the categories of safety testing of potential new medicines and other substances.

5. Please provide your views and comments relating to potential opportunities, along with the locus of responsibility, for further implementing the 3Rs relating to the use of NHPs for the safety testing of potential new medicines and other substances.

Appendix 5: References cited by stakeholders

JOURNAL ARTICLES:

Aboul-Soud MAM et al. (2021) Induced Pluripotent Stem Cells (iPSCs)-Roles in Regenerative Therapies, Disease Modelling and Drug Screening. Cells. Sep 5;10(9):2319. doi: 10.3390/cells10092319. [Cells | Free Full-Text | Induced Pluripotent Stem Cells (iPSCs)—Roles in Regenerative Therapies, Disease Modelling and Drug Screening (mdpi.com)]

Attarwala H. (2010) TGN1412: From Discovery to Disaster. J Young Pharm. Jul;2(3):332-6. doi: 10.4103/0975-1483.66810. https://www.sciencedirect.com/science/article/abs/pii/S0975148310230248?via%3Dihu

Bailey, J. et al. (2015). Predicting human drug toxicity and safety via animal tests: can any one species predict drug toxicity in any other, and do monkeys help? ATLA, 43(6): 393-403. doi: 10.1177/026119291504300607.

Ewart L et al (2022) Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology. Commun Med (Lond). Dec 6;2(1):154. doi: 10.1038/s43856-022-00209-1. [https://www.nature.com/articles/s43856-022-00209-1

[Author correction #1] Ewart et al. (2022) Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology. Commun Med (Lond). Dec 6;2(1):154. doi: 10.1038/s43856-022-00209-1

[Author Correction #2] : Ewart et al (2023) Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology - Commun Med (Lond). 2023 Feb 2;3(1):16. doi: 10.1038/s43856-023-00249-1.

Liu J-C et al. (2022) Multi-omics research in sarcopenia: Current progress and future prospects. Ageing Res Rev. Apr:76:101576. doi: 10.1016/j.arr.2022.101576. Epub 2022 Jan 29.]

Marshall LJ et al. (2023) Poor Translatability of Biomedical Research Using Animals - A Narrative Review. Altern Lab Anim. Mar;51(2):102-135.doi: 10.1177/02611929231157756. Epub 2023 Mar 7. [https://www.researchgate.net/publication/369067834_Poor_Translatability_of_Biomedical_Research_Using_Animals_-A_Narrative_Review]

Salter K. Is UK animal research governance facing a “new normal”? Considering the risks and benefits of “going online”. Altern Lab Anim. 2023:51(4):258-262. doi:10.1177/02611929231180605

Svensson MS, Nijman V, Shepherd CR. Insights into the primate trade into the European Union and the United Kingdom. Eur J Wildl Res. 2023:69(3):51. doi:10.1007/s10344-023-01681-3.

Veening-Griffioen, D. H. (2021) “Tradition, not science, is the basis of animal model selection in translational and applied research”, *ALTEX - Alternatives to animal experimentation*, 38(1), pp. 49–62. doi: 10.14573/altex.2003301.

DIGITAL LIBRARY

Mason G, Rushen J, eds. Stereotypic Animal Behaviour: Fundamentals and Applications to Welfare. 2nd ed. Cabi; 2008.

MEETING PROCEEDINGS

Jennings M. (2015) The harm-benefit analysis and project evaluation – A UK perspective. ALTEX Proc. 4:41-44.

Springer Link. Arguments Against Using Nonhuman Primates in Research. https://link.springer.com/chapter/10.1007/978-3-030-82708-3_23

WEBSITES:

Airtable NAMS Resources
https://airtable.com/appT1hakW9FM9a556/shrd7p5N7SEh7GGqg/tblQNuEZyPDLmc1Ji

All-Party Parliamentary Group (APPG) for Human Relevant Science: Report. https://www.humanrelevantscience.org/wp-content/uploads/APPG-report-March-2022.pdf

Animal Free Research UK. Eight steps to accelerate human relevant innovation. https://www.animalfreeresearchuk.org/wp-content/uploads/2022/05/AFR_Policy-report_A4_PW_Digital.pdf

Animal Free Research UK. How human-specifi c technologies can transform lives and supercharge the economy. https://www.animalfreeresearchuk.org/wp-content/uploads/2023/09/Human-Specific-Technologies-Briefing-NEW.pdf

Animal Procedures Committee (2002) The Use of Primates under the Animals (Scientific Procedures) Act (1986): Analysis of Current Trends with Particular Reference to Regulatory Toxicology. APC. https://web.archive.org/web/20060225185859/http://www.apc.gov.uk/reference/primates.pdf.

Animals in Science Committee. Research and analysis: advice on the use of the forced swim test. Animals in Science Committee response to a ministerial commission for advice. 5 July 2023. Accessed 9 October 2023. https://www.gov.uk/government/publications/advice-on-the-use-of-the-forced-swim-test.

Artificial intelligence in musculoskeletal conditions - PubMed (nih.gov) [Roman-Belmonte et al. (2021) Artificial intelligence in musculoskeletal conditions. Front Biosci (Landmark Ed) Nov 30;26(11):1340-1348. doi: 10.52586/5027.]

Campbell S, Timoshyna A, Sant G, et al. (2022) Options for managing and tracing wild animal trade chains to reduce zoonotic disease risk. TRAFFIC. Accessed 10 October 2023.

Certara. Certara's Simcyp Simulator Demo. https://www.certara.com/video/certaras-simcyp-simulator-demo

CN BIO. https://cn-bio.com/cn-bio-expands-service-offering-to-support-oncology-drug-discovery

Home Office UK. National Statistics : Statistics of scientific procedures on living animals, Great Britain: 2022. https://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on-living-animals-great-britain-2022/statistics-of-scientific-procedures-on-living-animals-great-britain-2022

Home Office (UK) Non-technical summaries for project licences granted July - September 2023 that require a retrospective assessment https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1154567/Non-technical_summaries_for_project_licences_granted_January_-_March_2023_Final.pdf

Home Office (UK). Statistics of scientific procedures on living animals, Great Britain: 2022. Updated 13 July 2023. Accessed 10 October 2023. https://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on- living-animals-great-britain-2022.

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. European Medicines Agency. EMA/CPMP/ICH/286/1995. December 2009. Accessed 11 October 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline- m3r2-non-clinical-safety-studies-conduct-human-clinical-trials-marketing-authorisation_en.pdf.

International Primatological Society. Harvesting of wild primates for use in biomedical research. Accessed 10 October 2023. https://www.internationalprimatologicalsociety.org/harvesting-of-wild-primates-for-use-in-biomedical-research.

International Union for Conservation of Nature (IUCN). Long-tailed macaque. IUCN Red List of Threatened Species. 7 March 2022. Accessed 10 October 2023. https://www.iucnredlist.org/species/12551/199563077.

Medicines and Healthcare Products Regulatory Agency. Case study Innovation: Clonal neoantigen specific tumour-infiltrating lymphocytes for cancer treatment https://www.gov.uk/government/case-studies/innovation-clonal-neoantigen-specific-tumour-infiltrating-lymphocytes-for-cancer-treatment

Medicines and Healthcare Products Regujlatoryh Agency. Innovation: Clonal neoantigen specific tumour-infiltrating lymphocytes for cancer treatment. 29 January 2020. Accessed 11 October 2023. https://www.gov.uk/government/case-studies/innovation-clonal- neoantigen-specific-tumour-infiltrating-lymphocytes-for-cancer-treatment.

NC3Rs (2020). Review of the use of two species in regulatory toxicology studies. Available at: https://www.nc3rs.org.uk/review-use-two-species-regulatory-toxicology-studies. https://www.nc3rs.org.uk/our-portfolio/review-use-two-species-regulatory-toxicology-studies

NC3Rs (2023). The role of review and regulatory approvals processes for animal research in supporting implementation of the 3Rs. Available at: https://nc3rs.org.uk/role-review-and-regulatory-approvals-processes-animal-research-supporting-implementation-3rs-2023.

Rawle, F. The role of review and regulatory approvals processes for animal research in supporting implementation of the 3Rs. A report by Dr Frances Rawle, commissioned by the National Centre for the Replacement, Refinement and Reduction and Animals in Research (NC3Rs). February 2023. Accessed 9 October 2023. https://nc3rs.org.uk/sites/default/files/2023-02/Rawle%20project%20report.pdf.

The Human Medicines Regulations 2012. No.1916. United Kingdom: HMSO. Accessed 11 October 2023. https://www.legislation.gov.uk/uksi/2012/1916/contents/made.

The National Archives. Schedule 8. The Human Medicines Regulations 2012. No. 1916. United Kingdom: HMSO. Accessed 11 October 2023. https://www.legislation.gov.uk/uksi/2012/1916/contents/made.

UK Biobank. https://www.ukbiobank.ac.uk/

UK Parliament. Drugs: Safety. Question for Department of Health and Social Care. https://questions-statements.parliament.uk/written-questions/detail/2023-07-24/HL9600/

WEBSITE CITED BUT NO LONGER ACCESSIBLE.

https://www.traffic.org/site/assets/files/18246/traps_2_supply_chain_management_traceability_review_rep ort_2-1.pdf