Incorporating new approach methodologies in the development of new medicines

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Contents

Key terms

New approach methodologies (NAMs):
Approaches that enable the full or partial replacement of animal use in chemical or drug toxicity assessments.

Full replacement:
Avoids the use of animals entirely (e.g. human volunteer studies, human tissues and cells, established cell lines, and computational models).

Partial replacement:
Involves species not considered capable of experiencing suffering (e.g. invertebrates like *Drosophila*, nematodes, or immature vertebrates), or animal-derived cells and tissues.

Context of use:
The specific application or decision a method is intended to support within the development pipeline (e.g. prioritising candidates, supporting clinical trials, or replacing a particular animal study).

Qualification:
The process of demonstrating that a method is fit for a specific context of use (i.e. the regulatory purpose it is intended to support, such as dose setting or screening).

Validation:
The process of establishing that a method is reliable, reproducible, and relevant for regulatory decision-making.

Executive summary

New approach methodologies (NAMs)[1] are increasingly being explored across the medicines development pipeline, offering the potential to improve the human relevance of safety assessments and reduce reliance on *in vivo* (animal) testing. These include advanced *in vitro* (cell- or tissue-based) models such as organoids and organ-on-a-chip systems, *in silico* (computational) tools including artificial intelligence (AI) and modelling approaches, and other technologies that are already contributing to decision-making across the development pipeline.

To explore how NAMs can be more effectively integrated into medicines development, the NC3Rs, MHRA and ABPI[2] convened a cross-sector workshop with experts from regulatory agencies, industry and academia. Discussions focused on identifying where NAMs are currently being used, the scientific and regulatory challenges to broader adoption, and practical steps that could support progress.

This report summarises the key themes and insights from those discussions. It highlights the importance of early engagement with regulators, clear guidance on context of use, qualification, and validation (see key terms), and international collaboration to ensure consistent regulatory expectations. While animal studies remain a core part of regulatory safety assessment, there is growing interest in using NAMs where they can add value, particularly in areas where traditional models are limited or less predictive.

The UK is well placed to lead in this area, with a strong scientific base and a collaborative research environment. Ongoing dialogue and shared learning will be key to ensuring NAMs are developed and used in ways that support innovation, protect patient safety, and deliver meaningful 3Rs benefits.

Key messages

- **NAMs are already contributing to medicines development.** They are being used across the pipeline, from early discovery and candidate screening to later-stage safety assessments, offering human-relevant insights and reducing reliance on animal testing.
- **NAMs must support robust safety decisions.** Regulators require a high degree of confidence in any method used to support clinical trials. NAMs must demonstrate that they can inform decisions with equal or greater confidence than traditional approaches to ensure patient safety.
- **Broader adoption requires investment and collaboration.** Continued scientific development, coordinated validation efforts, and early engagement between developers and regulators are essential to build trust and accelerate uptake.
- **Clear guidance is key.** Developers benefit from early engagement with regulators to clarify expectations and ensure that NAMs are used in a scientifically-justified and decision-relevant way.
- **The UK is well positioned to lead.** With strong scientific expertise, regulatory engagement, and a collaborative infrastructure, the UK can play a global leadership role in advancing NAMs.

[1] See key terms for definition.

[2] National Centre for the Replacement, Refinement and Reduction of Animals in Research; Medicines and Healthcare products Regulatory Agency; Association of the British Pharmaceutical Industry.

Introduction and background

The development of new medicines is a complex, multi-stage process that involves both non-clinical and clinical testing to ensure safety and efficacy. Non-clinical testing refers to studies conducted prior to or alongside human clinical trials, using a range of models that increase in biological complexity. These include *in silico* (computational) models, *in vitro* (cell- or tissue-based), *ex vivo* (tissue- or organ-based) and *in vivo* (whole-animal) studies. These approaches are designed to assess potential toxicities, pharmacological activity, mode of action and other parameters to support and inform decisions for clinical trials in humans.

Animal studies have long played a critical role in medicines development and remain a cornerstone of regulatory safety requirements worldwide to help safeguard patient health. They have significantly advanced our understanding of disease mechanisms and been essential to the development of safe and effective treatments. However, because animal biology does not always fully recapitulate human responses it can be challenging to translate non-clinical findings to clinical outcomes – contributing, in some cases, to the failure of medicines in later stages of development. In light of this there is a growing global scientific and societal momentum to advance human-relevant approaches that have the potential to reduce reliance on animal testing. While there is growing interest in reducing animal use, the primary concern for regulators remains the protection of human health. Any new approach must demonstrate that it can support safe and effective decision-making for patients. This aligns with a global and industry-wide commitment to the 3Rs – to replace, reduce, and refine the use of animals in research.

Significant investment has been directed toward the development of innovative technologies known as new approach methodologies or NAMs. In this report, NAMs refer to replacement technologies that are used for assessing chemical or drug safety, and are considered across the entire medicines development pipeline – from early discovery, where they may help prioritise candidates based on safety or efficacy-related signals, to later-stage regulatory safety testing.

> **"The successful integration of NAMs into medicines development is a shared responsibility that demands coordinated, cross-sector collaboration built on trust, transparency and sustained dialogue."**

NAMs are already being used to support first-in-human (FIH) clinical trials, most commonly alongside animal testing, to reduce the numbers of animals used for safety and efficacy testing. Their application is particularly relevant in cases where no relevant animal model exists, such as for certain biological products targeting human-specific mechanisms. In these situations, NAMs can provide proof-of-principle data using patient-derived samples or cell-based systems to support safety and efficacy assessments. In conditions with urgent unmet medical need, such as end-stage or life-threatening diseases with no alternative treatments, the benefit–risk profile may support a more flexible regulatory approach and greater reliance on NAMs. For example, the immunotherapy agent tebentafusp progressed to clinical trials and approval without any *in vivo* data, due to the absence of pharmacodynamic activity in any animal species. However, most medicines development programmes still depend on animal data. To enable broader adoption of NAMs, coordinated efforts between industry, regulators, and academia are essential to build confidence in the data generated, harmonise approaches, and provide robust scientific justification to support their use.

For NAMs to be considered viable within regulatory frameworks they must demonstrate a high degree of scientific validity and predictive relevance to human biology. While NAMs are not necessarily intended to replicate or benchmark directly against animal models, they must provide sufficient evidence that the same decisions – such as progression to clinical trials or dose setting for humans – would be reached with equal or greater confidence. This requires robust justification, reproducibility, and alignment with known human outcomes, rather than comparative performance against animal data alone.

Recent advances in science and technology are accelerating the development of more human-relevant approaches, potentially improving the predictivity of efficacy and safety assessments and increasing the chances of successful medicine development without the need for animal tests. In light of these advances, governmental agencies have committed to phasing out animal use where possible, as seen in strategic roadmaps from the US FDA[3] and European Commission[4]. The pharmaceutical industry is also investing heavily in NAMs and are actively developing methods that enhance safety and efficacy evaluations. However, as international guidelines for medicines development continue to rely heavily on safety data from animals, this creates uncertainty around how and where NAMs can be effectively integrated into regulatory decision-making.

The workshop

The NC3Rs has been working with the scientific community for over 20 years to accelerate the integration of NAMs into medicines development by funding relevant research and technology development and fostering collaboration through knowledge and data-sharing to drive changes in policy, practice and regulations. On 7 November 2024, in partnership with the MHRA and ABPI, the NC3Rs held a workshop on the *"Incorporation of new approach methodologies to support the development of new medicines"*. This collaboration demonstrates a shared commitment to fostering innovation, regulatory progress, and scientific excellence in the adoption of human-relevant methods that do not rely on animals. By bringing together regulators, industry and academic experts, the event served as a platform to align priorities and showcase the UK's potential to lead internationally in the integration of NAMs into regulatory science.

The event brought together over 60 experts from the pharmaceutical industry – primarily from the UK, including large multinationals, contract research organisations (CROs), small and medium-sized enterprises (SMEs), and biotechnology companies – alongside regulatory agencies from Europe, the UK and US, to:

- **Explore current and future opportunities for incorporating NAMs into medicines development;**
- **Identify key challenges and barriers to broader adoption, and potential solutions;**
- **Develop recommendations to support the wider implementation of NAMs.**

This report summarises the output of the workshop discussions under these key themes. The workshop agenda can be viewed in the appendix.

[3]The US Food and Drug Administration (FDA): Roadmap to reducing animal testing in preclinical safety studies was published in April 2025.

[4]The European Commission is currently preparing a "Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments" which is due to be published in Q1 2026.

Current and future opportunities for NAMs in medicines development

NAMs are increasingly being explored across the entire medicines development pipeline – from early discovery through to clinical development – offering opportunities to reduce reliance on animal testing at various stages of development. These approaches are particularly valuable in contexts where high-throughput screening is needed, traditional animal models are less feasible, or where human-derived systems (e.g. tissue models, organoids or organ-on-a-chip technologies) more closely reflect human physiology and can enhance decision-making, support more predictive safety and efficacy assessments, and ultimately contribute to improved patient outcomes.

Current integration of NAMs in medicines development

NAMs are routinely applied for high-throughput target identification and screening during the early stages of medicines discovery and research, where the sheer volume of potential candidates makes animal studies unfeasible. In addition to supporting the pharmaceutical industry's commitments to the 3Rs, these approaches offer scalable and rapid assessment tools for large numbers of potential candidates, helping to prioritise those with the greatest potential. They can lead to time and cost savings while increasing the likelihood of clinical success. Organisations with the resources and capacity to implement these approaches are often motivated by the opportunity to streamline development and enhance decision-making earlier in the pipeline.

In addition to prioritising promising candidates, NAMs can also play a critical role in de-selecting compounds that are unlikely to succeed. For example, results from an *in vitro* drug-induced liver injury (DILI) screen may indicate that a candidate is unsuitable for clinical testing. When scientifically validated, NAMs can serve a similar function to animal tests by identifying compounds with potential toxicity, lack of activity, or other unfavourable characteristics, helping to avoid unnecessary investment in unviable candidates and reducing the risk of harm to patients or participants in later-stage clinical trials.

As therapeutic candidates advance towards clinical development, opportunities to apply NAMs are currently more limited. NAMs are primarily used to complement animal data by providing mechanistic insights to better understand observed cardiovascular effects or DILI for example, or to reduce the number of animal studies which need to be carried out, rather than as direct replacements. However, interest is growing in their use later in development and within regulatory contexts, particularly for human-specific modalities such as certain biological products including cell therapies, where animal models may be less predictive.

There are now examples of medicines taken to market without any, or limited, animal testing. Typically, these are cases where no relevant animal model exists, such as biological products targeting human-specific mechanisms, or where the therapeutic context allows for greater regulatory flexibility and risk tolerance. One such example is Immunocore's tebentafusp (KIMMTRAK)[5] which was presented as a case study at the workshop. This bispecific fusion protein therapy targets a human-specific protein for which no relevant animal species are available for non-clinical toxicology studies. As a result, the product was successfully taken to market without any *in vivo* toxicology testing.

> **"NAMs are already contributing to decision-making across the entire medicines development pipeline, from early discovery to clinical development."**

Despite growing interest in reducing animal use, regulatory expectations continue to prioritise science and relevant animal data unless robust justification is provided. Guidelines such as those from ICH[6] which set global expectations for the safety, efficacy and quality of pharmaceuticals, are widely adopted and generally followed for regulatory approval in major markets. While these guidelines may allow for some flexibility in how data is generated, the interpretation and acceptance of NAMs can vary between regulatory agencies and individual assessors. As a result, NAMs are most often used to support internal decision-making or to supplement regulatory submissions, providing additional human-relevant mechanistic insights and informing areas where perspectives beyond animal studies may be beneficial. Although regulators are increasingly open to the scientifically-justified inclusion of NAMs, legal responsibility for ensuring safety and efficacy can lead to conservatism. In a global market environment, inconsistent regulatory expectations can hinder the broader adoption of NAMs and reduce competitiveness.

Expanding the role of NAMs

The use of NAMs to support FIH clinical trials remains limited. This is largely due to the high level of scrutiny around decisions on safe starting doses, dose escalation and potential side effects in humans, which demand a high degree of confidence in the safety data – something that NAMs alone do not yet consistently deliver. Regulatory expectations for FIH trials are met through established animal testing, which are currently perceived to offer a more comprehensive assessment of systemic toxicity and risk. However, there may be greater flexibility to incorporate NAMs beyond FIH, when more is known about the molecule and its toxicity profile, and where existing clinical data may be available.

At later stages of medicines development, animal studies are conducted to assess long-term effects, evaluate how known toxicities may progress or resolve, and identify any new toxicities that could emerge, informing what should be monitored during clinical trials as well as who may or may not participate. NAMs could potentially replace some of these *in vivo* studies, particularly in scenarios where prior data indicate low clinical risk (e.g. minimal or well-characterised toxicity), or to reduce the current regulatory requirement for testing in a second species, for example to allow chronic studies in a single species rather than in both rodents and non-rodents. This approach would need to be supported by NAMs capable of predicting longer-term effects, an area where current tools are evolving. The 'Virtual Second Species' project, a collaboration between industry and academia supported by the NC3Rs CRACK IT programme[7], is addressing this gap by developing advanced computational models of dog tissues and organs. These *in silico* models aim to address safety, with the goal of reducing the need for longer-term dog studies and supporting a single *in vivo* species approach.

[5]Tebentafusp (KIMMTRAK) was approved without *in vivo* toxicology studies due to its human-specific target. Further details are available in the European Medicines Agency's (EMA) public assessment report and a peer-reviewed article published in *Drugs* (2022).

[6]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) sets global standards for drug safety, efficacy and quality.

[7]CRACK IT is a challenge-led competition that funds collaborations between industry, academics and SMEs to solve business and scientific Challenges to deliver 3Rs benefits, either by improving business processes or developing a commercial product. The Virtual Second Species Challenge applies advanced computational and mathematical modelling approaches to develop a suite of virtual dog tissues and organs to model toxicological endpoints for new chemical entities.

Key challenges

While scientific advances have led to the development of a wide range of NAMs, their readiness to replace animal models in regulatory safety testing varies significantly. In most cases NAMs are still used to complement rather than replace animal data. Only a limited number of NAMs have been accepted for use in regulatory decision-making, and only for specific contexts. For example, quantitative systems pharmacology modelling offers the ability to evaluate critical aspects related to the efficacy of a drug candidate, physiologically based pharmacokinetic models are increasingly used to predict human drug exposure and support starting dose selection/escalation, while human stem cell-based assays and zebrafish embryo models are now recognised under ICH S5(R3) for certain reproductive toxicity assessments. Microphysiological systems (e.g. liver- or heart-on-a-chip platforms) are also being explored to support internal decision-making and, in some cases, regulatory submissions. A notable example presented during the workshop was Newcell's human iPSC-derived retinal 3D organoid model[8], which has been included in an Investigational New Drug application as part of the non-clinical package. This case illustrates the growing potential of advanced NAMs to contribute meaningfully to regulatory submissions.

Broader regulatory acceptance remains limited and NAMs are rarely included in submissions. This highlights the need for continued investment in scientific development and clearer guidance on regulatory expectations – particularly around qualification and validation. Qualification refers to demonstrating that a method is fit for a specific context of use (e.g. screening or dose setting), while validation involves establishing its reliability, reproducibility, and relevance for regulatory decision-making. A shared understanding of where NAMs can provide equivalent or superior predictive value compared to traditional animal models is also essential.

> **"NAMs must demonstrate that they can inform decisions with equal or greater confidence than traditional approaches to ensure patient safety."**

The broader adoption of NAMs within regulatory contexts is influenced by several factors, including:

- **Limited regulatory familiarity with NAMs.**
- **Lack of confidence and risk aversion.**
- **Uncertainty around qualification and validation requirements.**
- **Lack of global harmonisation.**

Addressing these barriers requires a coordinated approach that promotes clarity, trust, and collaboration across stakeholders. The main challenges are outlined here, along with examples of practical solutions aimed at fostering greater acceptance and integration in decision-making.

[8]Newcell's human induced pluripotent stem cell (iPSC)-derived retinal 3D organoid model has been included in a regulatory submission as part of the non-clinical data package. Further details are available in Chichagova *et al.* (2020) *Stem Cells*. 38(2):195–201.

Limited regulatory familiarity with NAMs

NAMs are increasingly being used within industry for internal decision-making but the resulting data is not always included in regulatory submissions or may lack sufficient context to support its relevance. As a result, regulators may have limited opportunities to engage with and evaluate these methods in practice, which can slow the development of familiarity and confidence in their use. Since regulatory decisions on clinical trials can rest with just one or two individuals, despite efforts to ensure consistency of decision-making, outcomes can be influenced by varying levels of experience with NAMs and differing risk tolerances. This can lead to conservative interpretations, particularly when the scientific rationale for using NAMs is not clearly communicated.

To build regulatory confidence, it is essential that data from NAMs are presented in a clear, decision-relevant format. Proactive engagement between NAMs developers, industry and regulators through early dialogue and transparent sharing of scientific rationale can help bridge knowledge gaps and foster mutual understanding. Encouraging the inclusion of NAM data in regulatory discussions and documentation, even as supplementary information, will accelerate familiarity and provide regulators and the broader community with opportunities to evaluate its utility.

> **"The emphasis should be on the phasing in of NAMs – identifying where they can add value and be integrated into regulatory decision-making – rather than framing progress solely in terms of phasing out animal testing."**

Potential solutions to address limited regulatory familiarity with NAMs include:

- Support the provision of NAM data in a format that meets regulatory needs.
- Promote training and capacity building for regulators.
- Foster dialogue between regulators, industry (including large pharmaceutical and biotechnology companies, CROs and SMEs) and academia to build mutual understanding of regulatory testing needs and NAMs capabilities.
- Encourage and incentivise industry to include NAM data in submissions.
- Provide practical, worked case studies that demonstrate how NAMs have been successfully applied in regulatory contexts.

Lack of confidence and risk aversion

Despite growing interest, the use of NAMs within a regulatory decision-making context is hindered by the limited inclusion of NAM-based data in regulatory submissions, and the need to build a stronger evidence base and regulatory confidence in their use. This is compounded by a lack of practical experience, and uncertainty over evolving validation standards and how the data generated will be interpreted. Regulatory assessors often have limited exposure to NAM datasets, which can slow the development of familiarity and confidence in their use. Other factors such as time constraints faced by regulatory assessors and the need to operate within existing regulatory frameworks can also reinforce a cycle of conservatism. A lack of precedent for NAMs in regulatory submissions can further reinforce this cycle, as both developers and regulators may be hesitant to rely on approaches that have not yet been widely accepted or tested in formal decision-making contexts. Breaking this cycle will depend on greater inclusion of NAMs in submissions and collaborative efforts to build familiarity and trust in their application.

A fundamental barrier to broader adoption of NAMs is the need for established and validated models that both regulators and industry can trust to reliably inform safety decisions. Regulatory agencies have a primary responsibility to protect patient safety, and any method used to support progression to clinical trials must provide a high degree of confidence that its use will not result in harm to humans, particularly in contexts where established animal models have historically been relied upon to mitigate such risks. This means that NAMs must demonstrate not only scientific validity and reproducibility, but also predictive relevance to human biology. Without this assurance, both regulators and developers are likely to default to traditional animal models, even when NAMs may offer more human-relevant insights in some instances. Building this confidence requires rigorous evaluation, transparent reporting, and shared understanding of the strengths and limitations of each approach.

To address these issues, it is essential to define clear contexts of use for NAMs – that is specific circumstances for which the data can be used – whether for screening, filling data gaps, or supporting FIH clinical trials, and to ensure that methods are scientifically justified, reproducible, and fit for purpose. Establishing a safe harbour mechanism – a structured, risk-free environment for early dialogue between developers and regulators – would allow developers to seek early scientific and regulatory advice without fear of regulatory consequences, fostering innovation and trust. Structured guidance on qualification and validation requirements (see next section), along with proactive engagement between regulators and developers, would further support consistent and confident use of NAMs.

Potential solutions to build confidence and reduce risk aversion include:

- Develop clear, harmonised guidance on the acceptance of NAMs for specific contexts of use.
- Regulators to create safe harbour mechanisms for early scientific advice on NAMs.
- Encourage open discussion of the scientific rationale and limitations of NAMs and animal models.
- Share and publish both successful and unsuccessful case studies to build trust.
- Create mechanisms for sharing anonymised data to support broader learning and transparency without commercial risk.

Uncertainty around qualification and validation requirements

Establishing how to validate a NAM remains a major barrier to broader adoption. There is a clear need for standardised and harmonised validation criteria, tailored to specific contexts of use and recognised across international medicines regulators. The level of validation required for early-stage screening or prioritisation will differ from that needed for dose setting in FIH clinical trials. Without clarity around validation expectations and criteria, uncertainty persists and is slowing progress.

High validation costs and limited funding opportunities present a significant barrier. Coordinated and well-funded validation networks, such as those the UK previously accessed via ECVAM[9], could streamline efforts, reduce duplication and establish new benchmarks for regulatory acceptance.

Bridging the gap between academia and industry – including large pharmaceutical and biotechnology companies, CROs and SMEs – is essential. While NAMs are developed across both academic and industrial settings, their application in the development of novel medicines lies primarily within industry. Greater collaboration, supported by education on the medicines development process, will help ensure NAMs are designed to meet regulatory and practical requirements – such as scalability, cost-effectiveness, ease of implementation, and compatibility with high-throughput workflows. Initiatives like the NC3Rs CRACK IT Challenges programme and the NC3Rs NAMs Network[10] exemplify this approach by connecting developers with end-users to ensure methods are fit for purpose and to support their broader adoption.

> **"Global alignment on the regulatory use of NAMs is essential to ensure consistent standards, reduce duplication, and accelerate access to innovative therapies."**

Clear guidance is needed to define the minimum data requirements for FIH clinical trials. While NAMs are not designed to mimic traditional animal models, it is important to demonstrate that they can support the same regulatory decisions with equal or greater confidence. This includes establishing the qualification[11] of NAMs for specific contexts of use – showing that a method is fit for purpose and can reliably inform decisions such as dose setting or progression to clinical trials. NAMs may also offer enhanced human relevance or predictive value in certain contexts. A growing body of peer-reviewed publications and case studies showcasing successful applications of NAMs will help build confidence and encourage wider acceptance. Demonstrating that NAMs can inform safety decisions as reliably – or more reliably – than traditional approaches is essential for ensuring patient safety and building regulatory trust.

Regulatory divergence remains a concern, both within and across agencies, where individual assessors may interpret guidelines differently. In some cases, regional authorities or assessors may continue to default to animal data or interpret guidelines as rigid requirements or 'law', rather than as more flexible frameworks. Updated international regulatory guidance should explicitly support the use of validated

[9] EURL ECVAM (EU Reference Laboratory for alternatives to animal testing) promotes and facilitates the use of non-animal methods in testing and research and is part of the Joint Research Centre (JRC), the science and knowledge service of the European Commission.

[10] The NC3Rs NAMs Network connects researchers, technology developers, industry and regulatory to accelerate the adoption of NAMs. It fosters dialogue, collaboration and technology sharing to maximise their scientific and 3Rs impact. Through targeted activities the Network promotes multi-disciplinary conversations and partnerships to accelerate NAMs uptake.

[11] The FDA and EMA define qualification as the process of demonstrating that a method or tool is fit for a specific intended use in the context of medicines development. Once qualified, the method can be used with confidence for that defined purpose in regulatory decision-making.

NAMs, requiring strong justification for the continued use of animals. This shift would create more opportunities to incorporate NAMs and promote a more progressive and consistent regulatory environment.

Retrospective validation strategies can also be effective. These include comparing NAM results with historical animal data or running NAMs in parallel with animal studies to assess whether they support the same decision outcomes (e.g. clinical progression or go/no go decisions). Increasing the use of clinical data as a benchmark is critical for enhancing the translational relevance of NAMs. Aligning NAM outputs with known clinical outcomes enhances their predictive validity and relevance to human biology, strengthening scientific credibility and supporting regulatory acceptance. Publishing expert consensus on how NAMs can be applied in practice, particularly through detailed case studies that integrate human data and clearly explain the decision-making logic, will further strengthen confidence among regulators and stakeholders.

Potential solutions to clarify qualification and validation requirements include:

- Define tiered validation requirements based on context of use (e.g. more rigorous requirements depending on screening versus setting a safe dose in a FIH clinical trial).
- Establish coordinated validation networks within the UK (e.g. similar to ECVAM).
- Use retrospective validation (e.g. comparing NAMs to historical animal or human data).
- Introduce incentives to run NAMs in parallel with animal studies to demonstrate concordance or greater predictive value and build confidence.

Lack of global harmonisation

Global harmonisation in the regulation of new medicines is critical to ensuring consistent standards, reducing duplication of effort, and accelerating patient access to innovative therapies. However, the lack of alignment in regulatory expectations across jurisdictions remains a significant barrier to the adoption of NAMs. While international frameworks such as ICH and World Health Organization (WHO) guidelines exist, differences in interpretation, flexibility, and risk tolerance – both between and within regulatory agencies – can lead to inconsistent acceptance and uncertainty around what will or will not be approved. Although these guidelines are intended to be flexible rather than prescriptive, varying degrees of conservatism in practice can limit opportunities to incorporate NAMs, discouraging innovation and creating hesitation among developers of both NAMs and new medicines. This inconsistency not only affects scientific progress but can also have broader implications for global competitiveness.

Medicines development is a global enterprise, and divergence in regulatory expectations can influence where companies choose to invest, conduct trials, and launch products. Regions with more progressive and predictable regulatory pathways may be favoured, potentially disadvantaging countries with more conservative or unclear positions on NAMs. To enable broader adoption of NAMs, there is a clear need for a standardised, reproducible framework that is recognised and accepted across global regulatory bodies. International collaboration is key to achieving this. The recently established International Medicines Regulators' Working Group on the 3Rs (IMRWG3Rs)[12], led by the EMA and involving regulators from the EU, US, Japan, Canada, Australia, and Switzerland, represents a promising step toward greater alignment in regulatory acceptance of 3Rs approaches and the integration of NAMs.

Other global efforts are also contributing to this shift. For example, the WHO, following a review[13] led by the NC3Rs, is developing general 3Rs guidance to support the global reduction of animal use in biologics testing. The outputs of these collaborative initiatives are expected to support greater international consistency in regulatory expectations and accelerate the adoption of innovative, human-relevant testing approaches.

Potential solutions to support global harmonisation include:

- Review existing regulatory guidelines to identify where NAMs could already be applied.
- Update international guidelines (e.g. ICH/WHO) based on findings from such reviews to provide clearer opportunities for the incorporation of NAMs.
- Promote harmonisation of regulatory requirements and mutual recognition of validated NAMs, building on frameworks such as the OECD Mutual Acceptance of Data system[14].
- Create a global network for sharing regulatory experiences and case studies to support consistent interpretation and implementation.

> **"Updated international regulatory guidance should explicitly support the use of validated NAMs, requiring strong justification for the continued use of animals."**

> **"The UK has a strong scientific base and a collaborative research environment, making it well placed to lead in the development and regulatory adoption of NAMs."**

[12]The International Medicines Regulators Working Group on 3Rs (IMRWG3Rs) was established in 2024 and includes the EMA (Europe), FDA (US), Pharmaceuticals and Medical Devices Agency (Japan), Health Canada (Canada), Therapeutic Goods Administration (Australia) and Swissmedic (Switzerland).

[13]NC3Rs review of animal use requirements in WHO biologics guidelines. This initiative supports the development of global 3Rs guidance to reduce animal use in biologics testing.

[14]OECD Mutual Acceptance of Data system for chemical safety testing. This international framework ensures that safety data generated in one OECD member country is accepted by others, reducing duplication of testing and supporting regulatory harmonisation.

Conclusions and recommendations

To enable the broader adoption of NAMs in medicines development pipelines, a coordinated effort across stakeholders is essential, emphasising shared responsibility, open communication, and the development of supportive regulatory frameworks. This section summarises key recommendations and next steps arising at and following on from the workshop discussions.

Shared responsibility and collaboration across the scientific community

The MHRA's active participation in this workshop highlights its openness to innovation and its role in shaping the UK's regulatory approach to NAMs. As the UK's national regulator, the MHRA's engagement is critical to ensuring that regulatory frameworks change in step with scientific advancements. Similarly, the ABPI's support, in addition to the active participation of industry attendees, underscores the pharmaceutical industry's commitment to advancing the use of NAMs and fostering a more efficient, human-relevant medicines development process.

Strengthening communication between stakeholders is essential, whether within organisations (e.g. between clinical and non-clinical teams or across sites), between sponsors and CROs, or across the broader industry. This will help identify where NAMs are suitable for decision-making, highlight gaps for future NAMs development and clarify opportunities for their integration into existing processes.

Improving dialogue between stakeholders, especially between industry and regulators will help build confidence and reduce uncertainty. Clear guidance and early engagement can help ensure that the use of NAMs supports efficient development timelines and positive regulatory outcomes, giving developers confidence in their integration. Regulators need to become familiar with the approaches so they can understand how and where they can meaningfully contribute to decision-making. Organisations such as the NC3Rs can provide a neutral platform and open forum for these discussions, as exemplified by this workshop, events held by the NC3Rs NAMs Network[15] and its recently established Regulatory Sciences Forum[16]. Building on the MHRA's and ABPIs involvement in this workshop, there is an opportunity to explore how similar collaborative mechanisms could be developed or expanded within the UK context, drawing on international examples of safe harbour approaches that have supported early regulatory engagement and innovation.

Safe harbours and data sharing

The creation of a structured safe harbour environment by regulators is essential to support the integration of NAMs into regulatory decision-making. Such a mechanism would enable early, open and risk-free dialogue between developers and regulators, particularly useful where NAM and animal data may diverge. This would require dedicated resources and commitment from regulatory bodies to review both traditional and NAM-derived data, alongside clear assurances to industry on how the information will be interpreted and used. Existing initiatives such as the EMA's Voluntary submission of data pathway[17] and the FDA's ISTAND pilot[18] provide valuable models for this type of engagement. These mechanisms allow developers to share pre-competitive NAM data outside of formal procedures to facilitate scientific dialogue and build regulatory confidence. Encouragingly, the EMA has begun tracking the uptake of NAMs, including how often these are discussed in scientific advice meetings and in what context[19]. Monitoring this engagement is critical to identifying barriers, informing future design of support mechanisms, and encouraging broader participation.

To build confidence in the short-term, publishing case studies, both successful and unsuccessful, can help illustrate how NAMs have contributed to decision-making. One way to support this is through an honest broker mechanism, where a neutral third party such as the NC3Rs facilitates the sharing of anonymised case studies and data between stakeholders. This approach allows industry to contribute data without commercial risk, helping to build a shared evidence base and foster trust in the utility of NAMs.

To further incentivise the inclusion of NAMs in regulatory submissions, guidance could encourage their use as a first-line approach, with justification required for the continued use of animals. Potential incentives could include expedited or priority review pathways for submissions incorporating validated NAMs, regulatory fee reductions, or even intellectual property advantages such as extended data exclusivity. Feedback from regulators on how NAMs have successfully contributed (or not) to decision-making, ideally through direct engagement, would also be valuable in clarifying expectations and building mutual understanding. Insights from the use of existing safe harbour mechanisms could also help shape future incentive structures and support more consistent adoption.

Development of guidance

The development of clear, internationally aligned guidance is essential to support the regulatory acceptance of NAMs, particularly as medicines are developed for a global market. This may involve revising existing guidelines or clarifying that they are flexible frameworks in which NAM-derived data can be accepted when scientifically justified. A review of current guidance to identify and communicate where NAMs are already applicable was strongly recommended, with the longer-term goal of developing a forward-looking framework that allows for either NAM or animal data based on scientific justification. A strong example of this approach is the NC3Rs' collaboration with the WHO to review animal use requirements in guidelines for vaccines – demonstrating their role as an honest broker and success in facilitating constructive dialogue between stakeholders on a global scale. While many governmental agencies have expressed a desire to phase out animal testing, the emphasis should be on the phasing *in* of NAMs. This approach will help determine where NAMs can add value, and how they can be integrated into a weight-of-evidence strategy.

The wide range of available NAMs can be challenging, as multiple methods may be suitable for the same testing endpoint. Clearer guidance on the reliability, strengths, and limitations of different NAMs would help address this and support decision-making and adoption. The rapid pace of scientific advancement means new and improved approaches are continually being developed, outpacing the long timelines involved in formal validation processes. Establishing general principles for qualification, similar to those applied in the CiPA initiative[20] for cardiac safety, and moving away from more formal validation requirements, could help ensure consistency and credibility and allow the incorporation of the most up to date technologies.

[15]NC3Rs NAMs Network symposium: Connecting NAMs developers with end-users in human safety assessment.

[16]The Regulatory Sciences Forum was established by the NC3Rs in 2024 to specifically address the lack of dialogue in the UK on NAMs between industry and regulatory agencies and is made up of scientific experts representing UK regulatory and governmental agencies, CROs, industry and academia, alongside independent specialists.

[17]The EMA's voluntary data submission pathway allows developers to share data from NAMs outside formal procedures to support early regulatory dialogue.

[18]The FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program supports early engagement on NAMs outside formal regulatory pathways.

[19]EMA NAMs Insights Report 2025. Insights into the uptake and application of New Approach Methodologies in regulatory interactions, 2025.

[20]Comprehensive *in vitro* proarrhythmia assay (CiPA) initiative to improve cardiac safety assessment without animal testing.

Next steps

The successful integration of NAMs into medicines development is a shared responsibility that demands coordinated, cross-sector collaboration built on trust, transparency and sustained dialogue. Moving forward, the following actions are key:

Develop clear, harmonised guidance

Produce internationally aligned guidelines on the context of use, qualification and validation of NAMs to support consistent regulatory acceptance.

Promote data sharing and case studies

Encourage the open exchange of both successful and unsuccessful NAMs case studies, potentially through honest broker mechanisms, to build a shared evidence base and regulatory confidence.

Support validation infrastructure

Establish coordinated UK-based validation networks and promote retrospective validation using historical animal and human data to demonstrate NAMs applicability.

Establish safe harbour mechanisms

Create structured environments for early, risk-free dialogue between industry and regulators, drawing on existing models from the EMA and FDA to support innovation and trust.

Foster cross-sector collaboration

Strengthen communication between academia, industry (including large pharmaceutical and biotechnology companies, CROs and SMEs) and regulators to align priorities and accelerate NAMs development and implementation.

Further information

Workshop slides are available on request. Please email enquiries@nc3rs.org.uk.

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Delivering on these priorities will require action from regulators, governmental agencies, and the wider scientific community. Independent organisations such as the NC3Rs are uniquely positioned to lead and support this effort, bringing stakeholders together, facilitating cross-sector dialogue, and acting as an honest broker to build confidence and drive genuine progress. The NC3Rs NAMs Network is already playing a key role in the space by fostering collaboration and sharing best practices, to help accelerate the integration of NAMs into medicines development. This work builds on an extensive and growing network of partners across the UK and internationally. As NAMs continue to evolve, their integration into medicines development must be guided by their ability to enhance patient safety and improve the predictivity of human outcomes.

This workshop has demonstrated the strong and growing momentum in the UK in advancing NAMs, reflected both in its joint organisation – a collaboration between the NC3Rs, ABPI and MHRA – and in the active engagement of key experts and decision-makers who shared their insights and expertise. The UK is well positioned to lead globally in this space, supported by a foundation of scientific excellence, regulatory innovation, and collaborative infrastructure. Realising this potential will depend on continued engagement from a diverse coalition of stakeholders – working together to ensure that human-relevant, non-animal testing strategies are developed, validated, and adopted in ways that promote and advance public health, scientific progress, and animal welfare.

> **"Realising the full potential of NAMs will depend on a strategic shift towards phasing them in – demonstrating their value in human-relevant safety assessment and integrating them into regulatory decision-making with confidence."**

About the authors

The **NC3Rs** is the UK's national organisation that provides scientific leadership to the development and implementation of new models and tools that minimise the use of animals in research and testing and/or improve animal welfare (the 3Rs).

The **MHRA** (Medicines and Healthcare products Regulatory Agency) is an executive agency of the Department of Health and Social Care in the UK which is responsible for ensuring that medicines and medical devices work and are acceptably safe.

The **ABPI** (Association of the British Pharmaceutical Industry) represents companies of all sizes which invest in making and discovering medicines and vaccines to enhance and save the lives of millions of people around the world. The ABPI works across England, Scotland, Wales and Northern Ireland, in partnership with governments and the NHS so that patients can get new treatments faster and the NHS can plan how much it spends on medicines. The ABPI has a long-standing partnership with the NC3Rs, funding a Programme Manager for Drug Development since 2006.

Appendix: Workshop agenda

Joint MHRA/NC3Rs/ABPI workshop: Incorporation of new approach methodologies (NAMs) to support the development of new medicines

7 November 2024, Central London

AGENDA

Time	Session
9.30–10.00	Arrival and registration
10.00–10.10	**Welcome and introduction** NC3Rs
10.10–10.30	**The future of NAMs within drug development** ApconiX
10.30–11.15	Perspectives ▪ Regulatory (MHRA) ▪ Industry (AstraZeneca) ▪ Contract Research Organisation (Charles River Laboratories)
11.15–11.40	Break
11.40–12.00	**Taking an investigational medicinal product into FIH clinical trials and beyond with no *in vivo* toxicology** Immunocore
12.00–13.00	New approach methodologies ▪ Complex *in vitro* models (Newcells Biotech) ▪ Organ-on-a-chip (Astrazeneca) ▪ Use of Quantitative Systems Toxicology in Pharmaceutical Safety Assessment (GSK) ▪ CRACK IT: Virtual second species (esqLABS)
13.00–13.45	Lunch

Time	Session
13.45–15.00	**Regulatory panel discussion** Panellists representing regulatory agencies including the MHRA, Belgium Federal Agency for Medicines and Health Products, Swissmedic, and FDA. Short perspectives and updates from each panellist followed by discussion on: ▪ How and where can NAMs be used within the drug development process? ▪ What are regulatory acceptable / appropriate justifications for use of NAMs? ▪ What are the challenges / barriers to wider uptake within a regulatory context?
15.00–15.30	Refreshments
15.30–15.40	**Introduction to breakout sessions** NC3Rs
15.40–16.40	**Breakout group discussions: Opportunities to move forward** How can we update the current paradigm? What can regulators, developers or sponsors do to facilitate the implementation of new testing strategies? Three breakout groups: 1. NAMs to support FIH clinical trials. 2. NAMs beyond FIH to support later stage development. 3. NAMs for the development of rare diseases, advanced therapeutic medicinal products (ATMPs), and personalised medicine.
16.40–17.20	**Feedback and discussion from breakout sessions**
17.20–17.30	Wrap up and meeting close
17.30–18.30	Networking reception

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