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White paper

Regulatory adoption of New Approach Methodologies (NAMs): What non-animal methods mean for developers in the context of the 3Rs

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Introduction

New Approach Methodologies (NAMs) are increasingly appearing in regulatory frameworks, guidance updates and scientific advice processes. Rather than remaining a theoretical or scientific concept, NAMs are now being evaluated as tools within structured regulatory pathways.

For developers, the key questions are practical: *when do regulators already accept NAM-based evidence, where are expectations still evolving, and how should these approaches be positioned in regulatory submissions?*

This article summarises how key regulatory agencies (MHRA, EMA, FDA), as well as other regulatory actors, currently frame NAMs, where adoption is most advanced, and how developers can navigate emerging regulatory expectations.

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What regulators mean by NAMs

Regulators generally define NAMs as non-animal methods capable of generating human-relevant information for safety assessment, efficacy understanding or mechanistic interpretation.

From a regulatory perspective, NAMs are best understood as a toolbox of complementary methods rather than a single class of technologies. This toolbox typically includes several categories of methods:

- **Human-relevant in vitro systems** – primary human cells, 3D cultures, organoids and microphysiological systems (organ-on-a-chip).
- ***In chemico* and *in silico* approaches** – mechanistic modelling, quantitative structure–activity relationship ((Q)SAR) tools and machine-learning models.
- **Model-informed approaches** – physiologically based pharmacokinetic (PBPK) modelling, in vitro–in vivo extrapolation (IVIVE), and mechanistic PK/PD models.
- **Mechanistic evidence frameworks** – including approaches structured around Adverse Outcome Pathways (AOPs)[1] linking molecular events to known adverse outcomes.

Across major agencies, the overall regulatory objective is consistent: improve human relevance while reducing reliance on animal studies where scientifically justified.

How agencies are supporting NAM adoption

Recent policy and legislative developments are beginning to shift not only the acceptability of NAMs, but also the conditions under which they are expected to be considered within development programmes.

While implementation differs by region, agency support for NAMs can broadly be understood across three dimensions: policy and legislation, advice and engagement procedures, and emerging guidance.

MHRA:

Policy/Legislation – The United Kingdom government has published a national roadmap[2] aimed at accelerating development and uptake of non-animal methods in regulatory science. This includes commitments to reduce reliance on animal testing, support validation initiatives and establish data-sharing frameworks to enable regulatory use of NAMs.

Advice procedures – Developers can engage with the MHRA through the Innovation Office and established scientific advice procedures. These provide opportunities to discuss novel methodologies, including NAM-based approaches, prior to their inclusion in regulatory submissions.

Emerging guidance – Recent reports[3] and MHRA guidance[4] outlines an approach to the use of NAMs in medicines development, including the introduction of ‘safe harbour’ mechanisms for data-sharing. These initiatives enable exploratory and iterative use of NAMs and support regulator familiarisation with emerging methodologies. The guidance also describes a planned route for early MHRA review of Module 4 for

products with one completed clinical trial and no animal studies, supported by draft Modules 2.4 and 2.6. This enables sponsors to obtain a non-binding opinion on the adequacy of the nonclinical package ahead of a future marketing authorisation application.

EMA:

Policy/Legislation – The European Union embeds the 3Rs principles within its regulatory framework for medicinal products, with ongoing policy initiatives aimed at reducing reliance on animal testing[5,6]. The European Commission is preparing a roadmap towards phasing out animal testing[7] to be published in 2026 which is expected to further shape the integration of NAMs across EU regulatory processes.

Advice procedures – The European Medicines Agency evaluates NAMs[8] through mechanisms such as the CHMP Qualification of Novel Methodologies procedure[9], the Innovation Task Force[10] and Scientific Advice[11] procedures. These mechanisms allow developers to discuss novel approaches with the agency to support their use in development activities. In parallel, the EMA introduced a voluntary submission of data route[12] intended to support EU database building and increased regulator familiarity with NAMs.

Emerging guidance – Currently, the EMA provides structured pathways for the evaluation of NAMs within existing regulatory frameworks, rather than through dedicated NAM-specific guidance. Current implementation therefore remains largely procedural and case-dependent, with expectations continuing to evolve through regulatory practice[13,14].

FDA:

Policy/Legislation – Legislative and policy developments have expanded the regulatory framework[15] supporting the use of non-animal methods in drug development. The FDA Modernization Act 2.0[16] removed the statutory requirement for animal testing in certain contexts, while initiatives such as the FDA Roadmap to reducing animal testing[17] signal a broader shift toward incorporating alternative approaches where scientifically justified. In practice, these developments support the use of NAM-derived data not only in marketing applications, but also in IND-enabling packages where appropriate. The agency has recently reported successful implementation of initial roadmap milestones[18].

Advice procedures – Developers may engage with the FDA through established pathways including pre-IND meetings, model-informed drug development (MIDD)[19] meetings and other formal interactions. In addition, programmes such as the Drug Development Tool (DDT) Qualification Programs[20] and the Innovative Science and Technology Approaches for New Drugs (ISTAND) Program[21] provide structured mechanisms for the development, evaluation and potential qualification of NAMs for regulatory use.

Emerging guidance – The FDA is publishing new guidance documents like the Draft Guidance on Reducing Testing on Non-Human Primates for Monoclonal Antibodies[22] and recently the Draft Guidance on the Use of NAMs in Drug Development[23] which further formalises expectations for their regulatory use. The guidance outlines core evaluation principles including context of use, human biological relevance, technical characterisation and fitness for purpose, signalling a move toward more structured

and standardised assessment of NAM-derived evidence within submissions.

Other regulatory agencies:

Additional medicines regulators are also beginning to signal increased engagement with NAMs and 3Rs-focused regulatory science, although public regulatory pathways remain less developed. Japan's PMDA has established a dedicated NAMs webpage and internal working group[24] focused on emerging methodologies and weight-of-evidence approaches inviting sponsors to scientific advice procedures on the topic. Other agencies, including Swissmedic, Health Canada, Australia's TGA and several EU national authorities, are increasingly participating in national initiatives and international collaborations on NAMs and 3Rs topics[25–28].

International bodies:

International frameworks support the integration of NAMs into regulatory decision-making. OECD guidance, such as Integrated Approaches to Testing and Assessment (IATA)[29], provides globally harmonised structures for combining multiple data sources.

At regional level, validation bodies such as EURL-ECVAM (EU)[30] and ICCVAM (US)[31] assess the scientific validity of alternative methods and contribute to their regulatory credibility. Regulatory convergence is further supported through international collaboration initiatives focused on the 3Rs.

These activities feed into updates of harmonised guidelines such as ICH S1B(R1)[32] and ICH S5(R3)[33], which reflect a shift toward weight-of-evidence approaches and increased consideration of non-animal methods within defined contexts of use.

In this context, it is important to distinguish between validation (establishing reliability for a specific context of use) and qualification (formal regulatory acceptance of a method for a defined application), both of which may support regulatory use of NAMs.

While the pace of implementation varies, the direction across major agencies is broadly aligned: NAMs are evaluated within defined regulatory pathways and are increasingly discussed during early regulatory engagement.

Regulatory approaches to NAMs across major agencies*

	MHRA	EMA	FDA
Overall positioning	Enabling and exploratory; emphasis on regulatory science and innovation	Structured integration via established regulatory pathways	Framework-setting; defining evaluation principles for regulatory use of NAMs
Primary mechanisms	Innovation Office; Scientific Advice; regulatory science programmes	Qualification of Novel Methodologies; Scientific Advice; Innovation Task Force	DDT Qualification Program; ISTAND; MIDD meetings; NAM guidance
Validation approach	Building evidence through pilot studies, data-sharing and exploratory use	Qualification procedures for broader use; case-by-case acceptance within submissions	Context-of-use driven; fit-for-purpose; increasing emphasis on technical characterisation and human relevance
Use in submissions	Encouraged, particularly in early engagement; formal expectations still evolving	Accepted within dossiers when adequately justified; often via prior engagement	Increasingly structured; NAMs reviewed when justified within IND/NDA packages
Distinctive feature	“Safe harbour” approach enabling non-binding data generation and regulator familiarisation	Established procedural pathways for method qualification	Formalisation of evaluation criteria (context of use, technical robustness, human relevance)
Developer entry points	Innovation Office engagement; early scientific advice	Scientific Advice; Qualification procedures	Pre-IND meetings; MIDD; DDT/ISTAND submissions
Current limitations	Early-stage implementation; limited formalised acceptance criteria	Procedural complexity; evolving expectations for integration	Endpoint-dependent acceptance; variability across review divisions

*Based on MHRA, EMA and FDA guidance, regulatory procedures and roadmap publications; see reference list for representative sources.

How regulators evaluate NAM evidence

Across agencies, four principles shape how NAM-based evidence is assessed

- **Context-of-use** – Regulators evaluate NAMs against a clearly defined regulatory question (e.g. dose selection, mechanistic investigation, or justification of species relevance). A model validated for exposure prediction, for example, cannot automatically replace systemic toxicity studies without additional supporting evidence.

- **Integrated evidence packages** – Rather than expecting a one-to-one replacement of traditional animal studies, regulators increasingly assess the coherence of the overall evidence package supporting a regulatory decision. This aligns with the concept of "fitness for purpose", whereby NAMs are assessed based on their ability to inform a specific regulatory decision rather than to universally replace traditional studies.

- **Transparency and uncertainty** – Clear documentation of assumptions, parameters, validation data and applicability domains is essential. Regulators expect sponsors to explain both the strengths and limitations of a given method. This includes detailed documentation of model assumptions, parameterisation, applicability domains and sources of uncertainty, reflecting increasing regulatory expectations for technical characterisation.

- **Human biological relevance and technical robustness** – Regulators increasingly expect explicit justification of the human relevance of NAM systems, alongside evidence of technical performance such as reproducibility, reliability and robustness. These elements are a key determinant of regulatory confidence in NAM-derived data.

Importantly, a NAM does not necessarily need to be fully validated to be considered for regulatory review; where justified, fit-for-purpose methods may be accepted within a weight-of-evidence framework.

These principles are reflected in a few established regulatory use cases, where NAMs have supported specific decisions within defined contexts of use:

Tebentafusp had no pharmacologically relevant animal model due to its human-specific T-cell receptor mechanism, so nonclinical assessment relied on human in vitro assays and mechanistic understanding. Cytokine-release risk was characterised using human T-cell–based systems. Regulatory decisions were based on a weight-of-evidence approach integrating these data with clinical results.

Ibrutinib illustrates the use of PBPK modelling to inform drug–drug interaction risk and dose recommendations. Model predictions, integrating in vitro metabolism data and clinical pharmacokinetics, were used to support labelling without requiring dedicated clinical studies in all scenarios. This represents a well-established NAM application within a defined context of use as part of an integrated evidence package.

Ivacaftor illustrates the use of human in vitro assays to support efficacy in rare Cystic

Fibrosis Transmembrane Conductance Regulator (CFTR) mutations. Functional studies of CFTR activity were used to extend indications to additional genotypes without requiring clinical trials for each mutation. This represents a NAM application within a clearly defined context of use, integrated with existing clinical evidence.

CHMP qualification opinion on the use of Virtual Control Groups (VCGs) in nonclinical studies[34] provides a clear illustration of how regulators operationalise NAM adoption. In this case, VCGs were considered acceptable to replace concurrent control groups in rat non-GLP dose-range finding studies, where they were shown not to alter key outcomes such as NOAEL determination. However, this acceptance was explicitly limited to a narrowly defined context of use, with further applications (e.g. in GLP pivotal studies) identified as future development steps. This example highlights that while regulatory intent supports reduction of animal use, implementation remains staged, evidence-driven, and tightly linked to specific decision contexts.

At a deeper level, regulatory adoption of NAMs is not driven solely by methodological capability, but by the need to manage decision risk. New approaches are introduced within narrowly defined contexts of use that constrain uncertainty to areas where regulatory consequences are limited. In practice, acceptance is therefore less about replacing individual studies, and more about demonstrating that the use of a given method does not alter key regulatory conclusions. This is reflected in the above case of VCGs, where acceptance was linked to preservation of outcome such as NOAEL.

As a result, NAM integration progresses not as a methodological shift, but as a controlled expansion of decision contexts in which alternative evidence can support regulatory decisions.

Where NAMs still face limits

Despite progress, several scientific and regulatory constraints remain. In addition to scientific limitations, regulatory decision-making thresholds remain endpoint-dependent, with higher evidentiary requirements for pivotal safety conclusions compared to supportive or mechanistic contexts.

Complex systemic endpoints – such as carcinogenicity, reproductive toxicity and long-term systemic effects – still rely heavily on in vivo data. These endpoints involve complex physiological interactions that current NAM systems cannot yet fully replicate.

Additional barriers include:

- variability in reviewer familiarity with emerging technologies
- technical expertise and infrastructure requirements
- cross-regional regulatory differences

Although formal regulatory pathways exist for innovative methodologies, detailed expectations for integrating NAM-based evidence into dossiers are still evolving. In practice, implementation remains context-dependent and often develops through case-by-case scientific dialogue between sponsors and regulators. For many applications, NAMs currently complement rather than replace traditional studies.

What this means for developers

In practice, challenges often arise not from the use of NAMs themselves, but from unclear positioning, late engagement, or misalignment with the regulatory question being addressed.

Drug developers aiming to incorporate NAMs into development programmes should consider several points:

- **Define the regulatory question clearly.** NAMs are evaluated within a specific context of use.
- **Engage regulators early.** Novel methods benefit from early scientific advice or consultation, particularly where use is indication-, endpoint-, or organ-specific.
- **Demonstrate fitness for purpose.** Provide appropriate validati on data and clearly describe applicability domains including appropriate technic al characterisation of assay performance and variability.
- **Integrate evidence.** Position NAM results within the broader nonclinical and clinical evidence package.
- **Be transparent about uncertainty.** Clear discussion of limitations improves credibility during review.
- **Leverage emerging procedural pathways.** Where available, mechanisms such as advance review of nonclinical packages (e.g. Module 4 supported by draft summaries - MHRA) can be used to obtain non-binding regulatory feedback and de-risk NAM-based development strategies prior to submission.
- **Share data in safe harbour schemes.** This can help familiarise regulators with data types and foster accelerated acceptance.
- **Follow the evolving landscape.** Monitor regulatory updates and emerging guidance, as NAM-related expectations continue to develop across agencies

Conclusion

Across global regulatory systems, NAM adoption in medicines regulation is no longer hypothetical. Model-informed approaches are already embedded in regulatory practice, and more advanced in vitro and computational models are moving through formal evaluation pathways.

For developers, the practical task is not simply to replace animal studies, but to position NAMs strategically within coherent, decision-focused evidence packages. Success depends on clear context of use, early regulatory engagement, and transparent justification of human relevance and technical robustness.

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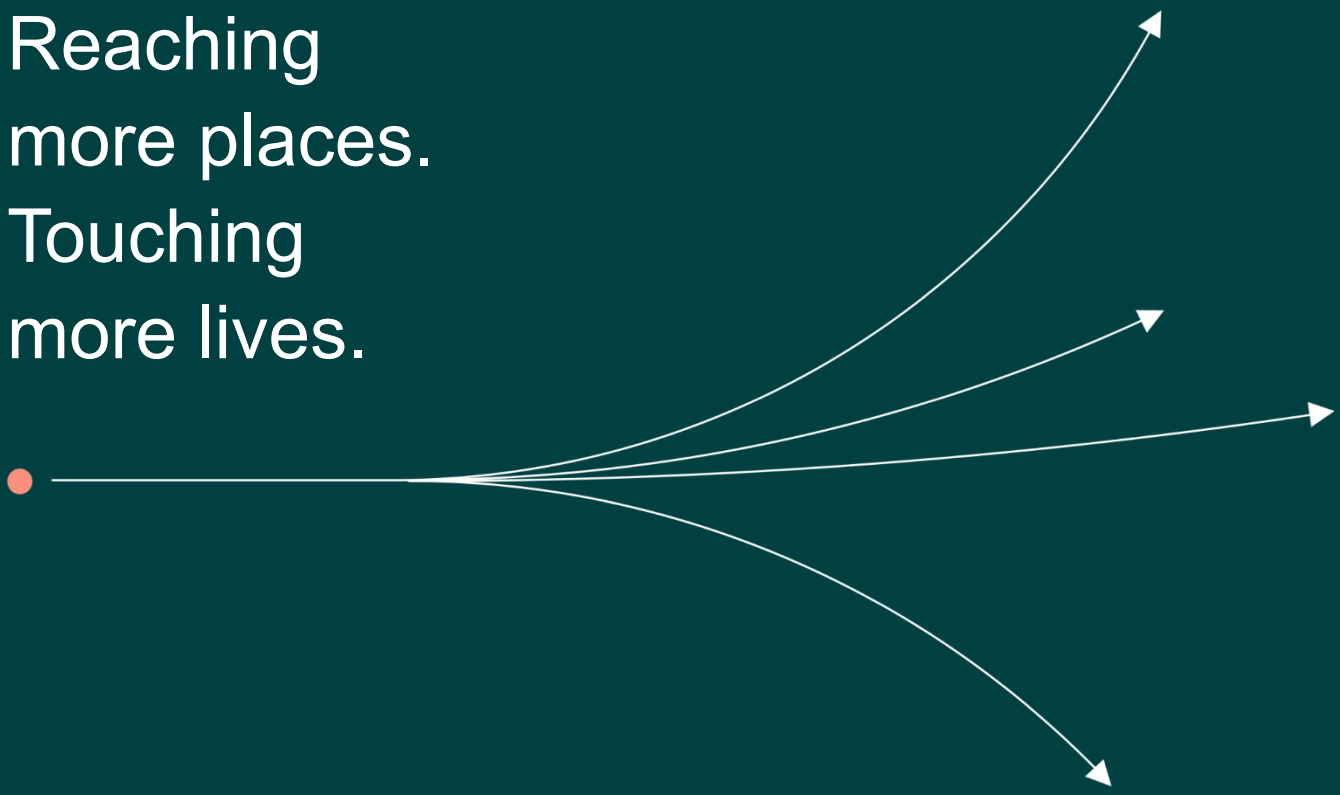

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