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NAMs without context of use slow EU adoption

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New approach methodologies are not a separate market or scientific category, but a heterogeneous set of methodologies whose relevance depends on a clearly defined context of use (CoU). The early definition of CoU should guide validation, qualification, and evidence generation to accelerate regulatory adoption across the EU.

NAM is a regulatory ecosystem term, not a product category

New approach methodologies (NAMs) (see Glossary) are human-relevant test methods, studies, or strategies that do not involve live animals and may include ***in vitro***, ***in chemico***, and ***in silico*** approaches, as well as combinations thereof. Although the term originated in the context of chemical safety assessment [1], it has rapidly spread into the biomedical community through recent regulatory initiatives aimed at reducing reliance on animal testing.[i] Today, NAMs are applied across different areas, including safety assessment, efficacy evaluation, disease modelling, early-stage drug discovery, and personalised medicine.

What has not spread with equal clarity is the concept itself. In the biomedical community, the term is often used as a synonym for an advanced technology. NAMs would be best understood if they were highlighted as a regulatory ecosystem term and through their regulatory functions and **context of use (CoU)**: the decision to be informed, the methodology's intended role, biological plausibility, applicability domain, position in the development pathway, and explicit limitations. Depending on CoU, a NAM may provide stand-alone evidence or one line of evidence within a **weight-of-evidence (WoE)** assessment.

For the development of new medicines, the **European Medicines Agency (EMA)** describes NAMs as **3Rs (Replacement, Reduction, and Refinement)**-compliant methodologies that may be incorporated into the assessment of safety and efficacy.[ii] The term encompasses approaches that may enter **regulatory assessment** if shown to be scientifically sound for the task proposed. What unifies them is a shared regulatory function: they are methodologies used to inform efficacy, safety, or quality evaluation.

Although the CoU of a NAM is well recognised in the chemical safety assessment across multiple legislative frameworks,[iii] the development of biomedical products requires NAMs to support a broad range of applications, including early discovery and candidate selection, pharmacology, efficacy assessment, patient stratification and personalised medicine, quality assessment, and nonclinical safety testing. Furthermore, unlike the medicine space, where EMA's **qualification** pathway is relatively well defined, the regulatory route for NAMs in the medical device and *in vitro* diagnostic medical device sectors is still evolving.[iv]

NAMs are therefore cross-cutting regulatory methodologies whose identity is defined by the decision they are meant to support.

Shared technology does not mean a shared market and regulatory pathway

It is important for the biomedical community to recognise that the same underlying technology may fall into different legal and commercial categories depending on its intended use. **Stem cells**, for example,

Glossary

3Rs (Replacement, Reduction, and Refinement): principles that guide the replacement of animals where possible, the reduction of the number used, and the refinement of procedures to minimise pain and distress.
Advanced therapy medicinal product (ATMP): medicine for human use that is based on genes, tissues, or cells.
Context of use (CoU): description of the purpose, application, and regulatory decision for which a method is intended.
Endpoint: biological or toxicological measurement used to assess the effects of a substance or treatment.
European Chemicals Agency (ECHA): EU agency responsible for implementing chemicals legislation to protect human health and the environment.
European Medicines Agency (EMA): EU agency responsible for evaluating and monitoring the safety, efficacy, and quality of medicines.
Hepatotoxicity assessment: evaluation of whether a substance causes damage to the liver.
Human relevance: extent to which a model or test accurately reflects human biology and predicts human responses.
***In chemico*:** studies performed using chemical or biochemical systems without living cells or organisms.
***In silico*:** studies performed using computer models, simulations, or artificial intelligence.
***In vitro*:** studies conducted outside a living organism, typically using cells or tissues in the laboratory.
***In vivo*:** studies performed in living organisms, such as animals or humans.
Innovation Task Force (ITF): EMA platform providing early scientific and regulatory guidance to method developers.
New approach methodologies (NAMs): nonanimal methods, including *in vitro*, *in chemico*, and *in silico* approaches used to generate safety or efficacy data.
Organoids: three-dimensional miniature tissues grown from stem cells that reproduce key features of real organs.
Organs-on-chips (OoCs): microfluidic devices containing living cells that mimic the structure and function of organs.
Qualification: regulatory process that demonstrates a method is suitable for a specific context of use.
Quantitative Structure–Activity Relationship ((Q)SAR): computational approach that predicts the biological activity, toxicity, or other properties of a chemical based on the relationship between its molecular structure and the known activities of similar compounds.
Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH): EU legislation regulating the safe manufacture and use of chemicals.
Regulatory assessment: evaluation of scientific evidence by regulatory authorities to support decisions on the safety, efficacy, or quality of products.

Stem cells: undifferentiated cells capable of self-renewal and of developing into specialised cell types.
Validation: process by which the reliability and relevance of a particular approach, method, process, or assessment are established for a defined purpose.
Weight-of-evidence (WoE): structured process that integrates multiple lines of evidence, considering their relevance, reliability, consistency, biological plausibility, and uncertainty, when no individual study or methodology is sufficient to support the intended conclusion.

can model disease, generate **organoids** for efficacy or safety assessment, support personalised testing, or form a cell-therapy product. Although these applications share a biotechnological basis, their legal status, regulatory pathways, and routes to adoption differ. Thus, a stem cell-derived liver model used for **hepatotoxicity assessment** may function as a NAM, whereas a stem cell-based therapeutic product may be classified as an **advanced therapy medicinal product (ATMP)**. Shared biotechnology does not erase this regulatory distinction.

Once NAMs are understood as methodologies rather than specific products or biotechnologies, the confusion becomes easier to see. *In silico* or *in vitro* models (e.g., **organs-on-chips [OoCs]**; Box 1) are often associated with a single innovation market because they are biologically or computationally sophisticated. What matters in regulation is not whether a platform is 'advanced', but whether it is being proposed as a therapy, a diagnostic, a medical device, a preclinical research tool, or an evidence-generating method for a regulatory decision. The same technology may sit in any of those positions. Its regulatory pathway changes accordingly.

For medicine development, EMA offers early dialogue through **Innovation Task Force (ITF)**[v] briefing meetings and a qualification framework for novel methodologies. This may lead to qualification advice, a letter of support, or a Committee for Medicinal Products for Human Use qualification opinion.[vi] EMA also allows voluntary submission of NAM data to support its future regulatory acceptance. Once a methodology is proposed for medicinal product safety or efficacy assessment, it enters a recognisable regulatory pathway and must be justified against a defined intended use.

In chemical safety, under **Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH)**, the **European Chemicals Agency (ECHA)** emphasises that companies should use existing information and alternative methods before performing tests on animals.[vii] This means that NAMs enter chemical regulation, through a route generally framed in terms of **validation** [3], evidentiary use, and regulatory acceptance under chemicals legislation rather than qualification. This is further reinforced by the European Commission's Roadmap towards phasing out animal testing for chemical safety assessments,[iii] which establishes a coordinated policy framework for the gradual replacement of animal testing with NAMs across multiple regulatory sectors while maintaining high standards of protection for human and animal health and the environment.

'Qualification' is therefore not a generic label for all NAM uptake across all sectors. It is one route, specifically developed in the medicine space.[vi] This is the conceptual starting point often missed by the community. NAMs are not a product class waiting to be commercialised as such. They are a family of methodologies that acquire regulatory meaning only when tied to a particular decision within a particular sector. That is why CoU is not an administrative afterthought. It is the step that turns a technology platform into a regulatory proposition.

Context of use is the operative unit

The CoU describes the circumstances under which NAMs are applied in medicines development and assessment. Developers must generate sufficient, robust data to demonstrate utility and regulatory relevance within a specific CoU.[ii]

CoU is neither the only barrier to NAM adoption nor a substitute for scientific validity. Rather, it converts general requirements into decision-specific evidence standards, including appropriate

Box 1. Organs-on-chips show why technical activity is not enough

Publications related to OoCs have increased steadily over time.[xviii] Portela *et al.* reviewed 139 studies describing 160 OoC models used for medicines safety assessment between 2010 and 2020 [2]. Most models were based on single-organ systems, with liver, kidney, and heart being the most frequently represented organs. These findings indicate that the field is not lacking technical activity; rather, it is characterised by substantial experimentation and a clear effort around high-priority toxicological domains [2].

What is striking is that the submission of OoC data to regulators remains limited. The problem, then, is not a lack of scientific model production or modelling complexity; it is the weak design of the evidence package submitted to regulators. Comparative analysis against human or ***in vivo*** reference data is present in only a minority of studies, benchmarking with appropriate reference compounds is often insufficient, and reproducibility and transferability across laboratories have not yet been consistently demonstrated. For instance, many OoC platforms are promoted as predictive of human toxicity without clearly specifying the regulatory question they are intended to address, such as whether they are designed to exclude compounds, rank candidates, or contribute to a WoE assessment. Without a defined applicability domain, performance criteria, decision threshold, reference compounds, comparator datasets, and interlaboratory reproducibility, additional biological complexity cannot, by itself, establish fitness for regulatory use.

For OoC models intended for regulatory applications, the CoU should therefore be defined as early as possible. When regulatory qualification is needed, this depends not only on that definition but also on the choice of relevant endpoints fit for the intended purpose, the use of appropriate reference compounds, and the demonstration of biological plausibility, reproducibility, and translatability. It is also important to start with simple systems in a defined CoU and to scale complexity gradually. A NAM does not become useful because it models more complex biology. It becomes useful when it generates reliable evidence that credibly supports a bounded decision [2].

comparators, performance criteria, acceptable uncertainty, and the relevant regulatory pathway.

Developers should state whether a NAM is intended to replace an existing method, complement it, or contribute to a WoE assessment. Under the International Council for Harmonisation ICH M7(R2), for example, two complementary **Quantitative Structure–Activity Relationship ((Q)SAR)** methodologies can support the assessment of the bacterial mutagenicity of pharmaceutical impurities within a tightly specified decision framework.[viii] An emerging example is the use of virtual control groups (VCGs) in place of concurrent controls. The EU-funded VICT3R (VIrtual Control groups To reducE animal use in toxicology Research) project reports that it submitted an EMA qualification request and that EMA has published a draught qualification opinion for VCGs in rat dose-range-finding studies.[ix,x] The opinion is not yet final, but it illustrates how a narrowly specified CoU can support regulatory evaluation while reducing animal use.

Human relevance alone is too broad to define an adoption strategy. The claim must identify the **endpoint**, product class, development stage, intended role, and consequences for decision-making. Without them, benchmarking becomes difficult, and the methodology cannot be placed within a regulatory argument.

ERA Action 17 reframes the problem

At the EU policy level, NAMs are gaining momentum. The European Research Area (ERA) policy action 17[xi] aims to accelerate the development, validation/qualification, acceptance, and uptake of NAMs in biomedical research and regulatory testing of medicinal products and medical devices through a coordinated approach across Member States. Although regulatory frameworks already exist, these operate within specific regulatory contexts and do not provide a broader mechanism for coordinating NAM development, validation/qualification, and implementation across stakeholders. As required by Directive 2010/63/EU,[xii] Member States are bound to replace animal procedures when valid alternatives become available. A dedicated cross-sector, EU-wide implementation mechanism is still being established.

In our opinion, the EU does not need another validation authority. It needs a sustainable, federated layer that connects

Table 1. EU funding instruments supporting the adoption of NAMs[a]

EU funding	Target/aim	Bottleneck addressed
HORIZON-JU-IHI-2023-05-01 Accelerating the implementation of NAMs and other innovative nonanimal approaches for the development, testing and production of health technologies[xiii]	Accelerate the practical implementation of fit-for-purpose NAMs in the development, testing, and production of health technologies by supporting evidence generation, performance assessment, stakeholder collaboration, and integration into development and regulatory processes.	Limited translation from research into practice, including insufficient standardised and decision-relevant evidence, limited validation and benchmarking, and weak integration of NAMs into industrial and regulatory workflows.
HORIZON-HLTH-2024-IND-06-09 Gaining experience and confidence in NAMs for regulatory safety and efficacy testing-coordinated training and experience exchange for regulators[xiv]	Increase regulatory experience, confidence, and interpretive capacity through coordinated training, practical exchange, and interaction among regulators, NAM developers, and users.	Uneven regulatory expertise and confidence, together with limited shared experience in evaluating NAM-generated evidence and applying it consistently to safety and efficacy decisions.
HORIZON-HLTH-2026-01-TOOL-03 Integrating NAMs to advance biomedical research and regulatory testing[xv]	Integrate NAMs into biomedical research and regulatory testing through clearly defined CoUs, fit-for-purpose validation strategies, alignment with relevant OECD and/or EMA guidance, and early and sustained regulatory engagement.	Insufficiently defined CoUs and fragmented evidence generation, including unclear intended uses, inadequate comparator and validation strategies, poor comparability across settings, and regulatory engagement occurring too late in development.
HORIZON-HLTH-2026-01-TOOL-06 Support to ERA action on accelerating NAMs to advance biomedical research and testing of medicinal products and medical devices[xvi]	Provide the operational support for ERA Action 17 by coordinating priority setting, development and infrastructure, joint validation or qualification activities, education and training, openness, awareness, acceptance, and uptake across Europe.	Fragmented priorities and coordination across Member States and sectors, including duplicated efforts, uneven infrastructure and expertise, and the absence of a shared route linking development, validation or qualification, regulatory learning, and implementation.
HORIZON-EIC-2026-AIC-02 Translating disruptive NAMs into practice[xvii]	Support the translation of mature and disruptive NAMs into regulatory, industrial, and commercial practice through benchmarking, end-user and regulator engagement, generation of robust evidence packages, scalability assessment, and real-world demonstration.	The translation gap between technical feasibility and adoption, including insufficient regulatory-grade evidence, limited scalability and industrial readiness, uncertain market positioning, and weak engagement with end users and regulatory stakeholders.

[a]Selected EU funding instruments address complementary barriers along the NAM adoption pathway: implementation and evidence generation, regulatory learning, CoU-driven development, European coordination, and industrial translation. The table describes authors' opinion on the intended contribution of each instrument and does not imply that regulatory acceptance or market uptake has already been achieved.

existing sector-specific mechanisms, prioritises and operationalises shared requirements, supports early regulatory dialogue, and tracks translation outcomes while leaving formal decisions to competent authorities. ERA Action 17 aims to address this systemic gap by bringing together key actors through working groups on development and infrastructure, validation and qualification, education and training, and openness and awareness. This framing recognises that fragmented validation priorities, uneven regulatory experience, poor comparability, and disconnected routes to regulatory acceptance are coordination failures rather than shortcomings of individual technologies.

Related EU funding calls address complementary bottlenecks along the adoption pathway (Table 1), ranging from fragmented validation priorities[xiii] and limited regulatory experience[xiv,xv] to EU-level coordination[xvi] and industrial translation.[xvii] Together, these instruments illustrate a transition from funding technology development alone towards coordinated regulatory and industrial adoption. Their success, however, will depend on whether funded projects define clear CoUs from the outset, generate documented evidence that meets regulatory expectations, and sustain collaboration among key actors throughout the innovation pathway.

Concluding remarks

For NAM developers, the first shift is conceptual: the opening claim should not be that a platform is broadly more human-relevant, but that it can inform one defined decision better, earlier, or more transparently than current approaches. This requires a specified applicability domain, relevant endpoints, a development stage, and an uncertainty tolerance.

The second shift concerns evidence design. Reproducibility, standardisation, transferability, benchmark selection, performance thresholds, and interpretation criteria should be built into the method rather than appended once the platform is 'finished'. The third shift is organisational: many NAMs will enter practice as batteries or as supportive evidence within a broader WoE package, allowing regulators and sponsors to accumulate experience before considering a narrower formal qualification claim.

Ultimately, the successful regulatory adoption of NAMs in the EU will depend less on demonstrating technological novelty than on defining the CoU that enables the generation of regulatory-relevant evidence for a specific decision in a real regulatory setting.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Microsoft Copilot to support language editing, English grammar, and style review. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Resources

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