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Panel discussions on the global regulatory acceptance and harmonisation of non-animal NAMs

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ABSTRACT

Two panel discussions on non-animal New Approach Methodologies (NAMs) in regulatory safety assessments were held as webinars. These webinars were initiated and hosted by the scientific committee Pro Anima with contributions from international experts in the field. The panel discussions thoroughly explored the current landscape surrounding international regulatory acceptance and harmonisation of NAMs. The discussion focused on the regulatory challenges, stakeholder engagement, validation hurdles, and international efforts to facilitate a broader and more efficient adoption of NAMs in safety decision-making. The discussion also covered the role of emerging technologies such as artificial intelligence (AI) in advancing NAMs and provided insights into successful case studies, challenges and opportunities, and ongoing initiatives.

1. Introduction

Pro Anima scientific committee is a pioneering structure in France whose objectives, since 1989, have been to participate in improved development and assessment of chemicals for human health; fostering dialogue and working towards a greater recognition of human-relevant new technologies and methodologies, as well as of the work of researchers developing these methods, that are today pooled under the acronym NAMs.

In the spring of 2024, Pro Anima launched the panel discussion series, *Science and Dialogue* (Science and Dialogue : Panel Discussion Series May 16, 2025), supported by the French hub of the European project PARC (Partnership for the Assessment of Risks from Chemicals) (Partnership for the Assessment of Risks from Chemicals | Parc May 16, 2025) and the French 3R centre (FC3R) (Centre Français des 3R - GIS FC3R May 16, 2025), with the aims (1) to foster cross-disciplinary interactions between key players (researchers, industry, regulators); (2) to identify current and future scientific and regulatory obstacles and solutions; (3) to raise awareness and contribute to a greater acceptance of non-animal New Approach Methodologies (NAMs).

NAMs have many definitions which are dependent on researchers or the institution (*e.g.*, FDA, ECHA, EMA, EPAA, ICCVAM, NC3Rs etc.) and how they plan to use or apply the data (LLM JD, May 16, 2025). Both the FDA and EPA leave the definition of NAMs open to include methods that reduce or refine the use of animals in testing, while the NIH specifically uses NAMs as methods that replace the use of animals in testing (and even sometimes refers to NAMs as Non-Animal Methods). Generally, a NAM does not use live animals and sometimes may use animal or human tissue or cells. When animal experiments are performed together with a new testing approach, these are refinement and reduction activities. A new analytical technique, such as application of OMICs, can be added to an existing animal test rather than be performed as stand alone, but again this will be a refinement if the new method results in a reduction or complete cessation of pain, discomfort or anxiety of the animal (E. Editor May 16, 2025).

Consequently, NAMs are defined here as non-animal New Approach Methodologies. This definition of a NAM only applies to full replacement when using human-derived test methods and test systems, such as new applications of complex (3D) *in vitro* models, *ex vivo* or *in chemico* test methods and *in silico* approaches or a combination of these.

As perceived by numerous stakeholders in the field, we are in an exciting and challenging time for science, biomedicine, safety and chemical assessment, building the knowledge and frameworks for tomorrow and the future. However, we are also in the nebulous territory that a paradigm change entails: the transition from safety decisions based on using experimental animals towards the use of relevant scientific methods, and the challenges associated with superseding historical approaches (Report on the Capacity of Legal and Regulatory Frameworks to Accommodate NAMs - PrecisionTox May 16, 2025). As raised during the discussion around the European Commission (EC) roadmap to phase out animal testing and phase in NAMs (Roadmap towards phasing out animal testing for chemical safety assessments - European Commission May 16, 2025); and in the NGRA (Next-Generation Risk Assessment) pipeline (Hristozov et al., Jul. 2024), there is currently a key challenge to accelerate implementation of NAMs that lies in their regulatory acceptance, harmonisation and stakeholder adoption.

Referring to an article published on the NC3Rs' website in early 2024, when asked about the future of NAMs in regulatory testing, Dr. Suzy Brescia, Regulatory Toxicologist at the UK Health and Safety Executive, answered: "It is not a matter of if, but of when" ('NAMs May 16, 2025). The very first panel discussion addressed the "how?" in "Regulatory Acceptance of NAMs: How to define criteria?". There is a global trend in international legislation, institutional bodies and industries towards the acceptance and implementation of non-animal methods for safety decision-making (Ramanarayanan et al., Aug. 2022; Wood et al., Aug. 2024). Conversely, there is a clear issue in terms of test guideline processes, such as the OECD Test Guidelines (Guidance Document on the Validation and International Acceptance of New or Updated Test

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Methods for Hazard Assessment May 11, 2025) referred to in many regulations, that are still very slow to accept or recognize new (validated) non-animal methods to replace historic mammalian testing that have not been based on clear scientific evidence nor validation. This issue should no longer compromise the clear wish, need and importance for regulatory agencies, scientists and other stakeholders for harmonisation of both guidelines and acceptance criteria to answer the global health and chemical safety challenges that lie ahead. Global recognition of the need to streamline processes and support regulatory implementation of NAMs has led to ongoing efforts at the OECD to revise Guidance Document 34 on validation of new approaches (Harrill, 2024; J. Barroso), acknowledging that current validation is lengthy, costly and a rigid process, which should become more efficient, flexible and evidence-based.

Therefore, the second panel discussion addressed and explored current challenges, opportunities and ongoing actions in favour of harmonising NAMs to ensure new human-based methods can and will be regulated, accepted worldwide and under the same criteria. We wondered how this can actually be possible and implemented among countries, sectors and disciplines, and thus asked the panellists the following question: "Harmonisation of NAMs, can it really be global?".

These two panel discussions provided an in-depth examination of the current state of NAMs, their regulatory challenges, and the pathways to their broader adoption. The sessions highlighted key issues on: (a) the validation and harmonisation of NAMs across different regions; (b) considerations around the need for stakeholder collaboration and engagement; (c) the role of regulatory, legislative and technical advancements; and (d) the critical role of education and communication in facilitating the implementation of NAMs. The discussions also focused on the role of emerging technologies, such as AI, in the advancement of NAMs and gave an overview of successful case studies and current initiatives.

2. Regulatory and legislative challenges

One of the central topics addressed during the panel discussions was the regulatory and legislative challenges associated with increased uptake of NAMs. The panellists highlighted significant differences in how NAMs are integrated into regulatory frameworks across various regions of the globe.

In the United States, flexible legislation such as the *FDA Modernisation Act 2.0* (R. [R-K. Sen. Paul, 2025) that "authorizes the use of certain alternatives to animal testing […] to obtain an exemption from the Food and Drug Administration to investigate the safety and effectiveness of a drug" and also "removes a requirement to use animal studies […] for a biological product that is biosimilar or interchangeable with another biological product" and the Lautenberg Chemical Safety Act (J. [R-I.-15 Rep. Shimkus, 2025), alongside strong infrastructure, are fostering NAMs' adoption. Organizations like ICCVAM (Interagency Coordinating Committee for the Validation of Alternative Methods) (About ICCVAM, 2025) and NICEATM (National Institute of Environmental Health Sciences' National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods) (NICEATM: Alternative Methods, 2025) play a crucial role in promoting and validating NAMs. The US has also seen recent initiatives launched such as a new interactive NAMs database of alternative methods accepted by US agencies (Alternative Methods Accepted by US Agencies, 2025) (Collection of Alternative Methods for Regulatory Application: CAMERA, to be released mid-2025) and the Complement Animal Research in Experimentation (Complement-ARIE) funding program (Complement-ARIE Challenge Prize Winner Summaries | NIH Common Fund, 2025), which aims to advance and accelerate the implementation of human-based methods in biomedical research.

Europe faces additional substantial hurdles because of a more complex regulatory landscape with a strong historical reliance on animal testing. However, there are clear signs of progress, such as the EC work and report on its first workshop on "The Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments" (European Commission, 2023), efforts by the European Partnership for Alternative Approaches to Animal Testing (EPAA) with the Designathon launched in May 2023 at a workshop at ECHA (EPAA, 2025) and the multinational European project PARC that promotes cooperation, advanced research, and aims to increase knowledge and relevant methodological skills for NGRA. There remains a need for more concrete guidance from regulatory agencies to efficiently support and encourage the integration of NAM-based information in regulatory submissions. Additional barriers are the differences between countries in the European continent. For example, while Switzerland has made strides in promoting NAMs through the 3R Center Switzerland, 3RCC, the SCAHT - Swiss Centre for Applied Human Toxicology and open dialogue with Swissmedics (Swiss EMA), in terms of NAMs adoption, it remains behind countries such as The Netherlands that recently launched a transition center towards animal-free innovation (S for More, 2025). The EU regulatory framework is evolving with, for example, the replacement of the rabbit pyrogen test (RPT) by the monocyte activation test (MAT) by the European Directorate for the Quality of Medicines & healthcare (EDQM) (European Pharmacopoeia to put an end to the rabbit pyrogen test - European Directorate for the Quality of Medicines and HealthCare - EDQM', 2025). This is a one-on-one replacement that has now become the default in the European Pharmacopeia. Still, more concrete guidelines and support are needed to ensure consistency of approach across the nations. The panel emphasised that while Europe's regulatory bodies are open to NAMs, the adoption of these methods is still constrained by the strong historical investment in and reliance upon animal-based methods and the absence of unified modernisation statements and comprehensive regulatory changes together with research centres and fundings that actively invest in the translation and implementation of NAMs. In comparison to the US, the investment in NAMs from governmental and public-funded budgets is neglectable in EU areas and needs to be increased for staying competitive.

In India, recent regulatory reforms have allowed the use of NAMs for drug testing and banned animal testing of cosmetics (India Takes Historic Step Towards Eliminating Animal Testing in Drug Development, 2025). However, NAMs are still emerging in the country, and a unified regulatory framework is being developed. The Center for Predictive Human Models (CPHMS, Atal Incubation Centre-CCMB) (CPHMS - AIC-CCMB, 2025), a collaborative initiative between Humane World for Animals India and Atal Incubation Centre-CCMB, is India's first think tank dedicated to enabling a shift from observational science to a more mechanistic, human-relevant paradigm. It has seen increased NAM-related activities, indicating progress in this area, while the regulatory landscape is still evolving. In a recent workshop organised by CPHMS, the Central Drugs Standard Control Organization (CDSCO), and the Indian Council of Medical Research (ICMR) in July 2024, the need for minimum guidelines for complex *in vitro* models and *in silico* methods was recommended (Mahadik et al., 2025). Recently, Draft Revised Guidelines on Similar Biologics- Regulatory requirements for Marketing Authorization in India, 2025 have been released for stakeholder comments where it has been recognised that "*in vitro* assays are in general more specific and sensitive than *in vivo* studies in animals for detecting differences between the similar biologic and reference biologic product (RBP)" and in consideration of this, the *in vivo* toxicity studies have been waived off unless there remains uncertainties concerning the similarity of RBP and few other scenarios highlighted in the draft guidelines (valueaddedin, 2025).

Regulatory acceptance and adoption of NAMs is currently hindered by differences in legislative frameworks, especially between the US and Europe. As an example, the US EPA is already using *in vitro* developmental neurotoxicity (DNT) battery assays as part of a weight of evidence for certain risk assessments because their legislation allows it. In Europe, a change in legislation is needed to allow such NAMs to be used. NAMs are sometimes more easily integrated in the US due to flexible

legislation, and the government invests time and money in their qualification with initiatives such as the ISTAND pilot program, that is going to support the development of novel approaches to drug development that may be acceptable for regulatory use (C. for D. E. and Research, 2025). Europe still requires regulatory changes and delegated rule-making powers to concretely accept data from non-animal human based only tests. It was suggested during the discussion that it would be interesting in the future to set aside geography, and activity in specific industrial sectors, and convene all stakeholders and decision-makers to build an international dialogue coordinated, for example, by an independent committee or coalition, with specific experts' groups, such as the ICCS for the cosmetics (ICCS - Advancing Animal-Free Science for Cosmetics', 2025).

The discussion highlighted that while legislative changes, such as the *FDA Modernization Act 2.0*, represent progress towards non-animal testing, there is still a gap between regulatory intentions and current actual practices. Aligning laws with regulatory frameworks and decisions is essential for facilitating NAMs adoption.

In parallel, the panel also emphasised key additional elements: the importance of collective action and the role of initiatives like the European Citizens Initiative "*Save Cruelty-free Cosmetics - Commit to a Europe without Animal Testing*" (Save Cruelty Free Cosmetics - Commit to a Europe Without Animal Testing, 2025) in influencing regulatory shifts by driving the EC roadmap. In submitting non-animal NAM data within existing regulatory frameworks such as REACH (Towards Non-Animal Testing in European Regulatory Toxicology, 2025), industry and other key players have a significant role and responsibility as this can support the integration of NAMs within current regulatory structures. However, this has been identified as a 'chicken and egg' problem because industry may fear that NAMs data may not be accepted by regulatory agencies, (even though such NAM data is used for internal decision-making), and therefore do not include it within formal dossiers (L. Holden). Finally, having all the stakeholders on board, and more notably having regulators involved early on in the process can be helpful because that helps lowering such barriers in the method development and implementation to help push the methods forward.

The need for improved education and open communication between scientists in industry, academia and regulatory agencies was in that sense emphasised. Addressing concerns about the effectiveness of NAMs and demonstrating their ability to meet regulatory standards are both crucial for building confidence in these methods. Effective communication strategies are essential for advocating the appropriate use of NAMs and ensuring their successful acceptance and implementation.

3. Validation and technical barriers

Validation of NAMs remains a critical challenge, particularly in ensuring that new methods are reliable and reproducible. Traditional validation processes, such as ring trials, are often lengthy and costly and are often compared against unvalidated animal data missing the importance of species as well as *in vitro-in vivo* differences.

The role of international organisations such as the OECD in advancing NAMs was discussed. The OECD develops internationally accepted test guidelines for NAMs, but the application of these guidelines can vary across regulatory bodies (*e.g.*, differences between the US EPA and European agencies). Even though non-OECD member countries, like India, may not be legally bound to adhere to these guidelines, in practice they do follow these guidelines. Ongoing OECD projects, such as the revision of OECD GD34, and consortia organisations like ICCS (ICCS - Advancing Animal-Free Science for Cosmetics', 2025) and HESI ('Home', 2025), play a critical role in advancing NAMs through public-private partnerships, sharing case studies and fostering international collaboration.

Moreover, an existing issue was highlighted that very often we are comparing the hazard assessment that goes on in traditional animal testing with a much wider capacity of NAMs to begin to explain some of the roots to adverse outcomes by exposure to chemicals and analyse mixtures of chemicals with subsequent derivation of a risk assessment related to specific use scenarios.

It was unanimously agreed that validation should not be referenced against the animal tests, as validation against traditional animal testing is unlikely to be successful due to species differences and a lack of animal test validation against the human *in vivo*. Rather, the priority is to work out how to build trust and understand the robustness and transferability of each test to make robust safety decisions. There is a lot of discussion about the bridge between the *in vivo* animal data and the *in silico* and *in vitro* human data, because we have so often failed by making that comparison. We know there are interspecies differences, reflected by the 90–95 % failure rate from preclinical to clinical trials of pharmaceuticals, that has been there for about 30 years without any significant improvement (Sun et al., 2022; Ineichen et al., 2024). A good example is the use of *in vivo* rat skin absorption data by the US EPA for many years for pesticide operator exposure safety evaluations. They evaluated the rat *in vivo* and rat *in vitro* components of the dermal triple pack (*in vitro* human, *in vitro* rat, and *in vivo* rat), and confirmed that the rat *in vitro* was more conservative than the rat *in vivo* (Allen et al., 2021). The conclusion of this paper was that human *in vitro* would be a conservative prediction for human *in vivo* for operator exposures to pesticides. The US EPA now only requires human *in vitro* skin penetration data to be submitted as part of the pesticide safety evaluation.

The panel discussed the need for a concrete shift towards mechanistic validation and standardisation to speed up the validation process. This well documented approach focusing on biological relevance, reproducibility, and predictivity, could potentially accelerate the acceptance and adoption of NAMs (van der Zalm et al., 2022; Iccvam, 2024).

AI and *in silico* methods were discussed as emerging tools with the high potential to improve risk assessments and validate NAMs (Hartung, 2019; Luechtefeld et al., 2018). While these technologies are still in their early stages of adoption, they offer promising avenues for aggregating scientific data and enhancing the reliability of NAMs. The US FDA has now published some guidelines for AI use (O of the Commissioner, 2025). In the future it will be helpful if the readiness of AI tools could be assessed to guide regulators in their application. Currently, in The Netherlands The Virtual Human Platform for Safety (VHP4Safety) is being built, a fully *in silico* model aiming to predict human responses on the basis of human data alone (Kienhuis et al., 2025).

Additional barriers, such as cost and sovereignty, need also to be mentioned and was specifically highlighted for developing countries, like India, where the reagents and consumables are imported from outside the countries border, which causes problems at the border with customs delays resulting in increased cost and sometimes resulting in unusable test systems. The OECD approved methods (like Episkin SkinEthic RHE, and MatTek EpiDerm etc.) are also very highly priced for Indian markets which makes the adoption lower. Therefore, there is a need to either locally manufacture test systems or work with the commercial NAM suppliers to bring down their cost and make them more widely accessible.

Once barriers to adoption of NAMs were listed and identified (Holden; Sewell et al., 2024) panelists tried to identify how to overcome these.

4. The importance of case studies, complementary initiatives and tools

Several successful case studies and ongoing initiatives were highlighted during the discussion. The European Partnership for Alternative Approaches to Animal Testing (EPAA), (European Partnership for Alternative Approaches to Animal Testing - European Commission, 2025) and the PARC project (Partnership for the Assessment of Risks from Chemicals | Parc, 2025) were noted as significant efforts to integrate NAMs into regulatory frameworks. These initiatives aim to

encourage NAMs for various safety assessments and foster collaboration among stakeholders.

In the United States, the development of an interactive NAMs database and funding programs like Complement-ARIE (Strategic Planning | NIH Common Fund, 2025) are notable efforts supporting the advancement and regulatory acceptance of NAMs, demonstrating the importance of structured funding mechanisms in supporting NAMs development and implementation.

One panellist shared her experience to make the *in vitro* DNT battery test approved by the OECD. Early on, they interacted with the US EPA and EFSA, test method developers and industry representatives, and developed a roadmap. Then the OECD joined in 2015 and finally published the recommendations in 2023. She hopes that at least for the pesticide regulation, the *in vitro* DNT battery will be applied very soon. This would then serve as an example to follow for the acceptance of future NAMs. A six-step framework from NAM development to regulatory acceptance with DNT as an example was recently published as a guidance for transitioning through the NAM life-cycle up to regulatory acceptance (Blum et al., 2025).

These initiatives demonstrate a commitment to advancing NAMs through practical support, communication and resource allocation.

The panellists also suggested focusing on key endpoints, such as liver or cardiac toxicity (Turner et al., 2023), to develop harmonised guidelines. These approaches could help build confidence in NAMs and facilitate their global adoption across different regions and sectors.

A final interesting perspective was highlighted and concerned *soft law elements/instruments* that may be very helpful and important to take into consideration, such as guidance material, protocols, Q&A on regulatory agency websites, etc. Such soft law cannot override the hard law regulations, but where that hard law is not prescriptive, many of these tools can be changed with the will and the mindset to do so. These are guiding elements that can really signal to players that they can move forward a greater and effective acceptance and implementation of NAMs by the stakeholders.

5. Future directions and conclusions

The discussions underscored the need for more effective and global collaboration among all stakeholders involved in NAMs development, validation, acceptance and implementation; all of these contributing to the harmonisation process to transform the chemical safety landscape and face our contemporary challenges.

While significant strides have been made, challenges remain in the legislative framework, regulatory acceptance, validation, and stakeholder engagement. Successful integration of NAMs will rely on the ongoing coordinated efforts among regulators, industry, academia, governmental and non-governmental organisations, and citizens (Abarkan et al., 2022).

Securing dedicated funding (particularly for the validation of NAMs for regulatory use) and private-public partnerships will also be crucial for overcoming these challenges and realising the full potential of NAMs in regulatory science. The recent new funding call by Germany and the Netherlands is a promising new initiative by funders stimulating the validation process (ValNAM, 2025).

The panellists stressed that communication and a shared understanding among stakeholders, involving regulators early on in the process, are crucial for building trust and ensuring that NAMs are accepted and utilised effectively.

From these two panels, a call was made for continued dialogue and a co-exploration of innovative approaches to support NAMs development and implementation. Pro Anima will continue its panel series with new sessions coming up in 2026.

Next Steps / Perspectives

- **Continued Dialogue:** Foster ongoing discussions among stakeholders globally to address challenges and opportunities in NAMs adoption.
- **Enhanced Collaboration:** Strengthen partnerships between public and private sectors to drive NAMs innovation and implementation.
- **Data sharing and accessibility for NAMs:** Share data and NAMs that have shown good results so that regulators across the globe have access to this information in one place and can make informed decisions.
- **Increased Funding:** Advocate for dedicated funding mechanisms to support NAMs development, validation and regulatory integration.

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

During the preparation of this work the author(s) used ChatGPT in order to provide a first transcript of the two panel discussions. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Lilas Courtot: Visualization, Writing – original draft, Writing – review & editing. **Ellen Fritsche:** Writing – review & editing. **Nina Hobi:** Writing – review & editing. **Nicole Kleinstreuer:** Writing – review & editing. **Robert Lee:** Writing – review & editing. **Surat Parvatam:** Writing – review & editing. **Merel Ritskes-Hoitinga:** Writing – review & editing. **Clive Roper:** Writing – review & editing. **Carl Westmoreland:** Writing – review & editing. **Emeline Gougeon:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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