

Five clear steps to modernising chemical safety regulation

Rebecca Ram and Rob Harrison report on a roundtable of specialists convened by Lush Prize in November 2024 which discussed ways to achieve a globally harmonised human-relevant regulatory framework for improved health and environmental protection.

May 2025

Executive Summary

There is an unprecedented level of global dialogue and activity on the need to transition towards scientific approaches in regulatory testing, biomedical research and education without animals, for scientific, economic and ethical reasons.

With specific focus on regulatory testing, there is also a recognised urgency to develop and adopt new non-animal approaches to improve sustainability. There is a need for robust and reliable safety information on many thousands of new and existing chemicals which, it is widely agreed, the current system cannot keep pace with to provide.[1] The tradition of using animals in toxicity testing over many decades has cemented a conventional view of them as the 'gold standard' in regulatory toxicology. However, in parallel, their reliability in predicting real world responses to chemical exposure has been increasingly criticised.

The purpose of this paper is to present an overview of the 'state of play' and current thinking on the way forward to achieve a fit-for-purpose, internationally-harmonised regulatory framework for *all* chemicals assessment, which is reliant exclusively on animal-free, human- and environmentally-relevant technologies and approaches.

We have also produced a simple summary of critical elements in a language that we hope is accessible to policymakers and others, at a time when there is a sense that regulatory and political inertia may be holding back progress, despite scientific innovation continuing to demonstrate how advances towards superior, animal-free approaches can be achieved.

This paper is designed to incorporate the consolidated feedback of a number of highly experienced, cross-regional stakeholders working in the field, from industry, regulatory and NGO sectors, who were consulted during a roundtable discussion hosted by the Lush Prize in November 2024. Attendees are listed at the end of the document and we are very grateful for their participation. Views expressed in this paper are not necessarily accepted by all attendees. This paper also refers throughout to recent publications on the issue of regulatory frameworks which were recommended at the roundtable or subsequently identified.

The Lush Prize acknowledges that there is ongoing debate on the definition of 'NAMs' (New Approach Methodologies)[2]. Its use in this paper refers to entirely animal-free methods (including free of animal-derived components) unless directly quoting from others.

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[1] The unknown territory of chemical risks | European Environment Agency's home page [Accessed 22/04/25]

[2] 'NAMs' - Background and definition - Lush Prize

The five ‘clear steps’

We have grouped together ideas from the roundtable into five main themes, each of which are discussed in more detail in the report below. Within each broad area we have also tried to identify one ‘easy’ or clear step.

This is a dense and nuanced field and progress has been highly commendable, though relatively limited to date. A multi-authored review between industry, academia and the UK’s NC3Rs in 2017 noted that:

> *“Despite the widely acknowledged benefits offered by NAMs, there continue to be barriers that prevent or limit their application for decision-making in chemical safety assessment. These include barriers related to real and perceived scientific, technical, legislative and economic issues, as well as cultural and societal obstacles that may relate to inertia, familiarity, and comfort with established methods, and perceptions around regulatory expectations and acceptance.”*[3]

‘Easy’ is perhaps a frivolous word to use in this context. However, we feel that for regulators and policymakers clarifying the next steps and actions that can be taken could make progress seem less daunting and so they are easy ‘asks’ with clear and entirely achievable actions that can be taken, particularly with regard to the United Kingdom, which is yet to publish any kind of roadmap or strategy, despite ongoing requests from Members of Parliament.

In addition, given the difficult economic backdrop at the time of writing, one key element in providing action steps is choosing some that would require little additional funding to achieve at this time. A key message throughout remains that diversion (rather than addition) of funding and resources would achieve the progress required.

1. A co-ordinated approach to communication

Clear Step: Facilitate early non-linear, multi-directional communication between method developers, policymakers, service providers and regulators to drive knowledge exchange, confidence building and effective risk management.

2. Future-proof the regulatory language

Clear Step: A ‘search and replace’ function should be applied across all legislation and regulatory guidance. It would search for any instances where specifically *animal* tests were required and replace them with more flexible, dynamic and test-agnostic wording like ‘use best science’.

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[3] Steps towards the international regulatory acceptance of non-animal methodology in safety assessment - ScienceDirect

3. A focus on change management

Clear Step: Develop a UK roadmap with targets and goals, incorporating a change management workstream. In February 2025, the UK Government stated that "*DSIT, Home Office and DEFRA ministers have agreed to publish an alternative methods strategy to support the development, validation and uptake of alternative methods and the phasing out of animal testing. We expect to publish this strategy later this year."*[4]

Establishment of a UK roadmap is a priority to align with similar approaches recently in the European Union and the USA.

4. Updating the validation process for new methods

Clear Step: As part of the revised communications strategy in Step 1, publish requirements for NAM developers on what decision frameworks or research studies will be needed for validation and acceptance of a particular method. This aligns with the critical need to 'start with the end goal in mind'.

5. A shift of focus towards risk management outcomes

Clear Step: Phase in requirement of AI-based 'next generation-risk assessments' in parallel to current test submissions to build confidence in this approach.

Progress is already being made

Despite the very real obstacles that continue to exist, this paper also aims to demonstrate that real progress is being made at least somewhere in the world in 2025 in each of the five areas identified.

For example, in the last few years, particularly in the field of acute toxicity, methods which have been successfully developed are available and in use. Key areas include skin sensitisation, eye irritation and corrosion, and skin irritation and corrosion. Some of these NAMs are considered to have superior predictivity to animal methods which are far more relevant to human biology, such as the defined approach (DA) for skin sensitisation [5].

Some of the success on these endpoints is in significant part due to the drive in innovation provided by the deadlines in Europe which banned animal testing for cosmetics[6]. Sustained scientific and lobbying initiatives have seen these new methods translated into regulatory policy and guidance within the US too and also as internationally harmonised

[4] Debate on an e-petition relating to the use of dogs in scientific and regulatory procedures - House of Commons Library

[5] Non-Animal Methods to Predict Skin Sensitization (II): an assessment of defined approaches - PMC

[6] The UK as a leader in non-animal NAMs for safety science; an evidence-based proposal using the cosmetic testing bans as a legislative framework.

OECD test guidelines that are now accepted worldwide, in use and of game changing benefit to industries well beyond the cosmetics sector.

1. A coordinated approach to communication

One key message from our roundtable discussion is that collaboration and communication between all parties from the outset is essential for change. All relevant parties - including, but not limited to, scientific method developers, regulators, policymakers and all downstream users including Contract Research Organisations (CROs) - should be involved from the start to ensure success.

Early communication between method developers and regulators is an element that was widely recognised as an important early step that should be taken.

1.1 The method developers forum in the USA

In the USA, the resource centres for alternatives to animal testing are NICEATM and ICCVAM. NICEATM (a department within the US National Institutes of Health) is a committee of 18 different US agencies, including the Environmental Protection Agency (EPA) and Food and Drug Administration (FDA), as well as many other federal agencies in both the research and regulatory spaces. NICEATM collaborates closely with its regulatory partners to identify new approach methods that are ready for use.

Furthermore, use of these NAMs can extend beyond toxicity testing into drug development for improving research and safety of therapeutics. This includes developing NAMs that can actually inform efficacy and the development of more effective medical interventions.

In March 2024 ICCVAM published a new guidance document on the Validation, Qualification and Regulatory Acceptance of NAMs[7] which represents consensus among all 18 federal agency members led by the EPA and, in follow up, the Method Developers Forum was established[8] to operationalise the guidance document and provide an interface between method developers and regulatory end users.

To maintain progress ICCVAM is requesting regulatory colleagues to pre-record presentations on the current requirements of their decision frameworks concerning specific toxicity testing endpoints. The process has started with carcinogenicity, to be followed by cardiac toxicity, developmental and reproductive toxicity and systemic toxicity. Regulators involved are contemplating how they currently assess those particular endpoints with regard to what data they use, how they integrate those lines of evidence and where there are opportunities for new non-animal methods. The presentations are available on the NICEATM website[9] and serve as pre-read guidance for method developers to present their methods.

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[7] Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies (ICCVAM 2024 Report)

[8] ICCVAM: Method Developers Forum

[9] NICEATM: Alternative Methods

1.2 ‘Safe harbours’ in the EU

A similar idea was discussed at an EU roadmap roundtable organised by five animal protection NGOs in June 2024, where it was suggested that a concept of ‘safe harbours’ be explored to provide spaces where safety assessments based on non-animal approaches can be discussed early in the regulatory process.

It was also suggested at this EU roundtable that “*The EMA’s* [European Medicines Agency] *Innovation Task Force could serve as a model regarding a ‘safe space’ for discussion between method developers, substance manufacturers, and regulators to help build confidence in non-animal approaches. To facilitate interactions between method developers, substance manufacturers and regulators, it is crucial to identify the barriers to the widespread use of ‘safe harbours’ and make the necessary adjustments. This would require fostering mutual trust between registrants and regulators based on confidence and transparency in using non-animal methods in regulatory submissions*.”[10]

1.3 ISTNET and DART

The ‘all on board early’ approach has seen progress elsewhere, for example a cross-regional stakeholder meeting (US-EU) to establish the International STakeholder NETwork (ISTNET) Workshop for Creating a Developmental and Reproductive Toxicity (DART) Testing Roadmap for Regulatory Purposes[11] is considered a good role model for ‘roadmap’ progress over the last decade, incorporating academia, industry and regulators to provide case studies for stakeholder overarching examples for the use of NAMs in regulation. Experts involved in the collaboration observe that as everyone was engaged from the start, there was no requirement to convince anyone ‘near the end’ as all were working towards the same goal. Work continues to see similar collaborative success in other areas such as reproductive toxicity, and allows regulators to see - and be involved in - how change can be achieved.

1.4 ReCAPP

Further examples of collaboration working in practice include the ReCAPP (Rethinking Chronic Toxicity and Carcinogenicity assessment for Agrochemicals Project)[12] which brought a number of experts together from Europe, the US and Canada to develop an approach which was ultimately put forward as an OECD case study proposal, to eliminate the rat cancer bioassay, widely considered controversial for years for three-fold concern over very high numbers of animals suffering, lack of human relevance and sustainability.

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[10] EU roadmap for phasing out animal testing for chemical safety assessments: Recommendations from a multi-stakeholder roundtable

[11] View of International STakeholder NETwork (ISTNET) Workshop for creating a developmental and reproductive toxicity (DART) testing roadmap for regulatory purposes

[12] Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project (ReCAAP): A reporting framework to support a weight of evidence safety assessment without long-term rodent bioassays

1.5 Communication strategy

One key message from the Lush Prize stakeholder discussion and literature reviews is that an improved multi-pronged collaboration and communication strategy is needed too. Improving crosstalk between 'research and regulation' is considered a major objective, but there are many other factors to consider.

Stakeholder opinion was that regulatory guidance documents are overly prescriptive of animal use (see section 5 below). Case studies, once developed, might be used as guidance or 'blueprints', to provide a working example (see the Emulate case study at 1.9 below). This could build confidence and legal certainty for both regulators and multinational companies. Again, the key requirement throughout is collaboration and multi-faceted partnership with regulators and downstream users to demonstrate and build confidence in innovation; for example, by combining new human-relevant methods (e.g. organ-on-a-chip) with artificial intelligence to build datasets which contain a high degree of rigour and experimental quality, to establish confidence in method use with both sponsors (e.g. chemical and pharmaceutical companies) and regulators.[13]

1.6 Engagement between scientists and service providers

Stakeholders at the Lush Prize roundtable also emphasised another important need alongside bridging the gap between the science and the regulators, which is the service providers, or contract research organisations (CROs). Engagement with the testing labs is key for real world application and downstream use, to make sure new methods are tangibly used. Therefore, recommendation for academic researchers and test developers to start early-stage communication with downstream users is critical when considering the need for presentation to regulators. Equally, there is a need for all to focus on the specific research objective or end goal, from the start and throughout the process.

1.7 International harmonisation and consistency

Lack of global consistency and a need for alignment strategies continues to be a major challenge, as highlighted by a number of roundtable stakeholders. There is an ongoing need for collaboration to achieve global standardisation, for example via more OECD guidelines (see also Section 3 below). Additional inconsistency continues where an alternative method is approved in one region, but not another; therefore, companies will still perform the outmoded animal tests. This has resulted in discussion of initiatives to achieve mutual acceptance of data (MAD)[14] and 'one substance one assessment' (OSOA)[15].

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[13] Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology - PubMed

[14] The Mutual Acceptance of Data (MAD) System | OECD

[15] Information session on 'one substance, one assessment' for stakeholders and citizens - European Commission

Stakeholders continue their work to address this, by reviewing key regional chemical markets by sector and country, and getting the relevant people 'in the room' to break down communication barriers. However, something can be successfully accepted and used in one region, but rejected or ignored in others. This 'in-silo' operation and lack of cross-talk can lead to a 'lose-lose' situation, resulting in duplication of both animal testing and validation of NAMs.

A notorious example is the one-year (chronic toxicity) dog test for pesticides which took two decades to remove from national and international legislation in the European Union, India, Canada, Japan, South Korea and Brazil[16]. Similarly, multi-stakeholder collaboration continues towards harmonisation for other tests, for example to see global deletion of the abnormal toxicity assay for biologicals and vaccines[17].

Further key examples include the very recent and potentially game-changing announcement by the FDA on its Roadmap to Reducing Animal Testing in Preclinical Safety Studies[18], which states that monoclonal antibodies (a class of biological drugs) will be the initial focus for the roadmap which will include 'exploration of pre-existing international data' and 'global leadership and harmonisation', among many other components. In alignment with the FDA announcement, the National Institutes of Health also recently stated its intention to prioritise human-based research technologies to reduce animal use.[19]

1.8 Cross sector alignment

Another important factor to address is that although there are numerous sectors, whether a cosmetic, drug, pesticide or other purpose of use, chemicals are chemicals and the toxicity is the same.

So, as well as cross-*regiona*l consistency, there is a need for cross-*sector* alignment, as a new approach may be used in one industry but not another. As we know, more progress has been seen in certain industries, for example cosmetics, which other industries continue to benefit from. However, other areas are lagging behind the transition towards NAMs, for example safety testing for medical devices.

There are now established ISO standards for medical devices which are not accepted in every country in the world. Stakeholders who work in this field to address this have been successful in making progress since 2021 on engaging with cross-regional regulators to

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[16] Breaking news: Brazil will no longer require one-year pesticide test on dogs; reforms will save animal lives in the country and in the U.S. | Humane World for Animals

[17] Accelerating Global Deletion of the Abnormal Toxicity Test for vaccines and biologicals. Planning common next steps. A workshop Report

[18] Roadmap to Reducing Animal Testing in Preclinical Safety Studies

[19] NIH to prioritize human-based research technologies | National Institutes of Health (NIH)

build consensus for acceptance of NAMs for medical devices and were awarded a Lush Prize in 2024[20].

1.9 Emulate Case Study

In the organ-on-a-chip arena, Lush Prize 2024 Science winner Emulate's[21] 'Liver-on-a chip' technology[22] has been in development for over 12 years, with significant progress in regulatory acceptance, including in 2017 the signing of a cooperative research agreement with the FDA (see also the timeline below) .

Emulate is the first company to see its technology now in the qualification plan stage of FDA's ISTAND program, and has also recently seen FDA-published papers on reproducibility and basic toxicology[23] [24]. Approval of a qualification plan could be one to two years away, the success of which would enable pharmaceutical companies to use Emulate's platform in regulatory documentation.

Emulate incorporated confidence building in its model by collaborating with pharmaceutical companies (Johnson & Johnson, AstraZeneca) for independent validation and use of blinded studies and third-party-selected compounds for unbiased evaluation to demonstrate the performance of the technology. Emulate is also investigating the potential to expand the technology to other organ systems (heart, kidney, brain) using the established framework.

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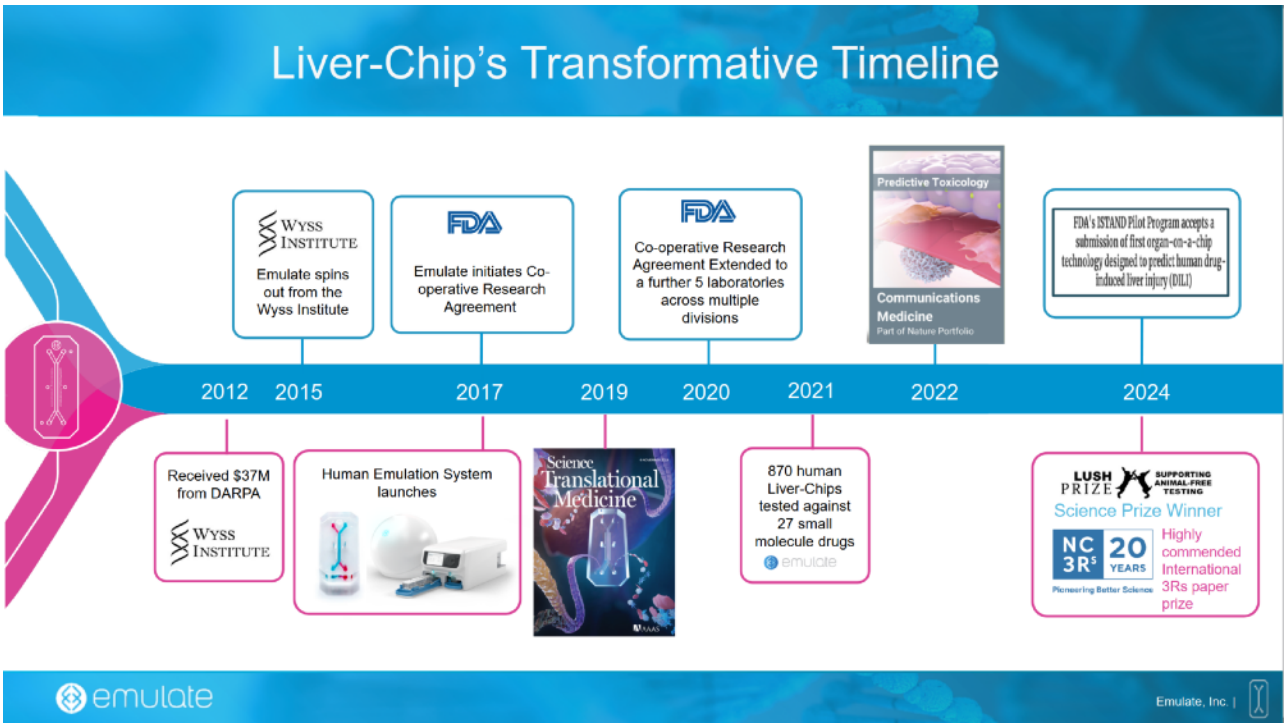
[20] 2024 Prize Winners - Lush Prize

[21] 2024 Prize Winners - Lush Prize

[22] Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology

[23] Utilization of a model hepatotoxic compound, diglycolic acid, to evaluate liver Organ-Chip performance and in vitro to in vivo concordance - PubMed

[24] Evaluation of the utility of the Beta Human Liver Emulation System (BHLES) for CFSAN's regulatory toxicology program - PubMed



2. A focus on change management

All stakeholders at our roundtable agreed that there is a need to shift focus towards implementation and change management, in parallel to the science. Not only should a change management strategy be implemented, but an understanding of why it is needed should be communicated multi-directionally, via support, guidance and training. This groundwork is considered vital to keep all relevant players engaged throughout the transition. It is also considered that any fit-for-purpose implementation strategy would include milestones and metrics to measure impact and progress.

2.1 Education and training as part of a robust change management strategy

Education and training are essential components of a change management strategy, whether for regulators, academics, method developers, chemical compliance officers, CRO end users and service providers, policymakers and many others. Training can also take many forms, for example providing 'hands on' training to individuals directly for new methods, to review and analyse the data produced from NAMs, or training for new early career regulators and researchers. Aside from more technical or science based training, there is an equally important ongoing need for training for a wide variety of audiences, for example (new) policymakers and associated staff, project managers, media, PR or administrative representatives, among many others.

Equally critical is the need to update or restructure training documentation or requirements to include non-animal methods as part of formal toxicology education or certification programmes. Roundtable attendees have achieved some success after sustained lobbying efforts to see non-animal methods recognised. However, they are still commonly optional or elective, while animal studies remain mandatory.

This is part of the need in education to challenge the misconception that NAMs are ‘nice to have’ or are at best, a ‘complement’ to animal studies.

2.2 An improved collective understanding of what is needed to achieve change

A key need to be addressed as part of the way forward is to develop a shared understanding of what is needed in order to overhaul and harmonise standards for chemical safety assessment.

Stakeholders at our roundtable broadly agreed that one first step should be to improve the collective understanding of all involved in how regulatory processes and information requirements work, including better context and understanding on how existing animal tests are currently used.

For example, some of the most controversial and traditionally used *subchronic* and *chronic* toxicity tests are currently used to derive toxicological points of departure (POD) (this is the point during the dose-response to a chemical which corresponds to a no observed adverse effect level (NOAEL), or lowest observed adverse effect level (LOAEL) which are used to establish a reference or benchmark dose). Roundtable stakeholders described how PODs are really based on non-specific endpoints in the vast majority of cases. This understanding could then be translated into opportunities to use NAMs (for example Adverse Outcome Pathways) to establish human equivalent doses as PODs, which can provide more clinically relevant, ‘real world’ exposure information than animal tests.[25]

2.3 Not a job for regulators alone

Some stakeholder opinion was also clear that while regulatory mobilisation to achieve acceptance is critical (and in fact central) to the process, all tasks cannot be considered to lie with regulators alone if the system is going to get the overhaul it requires. The idea that regulators always know how to adapt the system to make the best use of non-animal data is also a fallacy. Stakeholders also recount how, when asking regulators what they want, they don’t necessarily know what is out there or what requirements should be. In addition it is noted, resources in any environment are rarely enough to meet high pressure demands for change when considering recent roadmap initiatives or parliamentary mandates.

As one of the roundtable attendees put it: “*We can't just put the pressure on regulators and say it's their responsibility to reinvent the system. Ultimately, the pressure on them is enormous, and resources are scarce. I think what we need to do, and where I'm seeing real positive growth and movement, is to bring everyone around the same table*.”

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[25] Impact of High-Throughput Model Parameterization and Data Uncertainty on Thyroid-Based Toxicological Estimates for Pesticide Chemicals - PMC

2.4 Identifying information requirements

A ‘multi-player’ approach of collective knowledge at international level is important to define and establish the necessary changes. A key step to this would be for all players to reach consensus on what the information requirements should be, to then drive progress in assessment methods and classification systems. This is considered to be long overdue at the necessary scale and impact required. There is an ongoing need to get ‘regulators in the room’ for meaningful and informed discussion on all sides. Further to this, the regulators are not a single ‘entity’ and across different sectors it is very specialist and heterogeneous. This supports the urgent need to improve our collective understanding of what is required from all relevant stakeholders and legislation. During the roundtable, this was termed as the *‘3Ps - People, Processes and Principles’*.

There is no ‘one-solution-fits-all’. This is a dense and nuanced issue, which reflects the imperative to establish an overhauled, fit-for-purpose chemical safety strategy which a transition to non-animal approaches would bring. As highlighted in a recent study commissioned by the European Food Safety Authority (EFSA)[26], this is because many different decision-making contexts and processes exist, both within and across different chemical sectors, which are identified as one of the key challenges to overcome to allow transition to non-animal data and related assessment methodologies.

2.5 The transition process must improve to better comprise of both phase-in and phase-out

It is also important to note that for ‘transition’ to be complete it should comprise both phase-in of NAMs and phase-out of animal tests. Arguably until now it has only referred to the former. As a result, the last decade has seen unprecedented recognition and development of ‘NAMs’, yet numbers of animals used in safety testing largely remain unchanged or increase in certain areas, for example in testing for REACH purposes[27]. Furthermore, once a new non-animal test is available, any corresponding animal method could be actively retired by deletion from regulations or guidance documents. This helps move towards a more simplified regulatory system too.

2.6 Risk aversion, fear of change, altering mindsets and generational progress

Stakeholders at our roundtable generally agreed that there is a need to strike a balance between i) innovation, growth and flexibility of use in NAMs and ii) legal certainty for companies and regulators.

Regulators are necessarily conservative due to safety concerns. Risk aversion, uncertainty and ultimately fear of change are also key barriers to altering mindsets and

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[26] Mapping of Data Requirements and Assessment Methodologies Linked to the Regulatory Frameworks and Remits of the Relevant EU Agencies (ECHA, EFSA and EMA) and EC Scientific Committees (SCCS and SCHEER) | EFSA

[27] View of New European Union statistics on laboratory animal use – what really counts!

arguably are used as reasons to avoid adopting NAMs. The response to address this might be seen as two fold:

1) *The current system*: Balanced information is important. Risk and uncertainty are routinely mentioned in reference to NAMs, yet risk and uncertainty already exist in animal tests used for decades, and upon which millions continue to be spent. This can often go relatively unmentioned in comparison.

2) *A redefined system:* We talk more about this in Section 3 on validation below.

2.7 Understanding the role of phase-out deadlines in change management

At least one stakeholder at our roundtable felt that ending regulatory testing on animals by implementing legislative bans with future deadlines was the best way to ensure the required focus needed for the scientific and regulatory communities to find the solutions required.

We have seen that two previous campaigns to see deadlines imposed (e.g. 'Netherlands 2025', 'US EPA 2035') have later been sidelined or weakened, though promisingly, a proposal to reinstate the 2035 deadline was recently announced by the EPA[28].

Evidence of the ability of forthcoming deadlines to drive change was seen during the EU cosmetics testing bans. They stimulated scientific innovation in alternative methods of benefit to industries well beyond the cosmetic sector. They also created political will to see bans implemented to end animal testing far outside EU borders.[29]

2.8 Economic and logistical issues in change management

The current system is based on a conventional 'tick box' menu of tests and a long entrenched, company 'supply-and-demand' driven business infrastructure which needs to change too. It is important to remember this alongside more frequently cited scientific, legal and ethical factors.

Therefore, if a non-animal method isn't being demanded from a CRO, they are not going to offer it, and particularly not at a competitive price, as their main goal is to trade as a service provider for industry.

For companies and CROs to act and invest in new methods, they have to be cost-effective for them. Therefore, if a new non-animal method isn't considered a full replacement for any current animal test they are using, they are likely to continue using the latter alone, rather than purchase 'complementary' non-animal methods if they are not required, so the transition overhaul needs to consider this.

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[28] EPA chief Lee Zeldin eyes ban on animal testing - Washington Times

[29] The UK as a leader in non-animal NAMs for safety science; an evidence-based proposal using the cosmetic testing bans as a legislative framework.

There are other practical barriers to consider too, given that most methods developed and for sale are predominantly in the EU or US. This presents a further barrier for newer economies being able to afford to purchase the methods in Euros or US dollars. Even when methods/supplies are purchased, time taken for delivery, customs checks and other logistics may mean the method (e.g. a tissue culture kit) has expired and the components may no longer be viable for use when it reaches the lab.

That said, it is important to recognise entirely preventable obstacles in more established economies too. For example, senior researchers and professors in UK and US universities and hospitals have noted the logistical difficulties in securing widely available human tissue as waste products from surgery, which can replace animals[30]. Patient consent is required for this tissue to be used, but this is not usually an issue as patients rarely object if they can aid research and the tissue is going to be discarded in any case. Instead, the tissues often cannot be acquired simply due to lack of organisation of timings or bureaucratic hurdles from 'operating theatre to lab', even if they are only a few doors away from each other.[31] [32]

2.9 Roadmaps as part of formal change management strategies

Roadmaps have become a popular way to try to formulate and share change management strategies for modernising chemical safety testing around the world. Defined goals, objectives and metrics for measuring progress are always key elements of roadmaps.

Lush Prize produced a paper on this subject in February 2024 which identified eight roadmaps published or in progress in Europe and the USA since 2015.[33] The current EU roadmap consultation is probably the largest and most complex project of this type and is generating a lot of its own literature.[34]

Generally speaking, a roadmap on its own will not drive change and some kind of small secretariat and administrative resource is usually required to keep attention focussed. As stakeholders in our roundtable pointed out, work on trying to modernise the system is still often done in 'spare time' by those with a scientific, ethical or political interest in driving change, which is unlikely to be enough in the longer term.

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[30] The Use of Human Tissues for Research: What Investigators Need to Know - PMC

[31] Timing of consent for the research use of surgically removed tissue - Hewitt - 2009 - Cancer - Wiley Online Library

[32] From 'Consent or Anonymise' to 'Share and Protect': Facilitating Access to Surplus Tissue for Research Whilst Safeguarding Donor Interests - PMC

[33] A Roadmap for Modernising Chemical Safety Testing in the UK (2024)

[34] EU roadmap for phasing out animal testing for chemical safety assessments: Recommendations from a multi-stakeholder roundtable

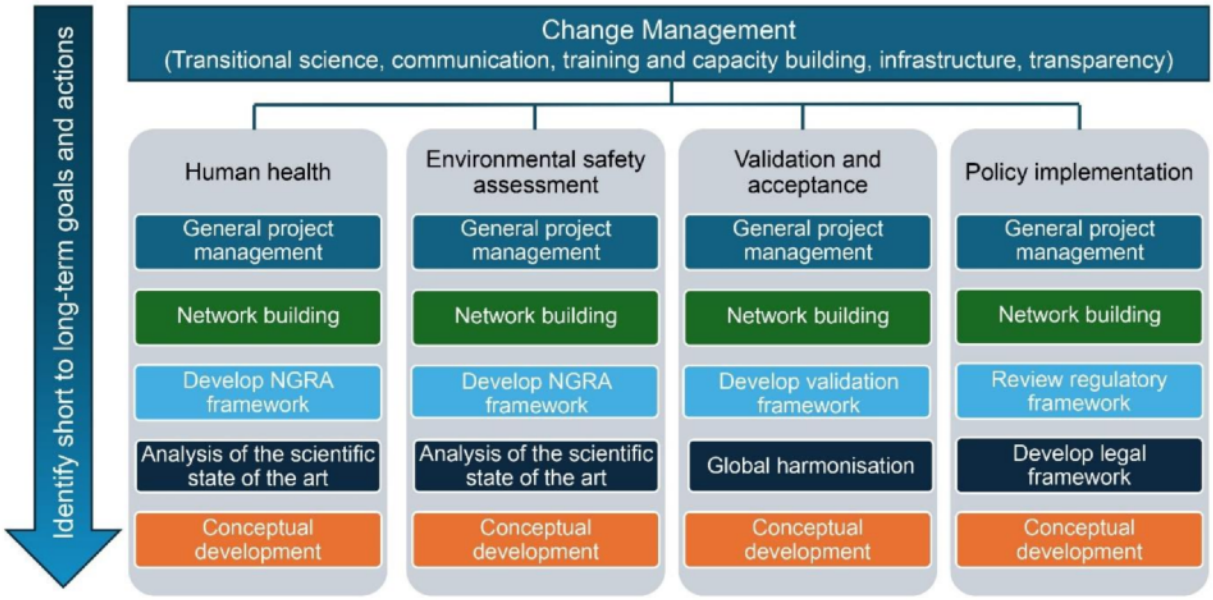


Fig. 3. Illustrative framework integrating the Commission, Partnership for the Assessment of Risks from Chemicals (PARC), and change management approaches highlighting the importance of avoiding siloed operations and fostering collaboration across working groups and positioning change management as an overarching element

Image: A graphic change management plan recently published in Walder, L. (2025). EU roadmap for phasing out animal testing for chemical safety assessments: Recommendations from a multi-stakeholder roundtable.[35]

3. A next-generation validation process

3.1 Background to validation, qualification and acceptance of new methods

Test method validation is a process based on scientifically-sound and independent evaluation that establishes the reliability and relevance of a particular test approach, method or process for a defined purpose. A standardised process for validation is widely considered essential to a harmonised, international system for regulatory testing too.

Over the last decade this has been actioned via development of standardised test guidelines, for example at OECD level for chemicals assessment, or ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines for pharmaceuticals testing.

Validation of new non-animal methods has traditionally been performed against ‘animal models’ as the ‘gold standard’. As a result the validation process can be prohibitive, difficult and time consuming.

Where new methods have been accepted, it has often taken decades to see meaningful impact. For example, the Monocyte Activation Test (MAT)[36] which replaces an in-vivo

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[35] EU roadmap for phasing out animal testing for chemical safety assessments: Recommendations from a multi-stakeholder roundtable

[36] Pyrogen testing revisited on occasion of the 25th anniversary of the whole blood monocyte activation test - PubMed

pyrogen test, has now replaced the use of 170,000 rabbits per year in Europe. But this took 35 years to achieve and incredulously, due to lack of regulatory application and enforcement of the MAT test, rabbit use for pyrogenicity testing even *increased* after it became available for use[37].

This has resulted in a collective view within the 'NAMs community' that establishing an overhauled 'next generation validation' process is required as one part of achieving the new paradigm for next generation risk assessment (NGRA).

NAMs can and must be assessed on their own scientific and commercial merit for the mechanistic information and human relevance they provide. This is long overdue in areas where animal-based methods as a 'gold standard' do not exist, to prevent available NAMs getting overlooked or sidelined.

Cost of validation is also a critical issue and barrier to progress. In a 2023 workshop hosted by the OECD (WNT - Working Party of the National Coordinators of the Test Guidelines Programme) the operational and financial aspects of validation were discussed, including "*the organisational complexity, the specialist competences required, and the high costs involved*.' According to the workshop report, a "*rough estimation shows that depending on the complexity of the method and the number of chemicals to be used in a validation study, at least 200-500K EUR are necessary to cover expenses of the lab costs to validate a method."*[38]. Data management, data review, study management, and in-kind contributions of participating labs when the study is under-funded (both personnel time and reagents) may be additional too.

As part of an improved collective understanding, there is a need to rewrite standards which leave the 'yes or no' binary philosophy of animal tests behind, to embrace a more progressive approach to assess the complexities and heterogeneity of human safety, which combinations of non-animal methods can better address, in order to meet 'real world' safety requirements. (Also see focus on risk in Section 4 below).

3.2 Publicly available framework for method developers on validation

Many stakeholders at our roundtable also agreed that regulators need to provide (and to some extent be *enabled to* provide) clear frameworks to evaluate new technologies, as lack of such guidance slows adoption.

Method developers state that there is a need for a publicly available framework from regulators on what their expectations are for validation of new technologies. Collaboration and communication are key to empower regulators to provide what is needed.

'Qualification' refers to the specific context of use of a test method for human medicines. Advice on qualification is provided by the EMA Committee for Medicinal Products for Human Use (CHMP) opinions. In-house/technical validation is required, but 'formal'

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[37] Food for Thought… The Human Whole Blood Pyrogen Test – Lessons Learned in Twenty Years

[38] 4.4. EC roadmap_phasing out animal testing_Dec 2023_ OECD Anne Gourmelon.pdf

validation isn't mandatory for qualification. Stakeholders involved in method development emphasised that there was a lack of clear guidance on qualification requirements for new technologies[39]. There have not been any CHMP qualification opinions issued yet for non-animal test methods. However, stakeholders pointed out that some models are currently undergoing the qualification process (see the Emulate case study below).

3.3 Funding for science should include validation too

As described in the European Commission document 'International Test Guidelines, Validation, Qualification and Standardisation'[40], accompanying the second workshop on the roadmap towards phasing out animal testing for chemical safety assessments which took place in October 2024, "*over 1 billion Euros have been invested in non-animal methods from EU frameworks over the last 20 years. However, the translation of these methods into ones accepted for regulatory use, like OECD Test Guidelines (TGs), has been extremely limited."*

It also notes that there may be diverse reasons for this *"but it can be observed that EU funded projects invest very little in validation activities since there is little incentive to do so, although a lot of attention has been given to the development of conceptual testing strategies and demonstration through case studies. The work packages 5 and 6 of PARC (Partnership for the Assessment of Risks from Chemicals)* [41] *will contribute to the validation and regulatory readiness of new methods and approaches."*

OECD Guidance Document (GD) 34 has been a key driver of validation and acceptance. As noted in workshop documents described above, GD34 is "*out of date with regard to progress in toxicology and the technology and science on which many of the NAMs are now based, in addition the process is too slow to be fit for purpose. The principles of validation as defined by GD 34 are universal, however the overall context has changed. There is an ongoing effort to update GD 34 (Project 5.7 on OECD workplan, foreseen to conclude in 2025*)."

At our roundtable, stakeholders emphasised the importance of recognising that formal validation studies have typically been more than 'just' validation studies. This means that beyond assessing the 'reliability and relevance' of methods, they have also acted as a focus and 'gathering point' for proposing regulatory use and facilitating acceptance, and so for validation *per se* to be made more efficient, the scope of studies would have to be restricted to scientific and technical objectives. However, then validation as the critical path from development to regulatory application may be diminished.

As described earlier, there is no 'one-size-fits-all' in any part of a new human-relevant testing paradigm, and industry stakeholders emphasised that from a testing lab

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[39] During our consultation and roundtable in November 2024

[40] Roadmap for phasing out animal testing in chemical safety assessments: second workshop - European Commission

[41] Partnership for the Assessment of Risks from Chemicals | Parc

perspective, there may be a need for flexibility and a common sense approach to allow adaptation of the validation process to suit specific circumstances, laboratory size and resources. For example, where a smaller scale but robust in-house testing system shows a new method to be reliable and human-relevant (for example, against a small subset of chemicals), the requirement to conduct expensive, large scale validation studies against several hundred substances and 'validate' against animal tests can be prohibitive to the new non-animal method being accepted and used.

3.4 The role of the OECD

As described in the earlier European Commission document [35] "*Over the past 25 years, validation studies have been conducted with the aim of developing OECD TGs. As a result, 'validation of a method' is often understood as 'development of an OECD TG', even though this conflates the scientific process of validation with the more political one of acceptance*".

As a result, 'science vs politics' has meant that validation may only be performed if there was sufficient international interest from regulators in developing an OECD Test Guideline. This is facilitated by the OECD WNT. However, stakeholders at our roundtable noted that this has proved useful in the past and that the two processes coupled together have driven more recognition of new methods to some extent.

Another key issue raised as a major bottleneck is the need for 100% consensus at OECD level, given the different experience, awareness and opinions of experts involved in new method approval.

It's also important to acknowledge the differences between pharmaceuticals and other regulatory chemicals. In the document accompanying its 2024 meeting, 'Maximising NAM uptake under existing EU Pharmaceutical Regulations' [42], the EPAA (European Partnership for Alternative Approaches to Animal Testing) describes how "*The pharmaceutical sector is less reliant than other sectors on OECD test guidelines, as there are a set of internationally harmonised guidelines specific to medicinal products; the ICH guidelines in the case of human medicines, and VICH in the case of veterinary medicines".*

3.5 Encouraging use once validation has occurred

An important point to emphasise is that *acceptance* and *use* of a method are very different, but to some extent have been perceived to be the same in the past. When a method is accepted, it needs appropriate guidance on how it should be applied and its context of use. As highlighted in the documents accompanying the second European Commission workshop on the 'Roadmap for phasing out animal testing in chemical safety assessments'[43] (specifically with regard to how to accelerate the global adoption of non-

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[42] Maximising NAM uptake under existing EU Pharmaceutical Regulations

[43] Roadmap for phasing out animal testing in chemical safety assessments: second workshop - European Commission

animal methods) such a process is provided by the International Organisation of Standardisation or the European Committee for Standardisation (CEN)[44]. These can offer significant business advantages, including connection of information requirements with standard tests, quality assurance and legal certainty and efficiency in submission and assessment for both regulators and companies.[35] This can lead to international reuse of data across sectors, a concept agreed by the OECD known as 'Mutual Acceptance of Data', based on consensus of the need for - and confidence in - any proposed test(s) from the OECD Working Group of National Co-ordinators for Test Guidelines (WNT).

However, it is also noted that CEN is '*comparably less used to date*' in standardising and approving test methods, (whether non-animal or animal-based), in comparison to conventional OECD and ICH guidelines for chemicals and human medicines respectively[35]. Furthermore, CEN is considered to have setbacks, including a lengthy prohibitive timeframe and the requirement of 100% (rather than majority) consensus from the WNT for method approval. The obstacle of 100% consensus was noted by stakeholders earlier in this paper.

As one of our roundtable panellists emphasised: "We have to go beyond validation. It is not only about guidelines, it's about supporting quality assurance, best practices, and good practices. Whatever we want to call them, there's a lot to be done in this space."

4. A shift of focus to risk-management outcomes

There is a widely accepted need to continue to disrupt the assumption that animal tests can provide 'gold standard' of safety assurance. All attendees at our roundtable pointed to a number of projects and literature that sought to answer the question 'what is the risk that this chemical will damage human or environmental health?' in a completely different way. Artificial intelligence-based (AI) approaches (such as the advance in Digital Twin technology) and microphysiological systems (MPS or 'organ-on-a-chip), in combination with other approaches, are creating major change in this field.

4.1 Chemicals 2.0

The European Commission Joint Research Centre (JRC) proposes how this could be achieved via their Chemicals 2.0 strategy[45] which explains how focus on risk management outcomes as a redefined 'gold standard' would provide a more efficient safety assessment than the traditional apical outputs provided by animal tests. Furthermore, it could improve protection of human health and the environment and provide a pragmatic, real world system via classification and labelling and risk assessment, which identifies less hazardous chemicals.

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[44] About CEN - CEN-CENELEC

[45] Chemicals 2.0 and Why We Need to Bypass the Gold Standard in Regulatory Toxicology

4.2 The exposome and the IMPACT project

In a recently launched US-EU collaboration headed by the Center for Alternatives to Animal Testing (CAAT) and including the FDA and others, the Implementation Moonshot Project for Alternative Chemical Testing (IMPACT)[46] proposes focus on the *exposome* - a concept used to describe the 'real world' environmental impact of both internal and external factors on an individual throughout their life, including chemical, physical, biological and social factors[47]. It parallels the relevance and transformative success of the Human Genome Project.

The overall goal of the IMPACT project is to transform toxicity testing from outdated apical poisoning tests in animals to exposure-based mechanistic data, to deliver improved human relevance. As outlined recently in the AMA Journal of Ethics, widespread adoption of chip models "*is hampered by public opinion and lack of scalability, standardization, and current regulatory uptake*"[48]. The IMPACT collaboration aims to change this.

The IMPACT project has a research collaboration agreement with the FDA to provide training in new methods to enable confidence building, trust and visibility to extend such activities further, for example from drug testing to other sectors such as pesticides.

4.3 AI and big data

The concept of AI and big data has emerged and gained a stronghold in the NAMs community in recent years. Stakeholders at our roundtable also stated how, alongside NAMs, use of previously available human data must be maximised: "*We need to discuss how to handle AI, but also how we can deploy AI to improve the validation process*".

The FDA wrote in 2025: "*Overall, in silico NAMs may act as powerful adjuncts or replacements for animal studies by predicting human-relevant outcomes through data and modeling. They are rapid, cost-effective, and can integrate vast amounts of existing knowledge – for instance, an AI model might instantly compare a new drug to hundreds of prior ones to assess risk, something impossible with animal testing alone. Importantly, as regulators gain confidence in these tools (through retrospective validation and prospective pilot use), they could be formally adopted to reduce or replace specific animal tests."*[49]

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[46] The Implementation Moonshot Project for Alternative Chemical Testing (IMPACT) toward a Human Exposome Project - PubMed

[47] The exposome : a new paradigm for the environment and health | WorldCat.org

[48] Which Concepts Are Key to Transitioning From Nonhuman Animal Models to Engineered Microphysiological Systems in Biomedical Research? | Journal of Ethics | American Medical Association

[49] Roadmap to Reducing Animal Testing in Preclinical Safety Studies

4.4 Evidence-based Toxicology Collaboration

The evidence-based toxicology collaboration (EBTC)[50] has engaged over recent years in ongoing evidence-building via systematic reviews. It has provided a parametric of objectively- and transparently-handled information and methodologies, which stakeholders consider are all vital tools which must be more formally linked together.

4.5 AOPs and weight of evidence (WoE)

Publications include many collaborative efforts across government, academia, and industry on both reviews of current NAMs available and the need to develop more. Ways to integrate NAMs as part of weight-of-evidence (WoE) approaches for hazard or risk assessment are proposed, for example by making use of the Adverse Outcome Pathway (AOP) framework.[51]

4.6 Next Generation Risk Assessment (NGRA)

NGRA is "an exposure-led, hypothesis-driven risk assessment approach that incorporates one or more NAMs to ensure that chemical exposures do not cause harm".[52] The hypothesis underpinning NGRA is that if there is no bioactivity observed at human-relevant concentrations, there can be no adverse health effects. At no point does NGRA attempt to predict the results of high dose toxicology studies in animals that were first used in the 1960s.

5. 'Future-proofing' the regulatory language

5.1 Test requirements

It is acknowledged that some regulations are to some extent inclusive of human-relevant approaches, for example the EU pharmaceutical legislation. How this manifests 'on-paper vs in-practice' is usually dependent on associated guidance or policy documents. There are situations where guidance actually goes beyond the regulatory framework and these are important to be aware of.

Another example is Annex XI of the REACH legislation which in principle allows adaptation of standard testing requirements to accommodate non-animal methods. However, this leads to grey areas with regard to those making the decisions at regulatory agencies and whether they will accept non-animal methods or request animal studies, the latter still being requested far more often than not, a decision at least in part due to years of animals as the conventional (rather than scientific) choice: *" Animal testing - an eonian path dependency - is an ongoing reminder of the generational harm a society endures*

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[50] Time for CHANGE: system-level interventions for bringing forward the date of effective use of NAMs in regulatory toxicology | Archives of Toxicology

[51] Frontiers | Adverse Outcome Pathway Development for Assessment of Lung Carcinogenicity by Nanoparticles

[52] Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

because of past decisions too difficult to rectify. Indeed, path dependency associated with animal testing has proven to be among the hardest to overcome".[53]

5.2 'Find and Replace'

Popular at our roundtable was the suggestion that progress could be achieved quickly by updating legislation to request the 'best science' as a minimum, rather than be prescriptive of either animal tests or specific NAMs. Several roundtable stakeholders agreed that the potential benefits of such a policy which allows a 'test-agnostic' or 'test-neutral' approach may be seen as the most pragmatic way forward to see NAMs being used more.

As one of panellists said: "If I had a magic wand, what I would like to do is have a find and replace function where I would be able to, in one field, look across all legislation and regulatory guidance and find any instances where it was prescriptive and said you had to use animal testing methods and somehow replace that with something test agnostic, something like 'use best science'."

Stakeholders on the roundtable involved in lobbying for reform described that they consistently hear of 'open door' attitudes from regulators on discussion and acceptance of NAMs, but that in practice it's a different story. For example, many of the written FDA policies on drug development are not flexible at all. Some may say 'animal or in-vitro', but none account for in-silico and some require only animal data. This inconsistency has created a situation where regulatory affairs representatives may think animal tests must be done.

It is accepted that an overly prescriptive and static regulatory framework risks becoming obsolete as the landscape evolves. Having method neutral language is a change that would future-proof current regulations while solutions and advances in science continue to develop.

5.3 The Vanda Case

Collaboration, with scientists interacting with the agencies case-by-case, is essential to try and overcome the view that animal tests must always be done. However, there are rarely incentives to do so and it is sometimes considered an uphill battle, especially in light of a recent notable example of a company (Vanda Pharmaceuticals) which took a stand and proposed to avoid a nine-month-long chronic toxicity test in dogs that they did not think was necessary for their gastroparesis drug, Tradipitant.

The FDA however insisted on the additional dog study being carried out, which Vanda have continued to refuse to do, on the scientific basis that it adds no relevant data for patients.[54] (It must also be noted that Vanda carried out earlier animal studies in accordance with FDA requirements). To date, more than a thousand people have been treated with Tradipitant, many of them for up to three months. Further, patients are

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[53] Path Dependency and the Maiming of the Biomedical Research Enterprise

[54] Vanda Pharmaceuticals Takes a Stand Against Unnecessary Animal Research

currently treated through an expanded access program, some for more than a year. Vanda has conducted two placebo-controlled studies and one open label study to study the efficacy and safety of Tradipitant in gastroparesis. The long standing legal case continues and as of January 2025, Vanda accepted an FDA Opportunity for a Hearing on a New Drug Application (NDA) for Tradipitant [55]

5.4 Revised wording for endocrine-disrupting chemicals (EDCs)

More encouraging are the development of new information requirements (or updates to existing ones) and guidance documents and processes on how methods can actually be used. A recent example is a collaboration between ECVAM, EFSA (the European Food Safety Authority), ECHA (the European Chemicals Agency), the European Commission and Member States to redefine criteria for endocrine-disrupting chemicals under the revised classification labelling and packaging (CLP) regulation, so that the legislative wording allows data obtained from non-animal approaches.

[55] Vanda Pharmaceuticals Accepts FDA Opportunity for a Hearing on New Drug Application for Tradipitant in Gastroparesis

Glossary

Acronym	Description
AOP	Adverse Outcome Pathway
CRO	Contract Research Organisation
DA	Defined Approach
DEFRA	Department for Food, Environment and Rural Affairs (UK)
DSIT	Department for Science, Innovation and Technology (UK)
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemicals
EMA	European Medicines Agency
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
In-silico	Methods conducted or produced by means of computer modelling or computer simulation
In-vitro	Methods conducted using e.g. microbiological, cell or tissue samples, organoids or others which may be human or animal derived. In vitro methods range from simple cell culture to advanced methods including (but not limited to) 3D organoids or organ on a chip models.
In-vivo	Study in a living system, usually refers to animal studies but can refer to human in vivo (e.g. clinical trials)
NAMs	New Approach Methodologies
NDA	New Drug Application
NGO	Non Government Organisation

NICEATM	The NTP (National Toxicology Program) Interagency Centre for the Evaluation of Alternative Toxicological Methods
OECD	Organisation for Economic Co-operation and Development
Organ-on-a-Chip	An organ-on-a-chip (OOC) is a type of advanced in vitro research model, using multi-channel 3D microfluidic cell culture, integrated circuit (chip) that simulates the activities, mechanics and physiological response of an entire organ or organ system.
WoE	Weight of Evidence

Methodology - Stakeholder roundtable consultation and literature review

This paper incorporates feedback from a number of stakeholders representing industry, academia, policymakers and NGOs who were consulted during an online cross-regional roundtable discussion (UK, EU, USA, Canada) hosted by the Lush Prize in November 2024, and individual follow up meetings as required (November 2024).

Attendees at the roundtable:

Julia Baines - PETA Science Consortium International e.V.
Elizabeth Baker - Physicians Committee for Responsible Medicine
Karl Bygrave - Lush Cosmetics
Ellen Fritsche - Swiss Centre for Applied Human Toxicology
Thomas Hartung - Centre for Alternatives to Animal Testing, Johns Hopkins University
Nicole Kleinstreuer - National Institute of Health, NICEATM
Gavin Maxwell - Unilever / European Partnership for Alternative Approaches to Animal Testing
Christian Pellevoisin - ISO Working Group ISO/TC-194/WG8
Troy Seidle - Humane World for Animals
Carol Treasure - XCellR8
Maurice Whelan - Joint Research Centre, ECVAM

Lorna Ewart from Emulate was consulted in a separate call

The questions we asked stakeholders at the roundtable were as follows:
• *How much of the problem now lies with regulatory challenges?*
• *How do blocks happen?*
• *Is looking for equivalence to animal-based models as the 'gold standard' still the major obstacle?*
• *How does validation remain a 'critical path' challenge?*
• *What three things could policymakers do to help?*
• *Is there best practice in any one region? What are the opportunities for regional best practice, harmonisation and consistency?*