30 June 2026
EMA/149393/2026

Information about the Voluntary Data Submission pilot

Data sharing on New Approach Methodologies under voluntary submission

The purpose of this document is to provide an overview of the Voluntary Data Submission (VDS) pilot on the submission of data on New Approach Methodologies (NAMs) within selected contexts of use (CoUs) and broader regulatory applicability areas (RAAs). Through the pilot, companies, contract research organisations, method developers, and other stakeholders are invited to submit NAM data for review and discussion independently from a Marketing Authorisation Application (MAA) and as a voluntary, non-binding and non-decisional mechanism that does not replace or interfere with existing regulatory procedures.

Definitions

New approach methodologies (NAMs)* *are defined as innovative test methods or testing approaches aimed to progressively replace, reduce, and refine (3Rs) traditional animal studies. These include in vitro, in silico, in chemico, ex vivo, refined in vivo and other advanced biology-based approaches and structured combinations of these (e.g. Weight of Evidence approaches). NAMs are designed to generate data that provide an equivalent or improved translation to support human or target species-relevant regulatory decision making.*

*****The NAM definition provided is still provisional pending the finalization of the Glossary in the context of the ongoing revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches.

Weight of evidence (WoE) *approaches are considered as flexible, qualitative or semi-quantitative expert-judgement-based approaches that integrate and weigh relevant evidence from various existing (e.g. peer-reviewed scientific publications, "legacy" data) or newly generated data sources. The data can include, but are not limited to, physicochemical methods, in silico models, grouping and read-across*

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approaches, in vitro methods, ex vivo methods, in vivo tests and human data. WoE approaches can inform regulatory decision-making, and, where required, guide the targeted generation of new data.

Context of use (CoU) *defines the specific intended application of a 3Rs testing approach or NAM in medicines development or regulatory assessment, and the conditions under which it can inform regulatory decision making. The CoU should:*

- *Specify the regulatory use or decision context in line with the stage of medicines development in which the NAM is intended to be applied (e.g. for discovery, to support first-in-human or later stage clinical trials or marketing of a medicinal product)*
- *Define the relationship of the test method to the endpoints of interest including biological plausibility*
- *Define the applicability domain and limitations of the above to ensure the NAM is applied within the defined CoU*

Background

The Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012) introduced the safe harbour approach of voluntary submission of data. Under this framework, data generated using novel 3Rs testing approaches may be submitted alongside data from established methods to support a MAA. The safe harbour was intended to support the evaluation of innovative 3Rs testing approaches for potential future regulatory acceptance, including the definition of an appropriate context of use and the assessment of methodological readiness and limitations. Importantly, it was also conceived as a means for regulators to gain experience and confidence in data generated by novel approaches.

Despite this intent, the safe harbour procedure has seen little to no uptake since the publication of the guideline. As a result, practical experience with NAMs within the EU regulatory system remains limited, and key questions related to feasibility, incentives, data handling, and regulatory added value remain unexplored. While industry has substantial in-house expertise and routinely applies NAMs in early-stage drug discovery and development, data sharing with regulators is typically limited to case-by-case interactions, mainly to support WoE approaches, especially in toxicological assessments. As NAMs are not part of regulatory-required testing, the associated data are often not included in clinical trial applications (CTAs) or MAA dossiers. When shared, NAMs data are frequently provided for information only and without sufficient contextual or supportive background to enable systematic regulatory learning. Although qualification activities for NAMs are increasing, many NAMs with potential regulatory relevance remain insufficiently visible or characterised within the regulatory framework. Therefore, there is the need for practical mechanisms that can lower barriers to data sharing and enable structured, non-decisional exchanges between NAMs developers/end-users and regulators.

In this context, EMA is launching a pilot project to reshape the safe harbour into a VDS framework, which is proposed as an exploratory step to test the feasibility, scope, and added value of voluntary NAMs data submissions outside the context of an MAA. The pilot aims to generate practical experience, identify operational and scientific challenges, and gather evidence to inform the possible development of a more structured and sustainable VDS framework in the future.

Objectives and expected benefits

The VDS pilot is intended to support the evaluation and regulatory integration of NAMs through the following objectives:

- Enhancing understanding and confidence in the assessment of NAMs data
- Providing a platform to discuss developer’s proposals on NAMs, CoUs and RAAs under the VDS framework

- Reviewing submitted NAMs data and associated documentation within predefined CoUs and broader RAAs;
- Identifying scientific and regulatory challenges with regards to regulatory use of NAMs data, including uncertainties and limitations, and discussing opportunities for integration of NAMs data within WoE approaches;
- Providing non-binding scientific feedback to NAMs data submitters on the potential regulatory relevance and 'fitness for purpose' of the submitted NAMs, including considerations on possible follow-up interactions with EMA regulatory pathways and procedures such as Innovation Task Force (ITF) briefings, Scientific Advice (SA) or Qualification Advice (QA);
- Contributing to the harmonised interpretation of NAMs data and WoE approaches across the EU network by promoting consistent scientific and regulatory approaches to the assessment of NAMs submissions;
- Supporting the preparation of an aggregated lessons-learned report and dissemination of outcomes after an initial pilot phase;
- Formulating proposals for and, where applicable, contributing to training activities for the network;
- Assist in the provision of the regulatory support and scientific advice to facilitate the development, validation and regulatory uptake of NAMs, in line with Article 138(zi) of the NPL

The VDS pilot is expected to provide benefits at both a general regulatory level and at the level of individual submissions.

Strategic regulatory benefits:

- Provide a flexible entry point for NAMs data outside formal MAA procedures
- Enable early and iterative dialogue between regulators and stakeholders
- Support development of CoU-based criteria for NAMs
- Strengthen regulatory understanding of NAMs development and applications
- Foster mutual learning and a more predictable pathway towards qualification and regulatory acceptance of NAMs

Submission-specific benefits:

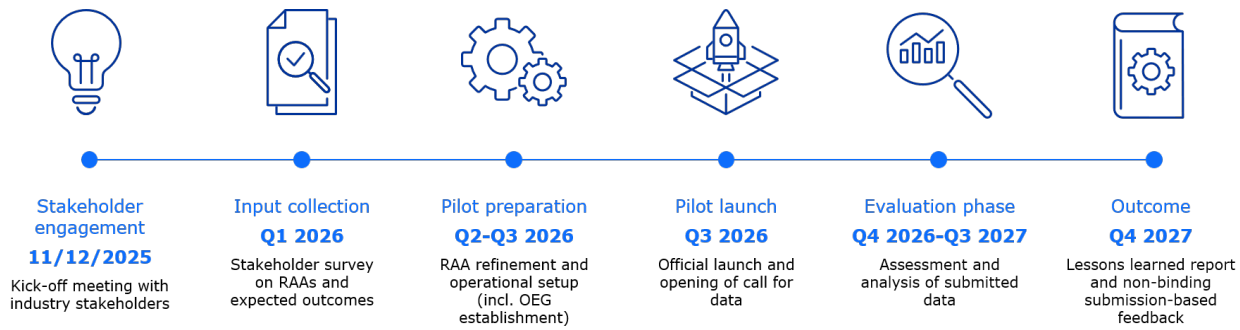
- Provide early and non-binding regulatory and scientific feedback to NAMs data submitters
- Assess the regulatory relevance, strengths, and limitations of submitted NAMs within defined CoUs
- Provide guidance on possible follow-up interactions with EMA regulatory pathways and procedures such as ITF briefings, SA or QA

Timelines

The pilot was presented during an introductory (kick-off) meeting with industry stakeholders on 11 December 2025. During this meeting, it became clear that additional input from industry was needed to clarify and prioritise relevant RAAs to ensure that the pilot remains focused and meaningful.

To support this objective, EMA circulated a stakeholder survey in January 2026 to gather input that would help prioritise RAAs for targeted calls for data submission during the pilot and to collect stakeholder views on the expected outcomes of the initiative beyond those already proposed. Based on this input, EMA prioritised the RAAs and prepared the operational setup for the pilot, including the establishment of the NAMs OEG operating under the VDS framework.

The pilot will be officially launched in Q3 2026. The call for data on NAMs and WoE approaches is expected to remain open until Q3 2027. The assessment and analysis of the submitted data continues throughout 2027.



Terms of participation and data submission

The scope of the pilot is limited to NAM data falling within predefined CoU and RAAs (see section: Annex on Regulatory Applicability Areas), and therefore only such data will be assessed and analysed.

Participation in the VDS pilot is open to companies, contract research organisations, method developers, non-governmental organisations, academic laboratories, consortia and others. As an initial step, eligible participants are requested to express their interest in the pilot by submitting an application form by e-mail or via EMA's secure file transfer system (EudraLink) to the dedicated e-mail address VDS@ema.europa.eu. Submitted applications will undergo an initial validation to confirm their suitability for the pilot; in some cases, alternative existing regulatory procedures may be considered more appropriate (e.g. ITF briefing, SA, QA).

Selected applications will be invited to proceed with submission of the full briefing package, including sufficiently documented data packages describing the methodology, its performance, and proposed CoU

(see next section: Data briefing package, documentation and requirements). The assessment of briefing packages is expected to follow the SA timeline. However, this may vary depending on the number, prioritisation and complexity of the submissions as well as OEG availability.

Participants are expected to engage in scientific dialogue and provide clarifications, as needed, throughout the pilot.

As all data must be submitted through EudraLink, participants are required to hold an EMA account (Home · EMA Account Management) and an active EudraLink account (EMA Service Desk). Data will be stored in EMA's secure SharePoint environment and will be used exclusively for the purposes of the pilot.

Submission phase	Activity	Useful links
Step 1	Expression of interest by submitting the application form via e-mail or EudraLink (more details on Step 4) to the dedicated e-mail address	Application form VDS@ema.europa.eu
Step 2	EMA internal validation and prioritisation	N/A
Step 3	Selected applicants invited to submit a full briefing package	N/A
Step 4	Set up required access, as needed - EMA account - EudraLink account	Home · EMA Account Management EMA Service Desk
Step 5	Submission of briefing package via EudraLink	N/A
Step 6	Secure storage and handling through EMA SharePoint. Data will be accessible to the OEG members and the EMA staff.	N/A

Data briefing package, documentation and requirements

Selected applicants will receive a briefing document with clear guidance on the information and data that needs to be provided for assessment. An overview of the sections included within the briefing document is provided below.

The briefing package will serve as the primary basis for review under the VDS pilot and should be aligned, where appropriate, with the format and level of detail of a written summary corresponding to Module 2.4 of the eCTD. Underlying study reports, datasets, or model outputs should be provided only where essential to support interpretation. Where NAMs are used to support product development or as part of a WoE approach, relevant product information should be shared; if full disclosure is not possible, participants should provide, as applicable, information on modality, pharmacological class, molecular target, mechanism of action, proposed indication, and target novelty.

The briefing package should include a high-level description of the relevant RAA and problem statement, specify whether the NAM is applied as a standalone method, in a battery, or within a WoE approach (with a concise description of the WoE framework where relevant), and for each NAM identify the endpoint of interest, underlying biological mechanism, and corresponding safety endpoint. The current or anticipated CoU and stage of development should be described, together with information on internal validation or characterisation criteria (e.g. biological relevance, robustness, reference compounds, portfolio-based validation), including, where applicable, parallel comparisons with in vivo data or externally conducted validation and the measures taken to ensure data reliability. Finally, the submission should address the intended regulatory application of the NAM or WoE approach, including whether it fills a regulatory gap, its compatibility with existing guidance, its principal advantages and limitations, and conclude with an integrated discussion of the risks addressed, how the data are used internally or in regulatory submissions, and the potential for broader regulatory application.

Outcome

At the end of the pilot, EMA will publish a "lessons learned" report summarising the main scientific, regulatory, and operational insights gained from the voluntary data submissions. This report will support outreach and dissemination to stakeholders and contribute to global alignment (e.g. IMRWG-3Rs and ICH). The outcomes of the pilot will also impact the non-clinical domain activities and workplan and support the drafting of CoU–based acceptance criteria (Annex of the EMA guideline on 3Rs).

In addition, NAM data submitters participating in the pilot will receive individual, informal feedback within the pilot timeframe. This feedback will include comments on the overall readiness of the NAMs or WoE approach, regulatory considerations on the adequacy of the data, and recommendations on possible next steps.

Data protection

All personal data provided will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union Institutions and bodies on the free movement of such data.

If you have any questions, complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@ema.europa.eu

You can contact the Internal Controller at datacontroller.humanmedicines@ema.europa.eu

You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu

The assessment and outcome publication of the pilot will be performed respecting commercially confidential information.

Annex on Regulatory Applicability Areas (RAAs)

Introduction

NAMs can be applied across different stages of development and regulatory evaluation. Depending on how and where they are used, they may contribute to the reduction, refinement, or replacement of animal studies. In this context, the use of NAM data, either individually or within a WoE framework, should be underpinned by a clearly defined CoU. This includes careful consideration of model relevance, as well as performance characteristics such as sensitivity and specificity, alongside an explicit acknowledgement of known limitations. To strengthen confidence in the assessment, NAM data may be integrated, where appropriate, with other relevant evidence sources, including in vivo studies, clinical data, and established class effects. Central to this approach, mechanistic elucidation and hypothesis-driven evidence generation are integral to the application of NAM data. NAMs can provide valuable insights into mechanisms of toxicity, enable characterisation of pathway-level liabilities, and generate biologically relevant data that inform human risk assessment. Such approaches may support dose optimisation, evaluation of potential interactions in combination therapies, investigation of the reversibility of toxic effects, and assessment of susceptibility in specific populations.

Regulatory Applicability Areas

RAA1: Risk assessment of biologics with no pharmacologically relevant species or biologics with partial response in non-clinical test species

When a biologic drug either shows high target specificity such that no pharmacologically relevant species exists beyond humans (based on a comprehensive assessment, including lack of binding to the relevant species ortholog, absence of functional activity due to insufficient homology, or lack of target expression), the use of NAM data may be considered within a WoE approach provided adequate scientific justification is established.

Similarly, where a biotechnology-derived pharmaceutical elicits a response in Non-Human Primates (NHPs) and/or other species that is only partially representative of human biology (i.e. species showing target engagement but with limited pharmacological activity, and/or not fully recapitulating human-relevant downstream effects or key endpoints), the use of NAM data may be considered to support interpretation of animal studies including to bridge gaps or address limitations of available animal models, where scientifically justified, either as a standalone line of evidence or as part of a WoE approach.

Such justification should include, as appropriate, evidence of prior clinical experience with the modality, demonstration of an understanding of the mechanism of action (MoA), and characterisation of the intended target (e.g. expression profile, biological function, and downstream signalling), as well as an evidence-based understanding of known or potential safety liabilities. In this context, NAM data used as

a primary source of evidence within a WoE framework may be used to characterise pharmacodynamics, toxicology or pharmacokinetics to address specific safety concerns relevant to human risk assessment.

NAMs can also complement targeted in vivo data when such studies are appropriate and where these are scientifically justified. Under these conditions, NAM-derived data may support first-in-human (FiH) dose selection and clinical trial initiation, and may contribute to regulatory decision-making, including the reduction, refinement, or replacement of certain NHP studies (e.g. chronic, reproductive, developmental, or juvenile toxicity studies), including those typically conducted post-FiH, as well as elements of registration or approval applications.

RAA 2: Developmental and reproductive toxicity (DART) Risk Assessment in Accordance with ICH S5(R3)

In line with ICH S5(R3), a WoE approach integrating NAM data and/or other relevant evidence may be used to inform developmental and reproductive toxicity (DART) risk assessment. NAM data indicating either the presence or absence of developmental risk may contribute to the WoE, provided their context of use, relevance and limitations are adequately characterised.

Where a synthetic small molecule, and in relevant cases a biologic drug, demonstrates developmental risk based on NAM data, this may support waiving subsequent DART studies, provided appropriate risk mitigation measures are in place. Conversely, where a WoE approach, which may include NAM data, demonstrates absence of developmental risk and the hazard is sufficiently characterised for the intended context of use, this may also support adaptation or waiving of subsequent DART studies. At minimum, this should include adequate characterisation of target biology, its role in development and reproduction, intrinsic pharmacological risk, patient population, and remaining uncertainties.

In some cases, a WoE approach based on existing evidence alone may be sufficient where the hazard is already well characterised, and additional NAM data may be generated and submitted to complement the WoE, where relevant to the context of use.

When a WoE approach, which may include NAMs data, demonstrates absence of risk, this may similarly support waiving subsequent DART studies, provided appropriate risk mitigation measures are in place. At minimum, this should include a complete characterisation of the target, its role in development and reproduction, characterisation of the molecule and intrinsic risks to development and reproduction, indication and patient population.

NAM data may also be submitted alongside (preliminary) in vivo embryo–fetal development (EFD) studies to support the definition of context of use and strengthen regulatory confidence, including beyond scenarios explicitly described in ICH S5(R3). Applicability should be considered across the medicine lifecycle, including implications for marketing authorisation, product labelling, and use in pregnancy, while supporting reduction of animal use and addressing remaining data gaps.

RAA3: Safety pharmacology

Within the framework of safety pharmacology evaluation (see ICH S7A), NAM data may as part of weight-of-evidence (WoE) approach may be used to support hazard identification, mechanistic understanding, and regulatory decision-making.

In this context, NAMs may be used for screening and prioritisation, and to generate targeted data addressing defined safety concerns. They may also support mechanistic clarification of observed findings and contribute to integrated safety pharmacology strategies, such as combined telemetry approaches. Where sufficiently justified, such data may contribute to the assessment of cardiovascular, CNS, or respiratory risk. Where appropriate, NAMs data may contribute to evaluate the impact on other organs, systems or functions in accordance with ICH S7A and may support broader safety evaluation as part of regulatory submissions.

RAA4: Hepatotoxicity and drug-induced liver injury (DILI) prediction

NAM data integrated within a WoE approach may be used to assess the risk of hepatotoxicity/drug-induced liver injury (DILI) for both small molecules and biological products. These data may provide mechanistic, functional, and exposure–response insights relevant to human liver biology.

NAM data may contribute to the identification of hepatotoxic liabilities, support the characterisation of dose–response relationships, and inform safe starting and maximum doses and dose escalation and de-escalation strategies. Where appropriate, these approaches may also enable the elucidation of mechanisms underlying liver injury (e.g. mitochondrial dysfunction, bile acid transport inhibition, immune-mediated effects), including those not readily captured in conventional non-clinical species.

Where NAM data indicate a potential hepatotoxic risk that is sufficiently characterised, this information may support risk mitigation strategies and inform decision-making across the development lifecycle, including clinical study design, clinical monitoring, and product labelling.