

Comparative Regulatory Timelines: Does Early Engagement for NAMs Actually Shorten Overall Preclinical Development

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Keywords: New Approach Methodologies (NAMs); Regulatory Affairs; Preclinical Development; Early Regulatory Engagement; Scientific Advice; Non-Animal Testing	Abstract New approach methodologies (NAMs), which include in vitro, in silico, and other non-animal methods of testing, are poised to revolutionize the traditional preclinical safety assessment paradigms. There has been growing support for NAMs by the regulatory authorities globally, due to ethical, scientific, and policy imperatives to reduce the use of animals in testing. Yet, all enthusiasm around the potential of NAMs notwithstanding, there lingers one crucial question: Does early regulatory engagement on NAM accelerate the preclinical development timelines? It is hoped that this review brings us to the state of existing literature and regulatory frameworks to appraise the impact of early dialogue with Regulatory agencies such as the FDA, EMA, Health Canada, and PMDA on development trajectories. The article looks at the timelines involved with traditional versus NAM-based preclinical approaches, the efficiency of early scientific advice procedures, and the obstacles to full adoption. Main focus is laid on the timing of early engagement strategies (e.g., pre-IND and Scientific Advice meetings) as potential key thinking points to reduce the overall development time and to allow NAMs to be accepted and validated earlier in the drug development process and thus streamline the regulatory submissions. The review concludes that while early engagement enhances regulatory clarity, its ability to accelerate timelines depends on key factors. These include regulatory agency familiarity with NAMs, data standardization, and the harmonization of international expectations.
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1. Introduction

The timely need within the increasingly dynamic environment of drug discovery and development is the need to have even more predictive, ethical, and efficient safety assessment tools available. There have always been animal studies with dominance in the field. Nevertheless, as computational models, organ-on-chip technologies, and high-throughput screening systems saw exponentially increased application, the practice of the so-called NAMs, including but not limited to in vitro and in silico testing platforms, has started to significantly disrupt traditionally accepted paradigms of preclinical toxicology. Given this change of landscape, regulators all over the world have recognized the possibility of NAMs to generate human-relevant data, minimize perceived animal-dependency, and eventually, speed up drug development procedures [1][2][3]. Despite the mounting scientific evidence base and regulatory receptiveness to inclusion of the NAMs around the world, a question mark remains as to whether the early interaction with regulatory authorities, especially the procedure of NAM adoption, can be met with the practical reduction of the cumulative view of preclinical timelines. Regulatory meetings at the early stages of development (pre-Investigational New Drug (pre-IND) meetings in the United States, or Scientific Advice procedures in the European Union) are meant to facilitate a better understanding of development plans, making it easier to fill any data gaps, and avoiding redundancies or off-track testing plans. It is these interactions that have taken center stage in maximizing drug development strategies. Nonetheless, it remains understudied whether they can be effective in shortening timelines when NAMs are used [4][5]. The urgency of this question can be viewed not only in terms of the developmental efficiency argument but also in terms of community health, ethical, and financial aspects. With pharmaceutical companies increasingly pressured to get safer drugs into the marketplace in shorter time frames at lower costs and with reduced animal testing, it is crucial to take a look at the utility of early

regulatory interaction in practice. This article will discuss this critical problem in reviewing existing regulatory structures and comparing the preclinical development timeline between traditional approaches and those using NAMs, as well as the analysis of structural and procedural impacts of preliminary interaction with an agency. Leaving this exploratory introduction to the issues of motivation and context behind NAMs, we turn in the following section to the conceptual and technological underpinning of these other styles of method direction.

2. Overview of NAMs in Preclinical Safety Assessment

NAMs have been developed as a multidisciplinary suite of strategies and technologies intended to increase the relevance and efficiency of safety testing. They comprise a range of in vitro tests (such as human-derived cell cultures, organoids, and 3D tissue models), in silico methods (including quantitative structure activity relationship [QSAR] models, machine learning-based predictive algorithms, and physiologically based pharmacokinetic [PBPK] models), as well as high-throughput omics platforms capable of revealing molecular signatures of toxicity [6][7]. NAMs offer several advantages over traditional animal-based research approaches. They are often faster, more cost-effective, and provide mechanistic insights that are difficult to derive from in vivo models. Most importantly, because NAMs rely heavily on human-relevant data and biology, they are more likely to predict human adverse effects accurately [8].

A clear illustration of the practical value of NAMs can be found in the use of organ-on-a-chip systems. For example, a liver-on-a-chip model has been used to successfully predict drug-induced liver injury (DILI), a leading cause of drug withdrawals, with greater sensitivity and specificity than standard animal models. This micro-engineered system replicates human liver tissue structure and function, enabling dynamic monitoring of hepatic responses to compounds in real-time, which provides a more accurate and mechanistic understanding of hepatotoxicity [9]. Numerous studies have now demonstrated that NAMs are capable of identifying toxic effects earlier and more effectively than traditional methods in critical areas such as cardiotoxicity, hepatotoxicity, and genotoxicity, among others. However, there are still significant challenges to their broad regulatory implementation. One major concern is the need to validate these new models against existing gold-standard animal tests. Additionally, many NAMs require large, high-quality datasets to train predictive algorithms, and there is a need to align endpoints derived from these models with the expectations of regulatory frameworks. Despite these barriers, NAMs are increasingly being integrated into later stages of drug development, particularly for screening, mechanism-of-action studies, and compound prioritization prior to in vivo testing [10]. However, for these scientific and technological advancements to achieve their full regulatory potential, they must be embedded within supportive and adaptive regulatory frameworks. The following section will explore current regulatory trends and the ongoing efforts to facilitate broader adoption of NAMs in safety assessment.

3. Regulatory Frameworks Supporting NAMs

In the last 10 years, some of the most important regulatory agencies, such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and Health Canada demonstrated a gradual inclination towards adopting NAMs. Guidance documents issued by these agencies, workshops they hosted, and public-private partnership cooperation initiatives have swelled to help NAMs advance the science and integrate it into regulation [11][12]. As an example, the FDA published the Predictive Toxicology Roadmap, which offers encouragement to adopt new approaches that are likely to give a more accurate prediction of human response and minimize the use of animals in testing. On the same note, the Innovation Task Force at EMA is a platform that allows early discussions about emerging technologies,

such as the NAMs, to determine their usages and fit within existing frameworks. In Japan, alternative methods are being recognized through the consultations of the PMDA on non-clinical safety studies [13]. Along with these initiatives, regulators still have a need to explain why animal studies should be replaced or supplemented by NAMs exhaustively. The probability of a NAM being accepted by the regulator often hinges on the high quality of the data that proves its reliability, relevance, and reproducibility. Further, it is necessary to continue to establish international harmonized advice on using and validating NAMs, as the pharmaceutical industry is international, as shown in Figure 1. The compatibility of these frameworks with prior regulatory engagement is a decisive factor in the capability of the NAMs to accelerate the preclinical route. That is why it is important to gain an insight into the mechanics of early engagement mechanisms, which will be discussed in the following section.



Figure 1: Regulatory frameworks supporting NAMs, highlighting key components including guidance documents, validation procedures, and legal mechanisms that enable the integration and acceptance of NAMs within regulatory decision-making processes

4. Early Regulatory Engagement Mechanisms

Early engagement mechanisms involve structured regulatory discussions whereby the sponsors can present their development plans, explain scientific and procedural uncertainties, and discuss their expectations in alignment with requirements. Interactions such as the pre-IND in the US, Scientific Advice in the EU are critical points in the drug development process, especially in the case of innovative or unvalidated methodologies such as NAMs [14][15][16]. The merits of early engagement in principle are the ability to reduce costs of potential delays in regulatory programs because studies are not aligned, support for gaps in the proposed data package, and the likelihood of regulatory acceptance of novel approaches. Contextual conditions relevant to how much preclinical development may be advanced by early engagement include the maturity of the NAM being suggested, the experience of the agency with the technology, and the quality of the presentation by the sponsor of its scientific case [17]. As an example, when speaking about NAMs, one needs to be more detailed about the substantiation, as is the case with traditional models. Regulatory agencies may need bridging studies or comparison with past in vivo data to establish the credibility of conclusions reached by the use of NAM. In this aspect, then, the sponsor is most likely to be burdened with developing the well-laid structures of science-driven arguments. Additionally, the willingness of agencies to engage early in NAM development could depend on the internal expertise and changes in the policy positioning [18]. However, effective early interaction results in substantial downstream efficiencies, such as elimination of unnecessary studies, consistent predictability during submissions, and enhanced ease of regulatory review. In order to see

whether these advantages translate into quantifiable savings in timeframes, it is now helpful to consider a comparison between traditional and NAM-based development processes.

5. Comparative Analysis: Traditional vs. NAM-Based Preclinical Timelines

In order to evaluate whether early regulatory interaction of the scenario of NAMs reduces the total preclinical development, it is paramount to contrast the NAM-based approaches with conventional in vivo routes. The traditional approach to toxicology has been predicated upon a sequential, time-consuming series of acute, sub-chronic, and chronic animal studies, and most of these studies are species-specific, with interspecies differences. It might be months or years to complete these studies, and a lot of resources and moral expenses are involved [19][20]. Conversely, NAMs, particularly those taken early in the discovery or preclinical process, can precipitate the identification of hazards, mechanisms, and de-risk lead compounds without the excessively long animal studies timelines. As an example, toxicity signatures can be detected in just days or weeks when using high-throughput screens based on omics technologies or organ-on-chip platforms. In addition, fast computational models (e.g., physiologically based pharmacokinetic (PBPK) simulations) can be iterated quickly to forecast exposure situations in humans under different conditions of dosing [21][22]. Nevertheless, such hypothetical efficiencies may be cancelled out if the regulatory bodies require affirmative animal research or other validation to justify the utilization of NAMs. The early involvement in this scenario is very crucial. Incorporation of Regulatory buy-in into the early interactions can forestall requests for extra studies, build belief in data quality, and enable concomitant growth exercises, hence compressing timelines [23].

According to retrospective analyses in regulatory submissions, there is a probability that more refined development plans are set when early scientific advice on NAMs is conducted, since sponsors tend to be exceptional in the area of data integrity and awareness of issues of regulations. However, there continues to be inconsistencies between regions and agencies, which underlines the necessity of strategic planning and successful communication during early engagement [24][25]. Building on these ideas of development cycles, there is a need to look at the more systemic effects of NAM-based approaches, such as resource optimization and the ethical implications of development strategies.

Comprehension of how NAMs are more efficient in the future can be used in favor of the adoption of NAMs, since they have significant efficiency when they are implemented early in the regulatory discussions. Table 1 below compares the traditional regulatory pathway to the early engagement in the process of an NAM-integrated pathway, highlighting how dramatically the time and resource demands can be decreased.

Table 1: Timeline Comparison-Traditional vs. NAM-Integrated Drug/Toxicity Assessment

Phase	Traditional Pathway	NAM-Integrated Pathway with Early Engagement
Initial Screening	6–12 months using in vivo assays	1–3 months via in vitro and in silico pre-screening
Mechanistic Understanding	Animal models over several study iterations	Rapid AOP-based analysis using molecular and cellular data
Data Collection	Sequential and costly animal testing phases	Parallel high-throughput testing and computational modeling
Regulatory Submission Prep	Often reactive; compiled late in development	Data-informed design with proactive dialogue and regulatory alignment
Regulatory Review	Extended due to uncertainty or lack of early clarity	Expedited by familiarity with NAMs and early engagement insights

Phase	Traditional Pathway	NAM-Integrated Pathway with Early Engagement
Total Timeline Estimate	~5–7 years	~2.5–4 years

Source: Compiled by the authors through synthesis of data and concepts from the literature [10, 24, 25]

6. Broader Impacts of NAMs: Ethical, Economic, and Operational Considerations

In addition to schedules and scientific validity, the advancement of NAMs into preclinical programs is ethically, economically, and operationally significant. The latter is primarily the decrease in the use of animals. Since the world is becoming more culturally liberalized and adopts more humane research practices, regulatory agencies and sponsors are facing greater pressure to implement the 3Rs, which are known as Replacement, Reduction, and Refinement, as applied to preclinical testing. The most important role in the fulfillment of this mandate is played by NAMs [26][27]. NAMs promise economic benefits in that they would save money by not needing long-term tests on animals and dropping unworthy ones sooner. This upstream attrition can be utilized to optimally allocate R&D resources in the sense that theoretically informed predictive modeling is made possible. Moreover, NAMs will allow minimizing the detrimental and wasteful late-stage failures that burden the modern paradigm of drug development through enhancing human relevance and predictability on the translational level [28]. NAMs also facilitate flexibility and on-demandability at the operational level. Robotic in vitro systems, cloud computing modeling platforms, and machine learning-based modeling projects enable real-time redesign of the studies, a collaborative multidisciplinary approach, and data reproducibility. These operational efficiencies, coupled with early regulatory alignment, have great potential to increase the agility of preclinical programs [29]. Such benefits, however, can be achieved on a full scale only within a friendly regulatory and institutional environment. Consequently, new information regarding strategic prerequisites and best practices that can be used to achieve successful incorporation of NAMs via early engagement is presented in the following section.

7. Strategies for Effective Regulatory Engagement on NAMs

In order to ensure that preclinical timelines can be shortened through early engagement, sponsors must adopt a strategic and evidence-based approach when presenting NAMs to regulators. A key first step is Regulatory Awareness, which includes understanding the pathways available for Early Engagement Mechanisms, such as pre-IND or scientific advice meetings. Sponsors should make use of these mechanisms at the right stage, since they provide an opportunity to present NAMs proactively and receive early feedback that can shape development plans and prevent costly delays.

Secondly, the quality of the information provided is central to building regulatory confidence. As highlighted in Figure 2 under Data Quality, the briefing package must contain a clear scientific rationale, comparisons with performance data (where available), and a mapping of how the NAM aligns with regulatory endpoints. Equally important is the need to anticipate potential regulatory objections, particularly on data reliability and reproducibility. By demonstrating high-quality and reproducible evidence, sponsors can address skepticism and strengthen the scientific credibility of their NAMs [30][31]. Timing also plays a critical role. Participation at the wrong time, when a NAM has not yet generated sufficient supporting data, can result in vague or inconclusive feedback. Conversely, engaging regulators too late raises the risk of skepticism or rejection. The optimal time to engage is when a NAM has generated sufficient scientific evidence to support evaluation, but before critical development strategies are finalized. Aligning the engagement timeline with Regulatory Awareness and Early Engagement Mechanisms (Figure 2) maximizes the impact of the discussion and reduces regulatory uncertainty. Another important dimension is the style of communication. Since NAMs often involve novel technologies unfamiliar to many stakeholders, sponsors should prepare transparent, jargon-free communication materials. Clearly explaining how the NAM advances established approaches in terms of human relevance, sensitivity, or mechanistic insights is crucial to earning

regulatory trust. Linking communication strategies to the Data Quality principle (Figure 2) reinforces the emphasis on clarity, reproducibility, and rigor in presenting evidence. Finally, international collaboration is critical for ensuring that regulatory acceptance of NAMs is not hindered by regional disparities. As Figure 2 emphasizes, the harmonization of regulatory advice across jurisdictions (e.g., through OECD and ICH initiatives, or via shared case studies) strengthens the global applicability of NAMs and avoids duplicative testing. Sponsors working across multinational markets should actively participate in these collaborative efforts to promote consistency and facilitate the wider adoption of NAMs.



Figure 2: Key strategies for effective regulatory engagement on NAMs, including collaboration, education, data transparency, and policy advocacy.

8. Conclusion and Future Perspectives

With the rising sophistication, data-intensiveness, and patient-centric pharmaceutical development processes, the contribution of NAMs to preclinical safety assessment will only expand. In addition to pledging to substitute or diminish animal testing, these practices also seek to transform the whole manner in which we define, foresee, and forestall toxicological hazards. In combination with the early and meaningful regulatory interaction, NAMs are capable of providing not only scientific benefits but also operational efficiencies that have long proven elusive to the traditional framework. However, the road ahead involves further investment in model validation and regulatory harmonization, not only at the agency level but at the sponsoring organizations' level as well. Although this paper establishes that early engagement has high potential to reduce the preclinical time in NAM-inclusive strategies, the actual effect of the promise presented here can only be achieved by the interaction of scientific rigor, regulatory openness, and strategic foresight. Since regulators, researchers, and developers have found a common denominator in a safer, faster, more ethical drug development process, it can be predicted that the next decade will have seen the normalization of NAMs as part of regulatory science. Ultimately, the future of pharmaceutical innovation will be led by organizations positioned to take full advantage of what NAMs have to offer: those organizations that engage regulators proactively, transparency advocates, and those organizations that invest in rigorous science will stand the best chance of leveraging NAMs to their best advantage and to help achieve the goals of pharmaceutical innovation in the future.

List of Abbreviations

Abbreviation	Full Form
EMA	European Medicines Agency

Abbreviation	Full Form
EU	European Union
FDA	Food and Drug Administration (U.S.)
HTS	High-Throughput Screening
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
NAMs	New Approach Methodologies
OECD	Organisation for Economic Co-operation and Development
PBPK	Physiologically Based Pharmacokinetic (modelling)
QSAR	Quantitative Structure-Activity Relationship

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