ScitoVation
PIONEERS IN CHEMICAL SAFETY ASSESSMENT

ScitoVation Insight | Issue 5

FDA's First 25 NAM Examples: What They Reveal About Regulatory Adoption

Key message: FDA's initial examples show how New Approach Methodologies (NAMs) have been used for defined local hazards. A broader safety assessment may also need evidence about mechanism and human exposure, where omics and exposure modeling can contribute.

In ScitoVation Insight Issue 2, we discussed the FDA's evolving strategy for incorporating NAMs into drug development. Since then, the agency has taken another step toward implementation. In September 2026, they released a public database containing 25 examples of NAMs identified in the regulatory review documents of approved drugs (1). All of these NAMs address local toxicity, such as eye irritation or skin sensitization. Each entry links a specific method to the review documents of an approved drug, giving assessment teams a concrete example to investigate (1).

In this article, we examine the methods represented, consider how complementary approaches were used, and discuss what we can learn from the examples. We also consider how this collection relates to the wider use of computational methods in safety assessments, including where omics and physiologically based pharmacokinetic (PBPK) modeling can contribute.

What the first entries actually tell us

The initial collection lists 25 uses of NAMs across 14 New Drug Applications (NDAs), covering eight methods. An application can appear more than once because each row records one method used in one application. The endpoints are eye damage or irritation, skin irritation, skin sensitization, and skin corrosion (1) (Table 1).

Table 1. NAMs represented in FDA's initial public use-case database. ScitoVation analysis of FDA's NAM Database of Use Case Examples (1). Counts represent listed method-application examples, not unique drug applications or approvals attributed to each method.

Method	Primary application	Examples
BCOP (bovine corneal opacity and permeability)	Eye damage/irritation	10
EpiSkin SIT and EpiDerm SIT	Skin irritation	5
h-CLAT and U-SENS	Skin sensitization: immune-cell activation	3
KeratinoSens	Skin sensitization: keratinocyte activation	2

Method	Primary application	Examples
Corrositex	Skin corrosion	2
DPRA (direct peptide reactivity assay)	Skin sensitization: protein reactivity	3
TOTAL		**25**

These examples provide an opportunity to look beyond guidance, examine how specific methods have appeared in drug applications, and consider what previous use of NAMs can tell us about selecting and applying them in safety assessments.

What types of methods were presented?

The 25 FDA examples predominantly feature established experimental methods:

- Under conventional OECD terminology, 22 examples involve in vitro methods, including isolated tissues and artificial membrane systems.
- Three involve the in chemico direct peptide reactivity assay (DPRA).
- None explicitly identifies a stand-alone computational method.

The Bovine Corneal Opacity and Permeability (BCOP) assay accounts for 40% of the entries. It is a well-established, approved method that assesses potential eye damage using isolated bovine corneas. Although it is one of the most informative assays and avoids testing in live laboratory animals, it does still rely on animal-derived tissue (2).

FDA describes the collection as selected and non-exhaustive, so it cannot establish which technologies dominate NAM use across drug development.

Why complementary assays matter

A single assay may address only one part of a hazard. Complementary methods become useful when they examine different biological events that matter to the same safety question.

Cobenfy (xanomeline/trospium), a treatment for schizophrenia in adults, illustrates this approach. Its application lists three assays examining different events in skin sensitization (1):

- **DPRA:** Evaluates chemical reactivity with peptides, an early molecular event in sensitization.
- **KeratinoSens:** Measures activation of a cellular stress-response pathway in keratinocytes.
- **Human cell line activation test (h-CLAT):** Measures changes in cell-surface markers associated with immune-cell activation.

OECD Guideline 497 formalizes this principle for skin sensitization by combining specified sources of evidence through set interpretation rules (3). The listing does not show how FDA weighed each assay. Its practical value is in identifying complementary methods to investigate a similar question.

Where the computational evidence fits

The initial 25 examples focus on experimental methods for local toxicity endpoints. None of the entries explicitly identifies a stand-alone in silico method, neither omics-based toxicology nor PBPK modeling appears in the initial set. Yet, this picture contrasts with broader analysis by FDA scientists.

In a study published in February 2026, Dao and Sadrieh examined NAM-related nonclinical study reports submitted to the FDA over approximately 15 years (4). Their keyword-based analysis found that almost half of the identified reports involved in silico methods (Figure 1).

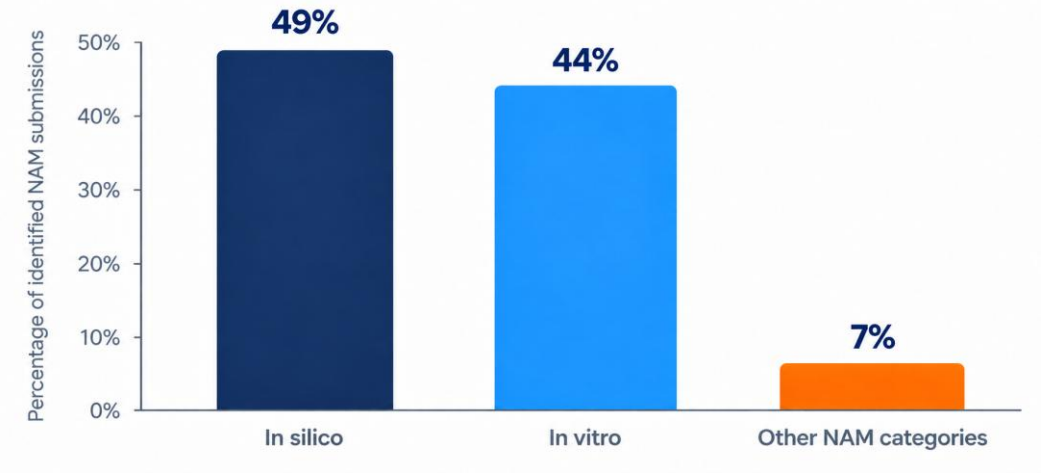

Figure 1. Distribution of NAM categories identified in FDA submissions in the analysis by Dao and Sadrieh (2026) (4).

It's important to note that the percentages describe identified NAM submissions, rather than the proportion of unique drug applications using each approach.

The two sources answer different questions. One shows selected examples from approved drug reviews; the other describes identified reports submitted during development. Their percentages should not be read as comparable measures of regulatory acceptance.

For an assessment team, the implication is to consider experimental and computational evidence according to the question each can answer.

How omics and PBPK address different evidence gaps

Omics identify biological responses

Transcriptomics and other omics technologies can reveal biological changes that conventional toxicity endpoints may not capture. Within a tiered NAM strategy, transcriptomic evidence can help address questions such as:

- **Which biological pathways respond?** Gene-expression changes can identify affected pathways and guide further investigation of potential mechanisms.
- **Do compounds produce similar biological responses?** Comparing responses can help test the biological basis of a proposed read-across.
- **At what concentrations do changes occur?** Concentration-response analysis can support the derivation of transcriptomic points of departure for further evaluation.

However, a biological response is not necessarily an adverse health effect. For omics evidence to inform regulatory decisions, developers must demonstrate the relevance of the experimental system, evaluate reproducibility and uncertainty, and explain how molecular changes relate to potential adverse outcomes.

Although targeted cellular assays such as KeratinoSens measure gene-regulatory responses, they are not equivalent to broad transcriptomic profiling. Therefore, the 25 examples leave unanswered how frequently broader molecular profiling approaches are being submitted and what weight regulators assign them.

PBPK connects experimental findings with human exposure

The FDA has long recognized PBPK analyses as tools for drug development and regulatory decision-making. Its 2018 guidance addresses the format and content of PBPK submissions, while the ICH M15 guidance adopted in 2026 provides a broader framework for evaluating model-informed evidence (5,6).

PBPK models integrate physiological characteristics, chemical properties, and pharmacokinetic information to predict internal exposure under different conditions. Depending on the safety question and supporting data, these models can help investigate:

- **Differences between exposure routes**, such as how oral and inhalation exposure affect internal concentrations.
- **Differences between populations**, including how age or physiological changes may influence exposure.
- **The relationship between experimental concentrations and human exposure**, using PBPK and quantitative in vitro to in vivo extrapolation (qIVIVE) where appropriate.

These applications often address questions distinct from the local irritation and sensitization endpoints represented in the 25 examples, including drug interactions, dosing, and pharmacokinetic variability.

Together, omics and PBPK can help connect laboratory results to human-relevant exposure. Transcriptomic assays may identify biological responses and concentrations associated with a point of departure, while toxicokinetic modeling can evaluate the relationship between those experimental concentrations and predicted human internal doses.

What this means for planning a NAM strategy

FDA's examples and the broader submission analysis offer several considerations for organizations developing a NAM strategy:

Match the method to the safety question

The selected examples predominantly feature established in vitro methods for defined local toxicity endpoints, many supported by OECD test guidelines. Evaluate each method's reliability, biological relevance, and limitations for the intended use. Previous regulatory use provides context, rather than assurance of suitability.

Build the assessment in tiers

Review existing evidence and use initial analyses to identify uncertainties. Select additional methods according to the information needed, allowing the strategy to develop as findings emerge. This helps focus further investigation on questions that could materially affect the safety conclusion.

Use complementary methods with a clear role

Several applications include multiple listed NAMs. Depending on the safety question, targeted assays can characterize specific hazards, omics can investigate biological responses, and PBPK/qIVIVE can help relate experimental findings to human exposure at all stages (Figure 2). Define how findings will be combined, conflicting results investigated, and confidence communicated.

Demonstrate how findings inform the decision

Submission frequency does not establish whether a method replaced a conventional study or influenced a regulatory outcome. Show how each analysis addresses the safety question and strengthens the assessment, documenting data, procedures, assumptions, and uncertainties so reviewers can understand and reproduce the analysis and assess its contribution.

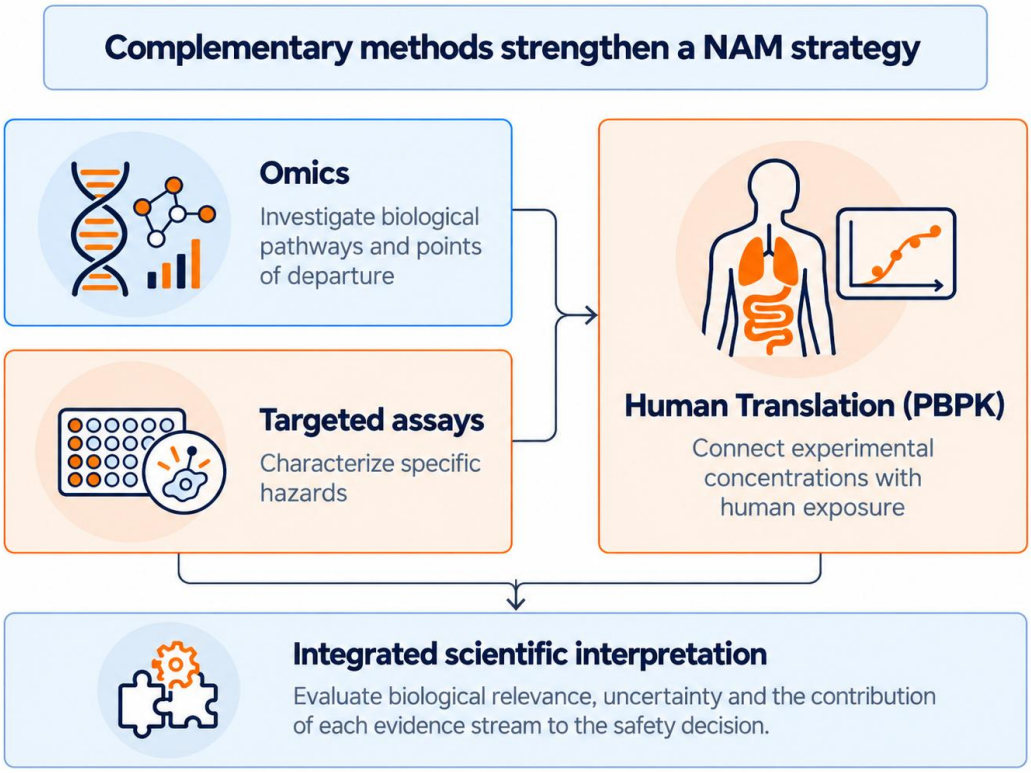

Figure 2. Complementary roles of targeted assays, omics, and PBPK/qIVIVE in a NAM strategy.

How ScitoVation supports NAM strategy

As NAM use expands, organizations need to determine which methods fit their safety question and how best to integrate evidence from different sources. ScitoVation places a tiered approach at the center of NAM strategy, starting with the safety question and available toxicological, experimental, computational, and regulatory evidence to determine which methods could add useful information and where further investigation is needed.

ScitoVation combines toxicology expertise with ScitoSim™, its computational platform, to support structured literature reviews, evidence synthesis, transcriptomic analyses of biological similarity and points of departure, and PBPK/qIVIVE assessments of human-relevant doses.

These capabilities can be used individually or together as the assessment develops. Expert scientific interpretation connects the findings, evaluating biological relevance, limitations, and uncertainty, and documenting how the evidence supports a defensible conclusion or guides the next stage of assessment.

Conclusion

The FDA's first 25 public NAM examples provide specific applications for sponsors to examine, particularly for established in vitro methods addressing local toxicity endpoints. Several applications contain multiple listed NAMs, offering examples to examine when considering complementary methods.

The collection represents one part of the wider NAM landscape. FDA's broader submission analysis demonstrates the representation of computational methods in drug-development submissions, while omics and PBPK offer ways to investigate biological responses and connect experimental findings with human exposure.

The opportunity is to build a tiered strategy around the safety question, selecting complementary methods according to the evidence needed and using the findings to guide subsequent work. The value lies in showing how each analysis contributes to a reliable, human-relevant safety assessment.

Want to find out which NAMs could support your chemical safety or drug-development question? Talk to a ScitoVation scientist about how a tiered NAM strategy could support the decision you need to make.

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