ICH M15 Guideline Explained: MIDD Framework for 2026

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Executive Summary

The International Council for Harmonisation (ICH), the body that brings together regulators and industry to align pharmaceutical technical standards, adopted the **ICH M15 Guideline on General Principles for Model-Informed Drug Development** at Step 4 of its formal process on **29 January 2026** ([1] database.ich.org) ([2] www.raps.org). It is the first ICH guideline devoted entirely to **Model-Informed Drug Development (MIDD)**, defined as the use of computational modeling and simulation methods that integrate nonclinical data, clinical data, prior information, and disease knowledge to generate evidence for drug development decisions (www.ema.europa.eu). In the European Union, the guideline comes into effect on **23 July 2026** (www.ema.europa.eu), and the US Food and Drug Administration (FDA) announced its final implementing guidance, docket FDA-2024-D-5580, in June 2026 ([3] www.fda.gov) ([4] www.fda.gov).

ICH M15 does not regulate any specific modeling technique. Instead, it establishes a harmonized, risk-based **evidence assessment framework** built around six elements: the **Question of Interest**, **Context of Use**, **Model Influence**, **Consequence of Wrong Decision**, **Model Risk**, and **Model Impact** ([5] database.ich.org). Model risk, derived by combining model influence and the consequence of a wrong decision, determines how rigorously a model must be verified, validated, and assessed for applicability before its outputs can be treated as regulatory evidence (www.ema.europa.eu). The guideline also formalizes two reporting artifacts, the **Model Analysis Plan (MAP)** and **Model Analysis Report (MAR)**, and a communication tool called the assessment table that sponsors use with regulators from the earliest planning stage through submission ([6] database.ich.org).

ICH M15 formalizes an approach that regulators have used piecemeal for three decades. The FDA's Pharmacometrics Group traces to 1991 (pmc.ncbi.nlm.nih.gov), and a 2005 FDA survey found that pharmacometric analyses were pivotal to regulatory decisions in more than half of the 42 New Drug Applications reviewed between 2000 and 2004 ([8] pmc.ncbi.nlm.nih.gov). The FDA's MIDD Paired Meeting Program, a PDUFA VII commitment, has granted at least 42 meeting requests since 2018 across therapeutic areas from oncology to infectious disease ([9] pmc.ncbi.nlm.nih.gov) and now explicitly references M15's assessment table in its meeting-request instructions ([10] www.fda.gov). Real-world MIDD applications documented in the peer-reviewed literature include the subcutaneous bridging approval of atezolizumab, dosing-frequency changes for nivolumab across eight tumor indications, simultaneous adult and pediatric approval of nivolumab plus relatlimab, pharmacogenomic-informed dosing for mavacamten, and the accelerated approval of tofersen using a modeled surrogate biomarker ([11] pmc.ncbi.nlm.nih.gov). A 2025 Pfizer-authored analysis estimated that systematic MIDD use saves a portfolio approximately 10 months of cycle time and $5 million per program annually ([12] ascpt.onlinelibrary.wiley.com).

Commercially, the pharmacometric modeling and simulation market was valued at **$1.72 billion in 2025** and is projected to reach **$6.10 billion by 2035**, an implied 13.8% compound annual growth rate ([13] www.insightaceanalytic.com). Industry groups including EFPIA, Teva, Pharmetheus, Parexel, and Medicines for Europe pushed during the comment period for more worked examples and clearer distinctions between model influence and model impact, concerns the final text only partially addressed ([14] www.raps.org). For life-sciences organizations building regulatory and AI strategy around this shift, ICH M15's practical significance is that MIDD evidence now carries a single, auditable rating framework that every ICH region is expected to recognize, replacing the previously inconsistent, region-by-region acceptance of modeling evidence that had generated the very uncertainty the guideline was designed to resolve ([15] www.regulatoryrapporteur.org).

Introduction and Background

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Drug development has long relied on a small number of pivotal clinical trials to answer questions about dose, safety, and efficacy. **Model-Informed Drug Development (MIDD)** offers an alternative or complementary path: instead of running a new trial for every question, sponsors build mathematical and statistical models from the data already available, then use those models to predict how a drug will behave under conditions that were never directly tested. The FDA defines MIDD as "an approach that involves developing and applying exposure-based biological and statistical models derived from preclinical and clinical data sources to inform drug development or regulatory decision-making" ([16] www.propharmagroup.com), and notes that, when successfully applied, "MIDD approaches can improve clinical trial efficiency, increase the probability of regulatory success, and optimize drug dosing/therapeutic individualization in the absence of dedicated trials"([17] www.fda.gov).

For three decades, however, MIDD grew as a patchwork of regional practices rather than a unified discipline. The FDA's Division of Pharmacometrics traces back to 1991, when its Pharmacometrics Group was formed within the Center for Drug Evaluation and Research's Office of Clinical Pharmacology (pmc.ncbi.nlm.nih.gov), and was later cemented into a standing paired-meeting program: "in 2023, the Prescription Drug User Fee Act (PDUFA VII)… cemented the pilot program into the MIDD Paired Meeting Program" (www.propharmagroup.com). Europe developed its own parallel concept, Model-Informed Drug Discovery and Development (MID3), defined by an EFPIA workgroup as a "quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data" ([19] www.open-systems-pharmacology.org). Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and other national authorities developed their own expectations in parallel. The result, as the ICH itself acknowledged when announcing M15's adoption, was that "this uncertainty has led to differences in the quality of MIDD applications and documentation in regulatory submissions, particularly when it involves novel methods or applications that are not covered in existing, topic-specific ICH Guidelines" ([20] www.raps.org).

The push for a harmonized standard accelerated after the Pharmaceutical Research and Manufacturers of America (PhRMA) trade group, drawing on its experience with the FDA's pilot program, engaged the ICH on the need for a global guideline, leading to the November 2021 endorsement by the ICH Assembly of a working group to develop a concept paper (pmc.ncbi.nlm.nih.gov); by November 2022, a 27-person Expert Working Group spanning 15 ICH parties, including regulators from the United States, European Union, Japan, and China alongside PhRMA, EFPIA, and JPMA, had begun drafting the guideline ([22] www.open-systems-pharmacology.org). This article explains what ICH M15 actually requires, how it interacts with existing FDA MIDD mechanisms, what the evidence base says about MIDD's measurable impact, and what sponsors, contract research organizations, and consultancies need to do differently as the guideline moves into force across ICH regions in 2026.

What Is ICH M15? Definition, Origins, and Regulatory Purpose

ICH M15, formally titled "General Principles for Model-Informed Drug Development," is a harmonized guideline that "provides general recommendations for planning, model evaluation, and documentation of evidence derived from Model-Informed Drug Development (MIDD)" and establishes a harmonized assessment framework for MIDD evidence (www.ema.europa.eu). Crucially, it is a process and evidence-assessment standard, not a technical modeling manual: the guideline explicitly states it "does not focus on details regarding technical aspects of the model development process" (www.ema.europa.eu) and instead governs how modeling evidence, whatever the underlying method, gets planned, evaluated, and communicated to regulators. It also, per an industry summary of the guideline's aims, "addresses planning, model development, data sources, model evaluation, documentation standards, and the application of models to support drug development and regulatory decision-making" ([23] www.regulatoryrapporteur.org).

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The guideline's scope is deliberately broad. Under M15, MIDD "applies to both current and emerging M&S methods, approaches, and applications" (www.ema.europa.eu) and explicitly lists "population pharmacokinetics and pharmacodynamics, physiologically based pharmacokinetics and biopharmaceutics, exposure-response, model-based meta-analysis, quantitative systems pharmacology and toxicology, agent-based models, disease progression models, and artificial intelligence/machine learning" as methods that fall within its reach, whether used alone or in combination ([24] database.ich.org). The Bhat et al. scoping review in the *Journal of Pharmacokinetics and Pharmacodynamics* summarized the definition succinctly: MIDD is "the strategic use of computational modeling and simulation (M&S) methods that integrate nonclinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence" (pmc.ncbi.nlm.nih.gov).

The document history is compact but deliberate. The ICH Assembly endorsed the guideline for public consultation at Step 2 on 6 November 2024 ([26] database.ich.org), regional regulators (including the FDA, which opened docket FDA-2024-D-5580 on 30 December 2024) ran their own comment periods, and the ICH Regulatory Members adopted the final Step 4 text on 29 January 2026 ([27] www.fda.gov). This staged process follows the ICH's five-step formal procedure, under which "Step 4 is reached when the Assembly agrees that there is sufficient consensus on the draft Guideline" ([28] admin.ich.org) and then "moves immediately to the final step of the process that is the regulatory implementation" ([29] admin.ich.org). RAPS reporting on the adoption noted that "the final guidance does not differ significantly from the Step 2 guidance released in November 2024," retaining the same six-element framework while adding clarifying text on how model influence and consequence-of-wrong-decision ratings should be justified ([30] www.raps.org), a text finalized after "ICH has been working on M15 since May 2020, with the formation of a discussion group focused on MIDD" ([31] www.raps.org).

ICH itself is not a regulator but a coordinating body: it is "a global initiative that brings together regulatory authorities and the pharmaceutical industry to harmonize scientific and technical standards for drug development and registration," aiming "to reduce duplication of clinical trials, ensure more efficient processes, and improve drug safety and efficacy through the development of international guidelines" ([32] www.open-systems-pharmacology.org). As of the 2024 count cited in industry conference materials, ICH comprised 23 members and had produced "75 Guidelines on Technical Requirements" spanning quality, safety, efficacy, and multidisciplinary topics ([33] www.open-systems-pharmacology.org), including founding regulators (the European Commission, Japan's MHLW/PMDA, and the US FDA), founding industry associations (EFPIA, JPMA, and PhRMA), and regulatory members from Argentina, Brazil, China, Egypt, Mexico, Saudi Arabia, Singapore, South Korea, Chinese Taipei, Turkey, and the United Kingdom, among others. M15 is intended to be read alongside, not instead of, existing topic-specific ICH guidelines, and the text specifically cross-references "E4, E5, E6, E7, E9, E11, E14, E17, M12, and M13, and S7B" (www.ema.europa.eu, which cover topics from dose-response information to drug interaction studies and pediatric extrapolation. As Certara's regulatory science team put it in a post-adoption FAQ, "ICH M15 is the first harmonized guideline focused specifically on Model-Informed Drug Development (MIDD)," and its release "signals a major global shift toward consistent expectations across agencies, making clear that modeling is now a core component of evidence generation" (www.certara.com).

The Six-Element MIDD Evidence Assessment Framework

The operational core of ICH M15 is a structured evidence-assessment framework captured in an "assessment table" that sponsors complete and share with regulators at both the planning and submission stages. The guideline states that "the key assessment elements include question of interest, context of use, model influence, consequence of wrong decision, model risk, and model impact" and that all are expected in the table

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regardless of stage ([5] database.ich.org). For every element rated low, medium, or high, "justification is always expected and essential in enabling the assessment" ([35] database.ich.org).

Question of Interest and Context of Use

Every MIDD analysis under M15 must start with an explicitly stated **Question of Interest**, defined simply as "the question that MIDD is intended to answer" (www.ema.europa.eu). The guideline notes this question can be broader than the intended use of any single model and recommends that, "if MIDD is planned to answer different questions of interest, it is recommended to use separate tables for each question" ([36] database.ich.org). Paired with this is the **Context of Use**, "outlined as a concise, clear, and explicit description of the role and scope of the model(s) used to answer the question of interest," including the data used to build the model and any additional evidence, such as clinical trial data, nonclinical experiments, post-marketing data, or real-world evidence, that will also inform the answer (www.ema.europa.eu). This pairing is what answers "ich m15 context of use" as a discrete query: context of use is not a technical specification of the model itself but a communication artifact describing what role the model plays relative to everything else regulators will consider.

Model Influence and Consequence of Wrong Decision

Model Influence captures "the intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence" (www.ema.europa.eu). The guideline is explicit about the anchor points of the rating scale: "in general, when model outcomes are the sole source to support the decision, model influence should be considered as high," whereas "if there is considerable data and evidence coming from other relevant sources, the model influence may be rated low or medium" ([37] database.ich.org). **Consequence of Wrong Decision** looks at the other side of the equation: "the potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information" (www.ema.europa.eu). The final text, following industry comment, added language clarifying that the rating "should take into consideration both the severity of potential negative effects as well as the likelihood that a wrong decision will result in potential negative effects" ([38] www.raps.org), a two-factor severity-and-likelihood construction that mirrors conventional risk-management practice.

Model Risk and Model Impact

Model Risk is the synthesis element: "the contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences," derived "by combining model influence and consequence of wrong decision" ([39] database.ich.org). It is, in the guideline's words, "key for determining the requirements for model evaluation" (www.ema.europa.eu), and the guideline is careful to note that "model risk should be interpreted in the context of answering a specific question of interest and is not to be perceived as a risk intrinsic to MIDD or M&S" (www.ema.europa.eu). This risk framework draws heavily on engineering practice: the Bhat scoping review documents that the ICH M15 credibility framework is based on the American Society of Mechanical Engineers' V&V 40-2018 standard for assessing computational model credibility, tracing this lineage to prior published work applying the standard to pharmacometrics ([40] pmc.ncbi.nlm.nih.gov).

Rounding out the framework is **Model Impact**, defined as "the extent to which the proposed MIDD strategy varies from regulatory standards, or expectations when no regulatory standard is in place, for answering the question of interest" (www.ema.europa.eu). This is the element that generated the most persistent confusion during public consultation. Pharmetheus wrote in EMA comments that "the distinction between model influence and model impact is unclear, and the two terms appear to overlap" ([41] www.raps.org), and Parexel separately

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"requested clarity on the two terms, noting that 'the two concepts appear to be strictly related'" ([42] www.raps.org). *Table 1* below summarizes the six elements and how each is used across the MIDD lifecycle.

Table 1. The Six Key Assessment Elements of the ICH M15 Framework

Element	What It Captures	Primary Use
Question of Interest	The question that MIDD is intended to answer	Anchors the entire analysis; separate tables recommended per distinct question
Context of Use	Role, scope, and data basis of the model(s) answering the question	Communicates scope and supporting evidence to regulators
Model Influence	Intended weight of model outcomes relative to other evidence	Feeds directly into the model risk rating
Consequence of Wrong Decision	Potential negative effect of an incorrect decision, by severity and likelihood	Feeds directly into the model risk rating
Model Risk	Combination of model influence and consequence of wrong decision	Sets the required rigor of model evaluation
Model Impact	Degree to which the MIDD strategy varies from existing regulatory standards	Signals when early regulatory alignment is most valuable

Read together, these six elements convert a subjective judgment ("is this model good enough to support this decision?") into a documented, auditable, and comparable rating, as defined in the two preceding subsections. Because the same table format is expected across FDA, the European Medicines Agency (EMA), and other ICH regulators, a sponsor can, in principle, build one assessment table per question of interest and reuse it across simultaneous global submissions rather than re-litigating model credibility in every jurisdiction.

Model Evaluation: Verification, Validation, and Applicability Assessment

Once the assessment table establishes how much model risk is in play, ICH M15's Section 3 defines what technical rigor is actually required, organizing model evaluation into three components: verification, validation, and applicability assessment. Critically, the standard of evaluation is not fixed but scales with the model risk rating established earlier: evaluation "should at minimum meet the current accepted standards, if available, and/or established scientific practices associated with the specific M&S method(s)… and be commensurate with model risk" (www.ema.europa.eu).

Verification activities "aim to ensure user-generated codes for processing the data and conducting the analysis are error-free, equations reflecting the model assumptions and their representation in the programming language or software are correct, and calculations are accurate" (www.ema.europa.eu). The guideline requires that this work "be documented and available for review by regulatory authorities" and that modeling activities "use a valid computerized system that is reliable, reproducible, and traceable" ([43] database.ich.org). This is a point of live industry concern: in EMA's public comment tracker, Medicines for Europe asked directly, "what level of validation is expected in the tools and process used for MIDD models? Would it be possible to consider different levels of validation, such as a model development environment and a model application environment?" ([44] www.raps.org), a question the final guideline leaves largely to sponsors' quality systems and future training materials rather than answering with a bright-line rule.

Validation and applicability assessment, sometimes called "fit-for-purpose" evaluation, activities "aim to assess the model performance and robustness," examining the adequacy and relevance of the underlying data,

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the model's conceptual structure, its assumptions, its development approach, and its diagnostics (www.ema.europa.eu). The guideline distinguishes the two: "validation focuses on the overall comparison of the model versus data, prior information, and knowledge, while applicability assessment focuses on the adequacy of the data and model for each intended use" ([45] database.ich.org). It also encourages, but does not always mandate, going further: "external validation with independent data is encouraged in order to assess the adequacy of model performance," and "depending on the question of interest, context of use, and model risk, external validation can further increase confidence and in some cases can be essential" ([46] database.ich.org). This proportionality clause explains why the guideline never publishes a single acceptance threshold: the rigor demanded of a low-risk exploratory model differs from that demanded of a model that is the sole evidentiary basis for a labeling claim, and the model risk rating is what draws that line.

The practical stakes of getting model evaluation wrong are not hypothetical. The Bhat et al. scoping review notes that a review of EMA marketing authorization applications submitted between 2022 and 2023 "found that most of the PB-PK models were not considered qualified for the intended use due to issues with model structure, the lack of relevant data for model validation, poor prediction of clinical data, and weak justification for model assumptions and parameters" ([47] pmc.ncbi.nlm.nih.gov), a finding directly relevant to physiologically based pharmacokinetic (PBPK) models, whose most frequent regulatory application is predicting drug-drug interactions. The evaluation standards in Section 3 of M15 are therefore not an abstraction but a direct response to documented deficiencies in how sponsors have historically justified model credibility.

Reporting and Submission: The Assessment Table, MAP, and MAR

ICH M15 formalizes two document types that structure how MIDD work moves from internal analysis to regulatory evidence. The **Model Analysis Plan (MAP)** is a pre-specified plan: "it is recommended to pre-define and document each intended model analysis in a MAP," and "a MAP typically includes an introduction, objectives, data, and methods" ([6] database.ich.org). The guideline defines "pre-define" precisely, as "documentation prior to accessing the data or performing the analysis, as appropriate considering the context of use" ([48] database.ich.org), a definition aimed squarely at preventing post hoc rationalization of model choices. EFPIA flagged exactly this risk during consultation, asking "how 'prospective' this planning needs to be" and warning about the possibility that "assessment table and MAP are filled out after the analysis has been completed" (www.ema.europa.eu), a concern that echoes long-standing methodological worries about undisclosed analytic flexibility in quantitative research.

The **Model Analysis Report (MAR)** is the corresponding output document: "the results of each model analysis submitted to regulators should be documented in a MAR," with sections that typically include an executive summary, introduction, objectives, data and methods, results, discussion, and conclusions ([49] database.ich.org). If deviations from the original MAP occur, "changes to the planned analyses should be justified and documented," a requirement designed to preserve the audit trail between what was planned and what was actually delivered ([50] database.ich.org).

Binding the MAP, the MAR, and the six-element assessment table together is a documentation expectation that extends to the underlying code itself. The guideline states that "all documents and files supporting submitted MIDD evidence, including data used in M&S analyses, relevant coding scripts… definition files, and other relevant electronic files used should be submitted or available for regulatory review and assessment" ([51] database.ich.org).

Reviewers on the industry side broadly welcomed the structure while pushing for worked illustrations. Pharmetheus told EMA that it "welcomes the guidance on the General Principles for Model-Informed Drug

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Development (MIDD) and considers it as a significant milestone in harmonizing regulatory decision-making and promoting the broader adoption of MIDD approaches," while separately noting that "the guidance would benefit from including case examples... to better illustrate the practical application of the assessment table" (www.ema.europa.eu). Teva separately suggested that, since the guidance "focuses on the assessment of MIDD evidence, rather than the technical aspects of model development, it would be beneficial to plan to issue additional guidelines and/or a Question and Answer (Q&A) document to be read in conjunction with this guidance" (www.ema.europa.eu). The ICH's own official training materials, referenced repeatedly throughout the guideline text, "are in development" as of the guideline's release, meaning the worked examples requested by industry are expected but not yet published ([52] database.ich.org).

ICH M15 and the FDA MIDD Paired Meeting Program: How the Pieces Fit Together

A frequent point of confusion is how the new ICH M15 guideline relates to the FDA's pre-existing MIDD infrastructure, particularly the **MIDD Paired Meeting Program**. The two are complementary rather than competing: ICH M15 is the evidentiary framework, while the paired meeting program is the procedural channel through which sponsors engage FDA on that evidence. The FDA describes the program as one that "will build on the success of the MIDD Paired Meeting Pilot by continuing to advance and integrate the development and application of exposure-based, biological, and statistical models... in drug development and regulatory review" (www.fda.gov). The program fulfills "a performance goal agreed to under the seventh iteration of the Prescription Drug User Fee Act (PDUFA VII)" (www.fda.gov) and runs on a strict cadence: "FDA will accept 1-2 paired-meeting requests quarterly each year throughout the PDUFA VII period," with additional proposals considered depending on resource availability ([55] www.fda.gov). As of mid-2026, FDA "will accept requests to participate in the program on a quarterly basis through June 1, 2027" ([56] www.fda.gov).

The most concrete integration point is procedural: the FDA page hosting the paired meeting program now flags, under "What's New," that "the FDA announced the availability of the ICH M15 General Principles for Model-Informed Drug Development guidance" in June 2026, and states plainly that "use of this guidance in preparing meeting requests and packages is recommended" ([57] www.fda.gov). Concretely, FDA now instructs sponsors requesting a paired meeting to include "a brief description of the key assessment elements (i.e., question of interest, context of use, model influence, consequence of wrong decision, model risk) as described in the guidance," and to attach, in the follow-up meeting information package, "the table for assessment of MIDD evidence described in the guidance... (Appendix 1)" (www.fda.gov). This means the FDA program, which predates M15 by roughly eight years, is being retrofitted to use the ICH M15 vocabulary and assessment table as its native format, rather than the two systems running in parallel with different terminology.

This retrofit did not happen instantly. Before M15, the FDA's own broader "Model-Informed Product Development" (MIPD) framework already treated MIDD as one of several applications: "MIPD aims to integrate information from diverse data sources to help decrease uncertainty and lower failure rates, and to develop information that cannot or would not be generated experimentally," and "encompasses model-informed drug development (MIDD)" as one component (www.fda.gov), a framing that extends beyond drugs into medical devices, food safety modeling, and even tobacco-policy simulation. Historically, the FDA program has skewed toward dose-related questions: the 2022 Madabushi et al. review of the pilot notes that "the most common issue is related to dose selection," alongside "alternative endpoints, patient risk management, and safety monitoring" ([60] pmc.ncbi.nlm.nih.gov), a pattern that ICH M15's six-element framework does not change but does now require sponsors to formally rate and justify.

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Implementation Guidance: Preparing for ICH M15 in 2026

Sponsors, contract research organizations, and pharmacometrics consultancies moving to operationalize ICH M15 face a compressed timeline. The EU guideline is binding from 23 July 2026 (www.ema.europa.eu), and the Bhat scoping review had already flagged, prior to formal adoption, that "the timelines for adopting and implementing the ICH M15 guidelines are the end of 2025 and 2026" ([61] pmc.ncbi.nlm.nih.gov), a forecast that proved accurate. A related news update on the adoption noted the guideline "will now move into the implementation phase (Step 5)" and that this step is "expected to support more consistent regulatory assessment of MIDD across regions and improve the quality and predictability of MIDD-related submissions" ([62] www.regulatoryrapporteur.org). Certara's implementation guidance frames the shift directly: "with ICH M15 now adopted, MIDD has moved from best practice to global regulatory expectation" ([63] www.certara.com), and separately advises that credibility "must be evidence-based and risk-informed, not just a validation checklist," with regulators wanting "transparency around assumptions, data quality, and uncertainty" ([64] www.certara.com).

Four practical steps recur across the guidance documents and industry commentary reviewed for this report. First, **establish the assessment table as a living planning document** rather than a submission afterthought: the guideline expects the table to evolve as MIDD planning matures, noting that "new questions of interest may emerge requiring separate assessment tables, and the associated plan could evolve as data and knowledge accumulate" ([65] database.ich.org). Second, **align MAP pre-specification with existing quality systems**, since the guideline requires "compliance with appropriate quality assurance… for data management and modeling activities" ([66] database.ich.org), which typically means bringing pharmacometrics groups formally under the same document-control regime as clinical operations rather than treating modeling as an ancillary analytical exercise. Third, **pursue early regulatory engagement proportional to model impact and risk**, since the FDA's paired meeting program is the direct mechanism for that engagement in the United States, and, per Dr. Sander Vinks of ProPharma Group, pediatrics and rare diseases "will be growing areas where Sponsors request MIDD / M&S assistance for their programs to meet and complete FDA requirements for pediatric trials" ([67] www.propharmagroup.com), a view echoed in his broader observation that MIDD should be used more in "rare diseases that have the greatest unmet medical needs" ([68] www.propharmagroup.com). Fourth, **build cross-functional fluency in the M15 taxonomy** beyond the pharmacometrics function itself, since, as Certara notes, "credibility cannot be assessed by modelers alone; it requires cross-functional agreement on decision needs, assumptions, and evidence standards" ([69] www.certara.com).

For organizations assessing readiness, the questions worth asking mirror the six assessment elements themselves: can the regulatory affairs, clinical, and quantitative sciences functions jointly state a question of interest and context of use for a live program today, and would they rate model influence and consequence of wrong decision consistently if asked independently? Consultancies working at the intersection of life sciences and AI increasingly frame this readiness gap in terms of documentation and data infrastructure rather than pure modeling capability, since a technically sound model that lacks a defensible, pre-specified MAP or a traceable link back to its source clinical data will struggle to clear the M15 bar regardless of its predictive accuracy. This is consistent with the broader industry trend toward AI-assisted drug development documented elsewhere: analysts at Deloitte have found that AI-enhanced drug discovery and development workflows can accelerate timelines by up to 60%, and McKinsey has separately estimated that AI could generate over $100 billion in annual value for the pharmaceutical industry ([70] intuitionlabs.ai) ([71] intuitionlabs.ai), underscoring why regulators are moving to formalize how model-derived evidence, increasingly generated with AI/ML components, gets evaluated before that acceleration can be trusted at scale.

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Data Analysis and Evidence

The quantitative case for MIDD's regulatory relevance predates ICH M15 by two decades and helps explain why the guideline was considered necessary rather than optional. An early FDA survey of pharmacometric impact, covering New Drug Applications reviewed by the Cardio-renal, Oncology, and Neuropharmacology divisions between 2000 and 2004, found that "of about a total of 244 NDAs, 42 included a pharmacometrics component" and that "pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs," with "14 reviews that were pivotal to approval related decisions," five of which identified the need for additional trials while six reduced the burden of conducting them ([72] pmc.ncbi.nlm.nih.gov) ([73] pmc.ncbi.nlm.nih.gov).

More recent portfolio-level evidence quantifies MIDD's efficiency dividend directly, building on decades of internal industry practice: "at Pfizer, the implementation of MIDD over the last 2 decades has been described in a series of publications," beginning with a paper that "discussed the escalating costs of drug development and emphasized the application of model-based drug development as a tool to improve drug development" ([74] ascpt.onlinelibrary.wiley.com). A 2025 follow-up in *Clinical Pharmacology & Therapeutics* quantified the payoff, building an algorithm estimating MIDD-related savings "at each stage of development across the entire drug development portfolio during a typical year between 2021 and 2023," concluding that "the use of MIDD yielded annualized average savings of approximately 10 months of cycle time and $5 million per program" ([12] ascpt.onlinelibrary.wiley.com), with the authors concluding that "systematic application of MIDD approaches yielded significant time and cost savings across the drug development portfolio in addition to informing data-driven decisions" ([75] ascpt.onlinelibrary.wiley.com).

On adoption volume, FDA's own pilot program data shows sustained growth: as of December 2021, "FDA has granted 42 meeting requests" under the MIDD paired meeting pilot, "span [ning] almost all major therapeutic areas including oncology, autoimmune diseases, hematology, cardiovascular diseases, neurology, psychiatry, infectious diseases, and diabetes" ([9] pmc.ncbi.nlm.nih.gov).

Commercially, this growth in regulatory acceptance is mirrored in market sizing. The pharmacometric modeling and simulation market was "valued at USD 1.72 Bn in 2025 and is predicted to reach USD 6.10 Bn by the year 2035," at a compound annual growth rate the report pegs at "13.8% CAGR during the forecast period for 2026 to 2035" ([13] www.insightaceanalytic.com) ([76] www.insightaceanalytic.com). The same analysis identifies "the increasing use of model-informed drug development (MIDD)" as "one of the main factors greatly boosting the growth" of the sector, and notes that "the drug development category held the largest share in the pharmacometric modeling and simulation market in 2025" (www.insightaceanalytic.com) ([78] www.insightaceanalytic.com). North America leads the market, attributed to its "well-established regulatory framework, robust presence of major industry participants, and highly developed pharmaceutical and biotechnology ecosystem" ([79] www.insightaceanalytic.com), though "the scarcity of qualified experts and the intrinsic difficulty of model construction are two of the main obstacles to the pharmacometric modeling and simulation market growth" ([80] www.insightaceanalytic.com), a talent constraint that ICH M15's documentation and evaluation requirements will likely intensify rather than relieve in the near term.

Case Studies and Real-World Examples

The following cases, all documented in the peer-reviewed literature, illustrate the kinds of MIDD evidence that the ICH M15 framework is designed to formalize. None are hypothetical; each represents a completed FDA regulatory action.

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Case Study 1: Atezolizumab, Bridging Intravenous to Subcutaneous Dosing

Genentech sought to convert atezolizumab (marketed as Tecentriq), an anti-PD-L1 monoclonal antibody approved for several cancers, from intravenous to subcutaneous administration. Rather than repeat efficacy trials, the sponsor used a population pharmacokinetic (PopPK) model built by adding bioavailability and absorption-rate parameters to the existing intravenous model, and this combination of clinical and simulated data "supported the regulatory approval of SC atezolizumab at a dose of 1875 mg every 3 weeks, administered in the thigh" ([81] pmc.ncbi.nlm.nih.gov). Notably, although the pivotal bridging study enrolled only non-small cell lung cancer patients, "the model-based bridging enabled the approval of SC (TECENTRIQ HYBREZA) across multiple indications" (pmc.ncbi.nlm.nih.gov), a direct example of what M15 would classify as a high-influence model given that it was the primary basis for extrapolating across indications not directly studied.

Case Study 2: Nivolumab, Reducing Dosing Frequency Across Eight Tumor Types

Bristol-Myers Squibb sought to change nivolumab's approved dosing from a weight-based regimen to fixed doses, including a less-frequent 480 mg every-four-weeks (Q4W) option, "supported by PK modeling, E-R [exposure-response] analyses, and safety data without direct clinical efficacy data" ([83] pmc.ncbi.nlm.nih.gov), drawing on a population pharmacokinetic model built from thousands of patients across tumor types. The regulatory payoff was substantial: "this dosing regimen obtained regulatory approval for eight tumor indications" ([11] pmc.ncbi.nlm.nih.gov), and the timing proved fortuitous for patients: "the fortuitous approval of the Q4W dosing frequency of nivolumab before the COVID-19 pandemic enabled cancer patients… to avoid unnecessary exposure to infection by reducing the frequency of clinic visits" ([84] pmc.ncbi.nlm.nih.gov).

Case Study 3: Nivolumab Plus Relatlimab, Simultaneous Pediatric Approval

The nivolumab-relatlimab combination (Opdualag) illustrates a use case M15's framework directly addresses: pediatric extrapolation without a dedicated pediatric trial. Using population pharmacokinetic models built from adult data and a simulated adolescent population representative of body weight, age, sex, and race distributions, the sponsors extrapolated dosing for patients 12 years and older. The result was that "the totality of the MIDD evidence led to the simultaneous regulatory approval of the nivolumab plus relatlimab fixed-dose for adult and pediatric indications in both the US and EU without the need for clinical trials in pediatric patients" ([85] pmc.ncbi.nlm.nih.gov), a rare instance of adult and pediatric labeling arriving together rather than with the usual multi-year lag.

Case Study 4: Mavacamten, Pharmacogenomic-Informed Dose Titration

Mavacamten (Camzyos), a cardiac myosin inhibitor for obstructive hypertrophic cardiomyopathy, presented a distinct MIDD challenge: metabolism by the polymorphic CYP2C19 enzyme means "mavacamten half-life increases from 6 to 9 days in normal metabolizers to 23 days in CYP2C19 poor metabolizers" ([86] pmc.ncbi.nlm.nih.gov). Exposure-response modeling combined with echocardiography-based efficacy and safety

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metrics allowed simulations of individualized dosing across virtual patient cohorts incorporating CYP2C19 phenotype variability. The modeling demonstrated that an echocardiography-guided regimen could replicate the safety and efficacy of the original therapeutic-drug-monitoring approach, and "mavacamten was approved for clinical use via a restricted Risk Evaluation and Mitigation Strategies (REMS) program" (pmc.ncbi.nlm.nih.gov), an example of a high-consequence, safety-critical decision in which M15's risk-based evaluation standard would demand rigorous external validation.

Case Study 5: Tofersen, a Modeled Surrogate Endpoint for Accelerated Approval

Tofersen (Qalsody), an antisense oligonucleotide for SOD1-linked amyotrophic lateral sclerosis (ALS), illustrates MIDD's role in accelerated approval pathways for rare, life-threatening disease. The pivotal trial's primary efficacy endpoint showed no statistically significant improvement, so investigators turned to a secondary biomarker, plasma neurofilament light chain, using causal-inference modeling to establish its mechanistic link to disease progression. This modeling work "established plasma NfL as a reasonably likely surrogate endpoint, which, when combined with the totality of evidence, supported the accelerated approval of tofersen for SOD1-ALS, addressing an urgent need for this rare and life-threatening disease" ([88] pmc.ncbi.nlm.nih.gov). This case is a textbook example of high model influence (the modeled surrogate carried substantial weight given the failed primary endpoint) combined with high consequence of wrong decision (a fatal, rare disease with no approved SOD1-targeted alternative), the exact combination that M15's model risk construct is designed to flag for the most rigorous evaluation.

Table 2 below summarizes the regulatory outcome and MIDD approach in each case described above.

Table 2. Documented MIDD Case Studies and Regulatory Outcomes

Product	MIDD Approach	Regulatory Outcome
Atezolizumab (Tecentriq/Hybreza)	PopPK bridging model, IV to SC formulation	Approved across multiple indications from one bridging study
Nivolumab (Opdivo)	PopPK and exposure-response modeling, dosing frequency change	Approved for eight tumor indications without new efficacy trials
Nivolumab + relatlimab (Opdualag)	PopPK pediatric extrapolation, simulated adolescent population	Simultaneous adult and pediatric approval in US and EU
Mavacamten (Camzyos)	Exposure-response and pharmacogenomic simulation	Approved with echocardiography-guided titration under REMS
Tofersen (Qalsody)	Causal-inference modeling of a biomarker surrogate	Accelerated approval for SOD1-ALS

Sourcing for every row is provided in the case narratives above; the table is a navigational summary rather than an independent citation set. A sixth pattern worth noting outside the table: MIDD's reach now extends into AI-driven patient selection. During the COVID-19 pandemic, machine learning methods were used to identify patients with anakinra treatment candidacy based on a predictive biomarker threshold that lacked an approved US assay, and this "marked the first time the FDA utilized AI/ML to identify the appropriate patient population for a clinical trial" ([89] pmc.ncbi.nlm.nih.gov), a precedent directly relevant to how ICH M15's AI/ML provisions will be tested going forward.

Implications and Future Directions

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ICH M15's most immediate implication is procedural convergence: sponsors running simultaneous FDA, EMA, and PMDA programs can now build one assessment table, one MAP, and one MAR per question of interest and expect broadly consistent regulatory vocabulary across regions, rather than translating pharmacometric arguments into each authority's idiosyncratic expectations. Certara frames the upside directly: because the framework is now shared, "modeling plans can be designed once and defended consistently across FDA, EMA, PMDA, and other agencies" ([90] www.certara.com).

A second, more structural implication concerns AI and machine learning. ICH M15 explicitly folds AI/ML methods into its scope, but the guideline was drafted in an environment where, as EFPIA noted in comments, "formal validation and verification processes for Artificial Intelligence (AI) methodologies are immature and likely lack sufficient, real-world regulatory experience, relative to the other listed M&S methods that are in-scope for this guidance," and "foundational AI models may also be licensed from third-party vendors without full documentation, explainability, or reproducibility… that are generally expected of the other" methods (www.ema.europa.eu). This tension will likely define much of the next two to three years of M15 implementation: the guideline's model-risk logic technically applies equally to a population pharmacokinetic model built with three decades of methodological precedent and a large language model with almost none, and regulators will need case-by-case practice, not just principle, to resolve how the same low/medium/high risk scale should be applied across that gap.

Future directions also point toward newer modalities. The Bhat review notes that MIDD's scope is expanding into "new therapeutic modalities such as silencing RNA (siRNA), new variants of antibodies and antibody-drug conjugates, gene therapies, chimeric antigen receptor (CAR) T cells, and other cell-based therapies," and separately flags that the FDA "has issued a roadmap for reducing animal testing in preclinical safety studies with new approaches such as microdosing and imaging in human volunteers, ex vivo human tissues, in vitro human-based systems, and in silico modeling approaches" ([91] pmc.ncbi.nlm.nih.gov), consistent with the FDA's own framing that it "has committed resources to transforming computational modeling from a valuable scientific tool to a valuable medical device regulatory tool and to developing mechanisms to rely more on digital evidence" ([92] www.fda.gov). The FDA has also begun deploying its own AI infrastructure into the review process itself: "the FDA also launched a new LLM-based tool, ELSA, in June 2025 to accelerate scientific evaluations and clinical protocol reviews," operating "in a closed government cloud environment to avoid exposure of the sponsor's documents containing intellectual property on the internet" ([93] pmc.ncbi.nlm.nih.gov), a development that could eventually reshape how MAPs and MARs are reviewed on the regulator's side, not just how they are prepared on the sponsor's side.

For life-sciences organizations building internal AI and analytics capability more broadly, ICH M15 is best read as a preview of where regulatory expectations for any model-derived evidence, not just classical pharmacometrics, are heading: documented context of use, explicit risk rating, proportional validation rigor, and traceable evidence chains. Consultancies operating in this space, including firms with a life-sciences and AI advisory focus, describe their role as helping organizations build "regulatory compliance" directly into AI systems from the outset rather than retrofitting it later ([94] intuitionlabs.ai), and offer "strategic guidance on digital transformation, AI adoption, and technology roadmapping" as organizations work out how documentation practices built for pharmacometrics extend to newer generative and agentic AI tools entering the same regulatory conversation ([95] intuitionlabs.ai). That advisory framing matters because M15's documentation burden, the MAP, the MAR, and the assessment table, is fundamentally a data and knowledge-management problem as much as a statistical one, and organizations that treat it purely as a pharmacometrics function risk under-resourcing the cross-functional coordination the guideline explicitly demands.

Frequently Asked Questions (FAQs)

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What is ICH M15? ICH M15 is the ICH's harmonized guideline, "General Principles for Model-Informed Drug Development," adopted at Step 4 on 29 January 2026, which provides general recommendations for planning, model evaluation, and documentation of MIDD evidence and establishes a harmonized assessment framework for that evidence (www.ema.europa.eu).

How does the FDA's MIDD guidance differ from ICH M15? They are not competing standards; the FDA's finalized guidance implementing M15 (docket FDA-2024-D-5580) is the US regional adoption of the ICH text ([4] www.fda.gov), while the pre-existing FDA MIDD Paired Meeting Program is a separate, older procedural mechanism (a PDUFA VII commitment running through mid-2027) that now explicitly incorporates the M15 assessment table into its meeting-request format ([10] www.fda.gov).

What is the ICH M15 context of use? Context of use is a mandatory element of the assessment framework: a concise, clear, and explicit description of the role and scope of the model(s) used to answer the question of interest, including the model's underlying data and any additional supporting evidence (www.ema.europa.eu).

How is model risk assessed under ICH M15? Model risk is calculated by combining two other rated elements, model influence and consequence of wrong decision, and represents "the contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences," with higher-risk models required to clear a higher bar of verification, validation, and applicability assessment before their outputs count as MIDD evidence ([39] database.ich.org).

When does ICH M15 take effect? The guideline reached Step 4 (ICH adoption) on 29 January 2026, and the European Union's implementation date is 23 July 2026 (www.ema.europa.eu); the FDA announced its own final guidance availability in June 2026 ([3] www.fda.gov).

What submission documents does ICH M15 require? The core artifacts are the assessment table (six rated elements), the Model Analysis Plan pre-specifying planned analyses, and the Model Analysis Report documenting results, with the guideline noting "if a MAP was developed, it should be provided as an appendix within the associated MAR" ([96] database.ich.org).

Does ICH M15 apply to AI and machine learning models? Yes: the guideline lists "artificial intelligence/machine learning" among the in-scope M&S methods ([97] database.ich.org), though industry commenters flagged that AI-specific validation practice remains less mature than for established pharmacometric methods.

Can MIDD replace clinical trials entirely? No. MIDD evidence is generally used "in combination with other relevant information and/or evidence to answer the question of interest" ([98] database.ich.org), though in documented cases such as nivolumab's dosing-frequency change, MIDD evidence has supported regulatory approval decisions without requiring dedicated new clinical trials for the specific question at hand.

Conclusion

ICH M15 closes a three-decade gap between how widely Model-Informed Drug Development has been used and how inconsistently it has been evaluated. What began as a scattered set of regional practices, an FDA pharmacometrics function dating to 1991, a European MID3 framework, and country-specific paired-meeting pilots, is now a single, risk-graded assessment vocabulary that every ICH regulator is expected to apply. The guideline's six-element framework, Question of Interest, Context of Use, Model Influence, Consequence of Wrong Decision, Model Risk, and Model Impact, does not tell sponsors how to build a better pharmacokinetic model; it tells them how to prove, in a standardized and auditable way, that the model they built is fit for the decision it is being asked to support.

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The timing is not incidental. With the EU implementation date landing on 23 July 2026 and FDA's final guidance already recommended for use in paired meeting requests, sponsors, CROs, and regulatory consultancies have a narrow window to convert internal pharmacometrics practice into M15-native documentation before regulators begin holding submissions to the new standard as a baseline expectation rather than an emerging one. The evidence base assembled over the preceding decades, from the 2005 finding that pharmacometrics was pivotal in more than half of surveyed NDA reviews to the 2025 estimate of roughly $5 million and ten months saved per program, makes clear that the underlying practice already delivers measurable value. ICH M15's contribution is not to prove that MIDD works; it is to make that value legible, comparable, and defensible across every major regulatory jurisdiction at once, at a moment when the same modeling and simulation methods are rapidly absorbing AI and machine learning components that will test the framework's risk-based logic in ways the drafters could only partially anticipate.

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Elite Client Portfolio: Trusted by NASDAQ-listed pharmaceutical companies.

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Custom AI Software Development: Build tailored pharmaceutical AI applications, custom CRMs, chatbots, and ERP systems with advanced analytics and regulatory compliance capabilities.

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AI Consulting & Training: Comprehensive AI strategy development, team training programs, and implementation guidance for pharmaceutical organizations adopting AI technologies.

Contact founder Adrien Laurent and team at https://intuitionlabs.ai/contact for a consultation.

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