

ARTICLE

Model-Informed Drug Discovery and Development: Current Industry Good Practice and Regulatory Expectations and Future Perspectives

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Good practices around model-informed drug discovery and development (MID3) aim to improve the implementation, standardization, and acceptance of these approaches within drug development and regulatory review. A survey targeted to clinical pharmacology and pharmacometric colleagues across industry, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) was conducted to understand current and future roles of MID3. The documented standards were generally affirmed as a “good match” to current industry practice and regulatory expectations, with some identified gaps that are discussed. All have seen at least a “modest” step forward in MID3 implementation associated with greater organizational awareness and share the expectation for a future wider use and impact. The priority within organizations was identified as a limitation with respect to the future of MID3. Finally, potential solutions, including a global overarching MID3 regulatory guideline, to facilitate greater acceptance by industry and regulatory decision makers are discussed.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There has been an increased focus by individual companies, professional bodies, and industry bodies in the publication of good practices related to model-informed drug discovery development (MID3) with the aim of increasing the implementation, standardization, and acceptance within companies and regulatory submissions.

WHAT QUESTION DID THIS STUDY ADDRESS?

Whether the recently documented industry good practices fit with current practice and match with regulatory expectations and what the current and future viewpoints are on the role of MID3 in making research and development and regulatory review.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results indicate that documented industry good practices are a “good match” to current industry practice and regulatory expectations “with some gaps” that are discussed. Increasing the acceptance of MID3 by industry and regulatory decision makers via improved education, communication, and process utilization is a priority.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This work adds to the ongoing debate about the value of good practices and regulatory guidelines in the area of MID3 to increase the efficiency of new medicine development.

Model-informed drug discovery and development (MID3) has been shown to play an important role in the efficient delivery of new therapies by both increasing the confidence in decision making across drug development and by eliminating costs or reducing cycle times.^{1–4} As part of this paradigm, quantitative modeling approaches are used across all phases of the drug development process: from biomarker selection in translational medicine to dose/regimen selection, evidence generation for regulatory approval, extrapolation to other disease areas or populations, and as an early input into pharmaco-economic assessment.³

The associated modeling approaches include empirical, semimechanistic, or quantitative systems pharmacology techniques with the aim of integrating current knowledge regarding the drug, disease, and mechanism of action to allow prediction (interpolation or extrapolation) of new outcomes under new conditions, such as untested doses, regimens, populations, or disease factors.³

Over the past few years, there has been an increased focus on the development of good practice in MID3 in general³ and in the provision of good practice for specific applications, such as population pharmacokinetics

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(PKs),^{5,6} exposure response,⁷ model evaluation,⁸ physiologically based PKs,⁹ and within the statistical domain,¹⁰ with the aim to enhance consistency, quality, and reproducibility and, therefore, facilitate associated decision making. Although some of these have been authored by individual companies,^{5,7} others represent an integrated viewpoint from industry/trade bodies^{3,9,10} and professional bodies.^{6,8} Some of these have been developed as follow-up actions from joint regulator/industry workshops.^{3,10-15} Furthermore, there is a good alignment of good practice recommendations across the clinical pharmacology and statistical communities.¹⁶ Moreover, MID3 approaches have received an increased focus within guideline development discussions, such as in the European Medicines Agency (EMA) extrapolation reflection paper,¹⁷ in International Conference on Harmonization (ICH) E11 addendum,¹⁸ and in overarching activities to enhance regulatory decision tools to support drug development and review (Prescription Drug User Fee Act 6 Advancing Model-Informed Drug Development).¹⁹

Although these good practices aim to move the area forward with respect to the implementation, standardization, and acceptance of these approaches within regulatory review, particularly in support of higher impact applications,^{3,11,20} there has so far not been a wider debate on how well they match to what is currently being practiced by industry and expected by regulators. To this end, a survey was initiated to investigate two overarching questions:

1. Do the recently documented industry good practices fit with current practice and match with regulatory expectations?
2. What are the current and future viewpoints from both industry and regulators on the role of MID3 in research and development (R&D) and regulatory review?

Initial results of the survey were presented and discussed at the American Conference on Pharmacometrics 8 (ACOP8) meeting. In this article, we present the integrated view of this survey and the discussion.

METHODS

A survey was developed in collaboration with the European Federation of Pharmaceutical Industries and Associations (EFPIA) MID3 workgroup aimed at getting answers around the two above mentioned questions from regulators and industry. The final survey included 15 detailed questions covering six aspects (practice, implementation, impact, status, organizational priority, and enabler/disablers) that are illustrated in **Figure 1**. The practice aspect aligns with the first overarching question, whereas the other five aspects align to the second overarching question. The target audience for the survey was clinical pharmacology and/or pharmacometrics departments within each organization. Respondents were directed to provide, if possible, a consolidated response on behalf of their department within their organization.

The pharmaceutical industry perspective was surveyed through contacting clinical pharmacology and/

or pharmacometrics leaders from across 23 EFPIA/Pharmaceutical Research and Manufacturers of America companies (PhRMA). Of these, a total of 18 responses were provided (“industry response”).

The integrated results, based on the majority view, across industry responses were used to aid comparison with results from the EMA and the US Food and Drug Administration (FDA).

The EMA perspective was provided by responses from 13 participants from the European regulatory network. This number includes EMA staff and Modeling and Simulation Working Group members (staff from national regulatory authorities and three academic members). The responses were summarized to aid comparison with industry and the FDA responses.

The FDA perspective was provided as the consolidated response from a group of 11 individuals with representation from the Division of Pharmacometrics, Division of Applied Regulatory Science, and Immediate Office in the Office of Clinical Pharmacology, FDA. This group included senior reviewers, team leaders, and directors across all the units.

The survey was completed between May and September 2017 in advance of the ACOP8 meeting, where the results were first presented through summary presentations from industry, the EMA, and the FDA.

RESULTS

The industry, the FDA, and the EMA summary results for the six aspects of the questionnaire are presented as indicated by **Figure 1**. Results for practice (aspect a), implementation (aspect b), impact (aspect c), and priority (aspect e) are integrated into **Tables 1 and 2** and **Figure 2**; utility (aspect d) is presented in **Figure 3**; and enablers/disablers (aspect f) are presented in **Figure 4**. Note the results for question 7 (Q: use of MID3 in various phases of drug discovery and development) are not presented here, as this was considered to have been misinterpreted leading to a number of responses exceeding 100%.

The full questionnaire, with anonymized raw industry responses and including free text comments, is provided in the **Supplemental Material**. In addition, the ACOP presentations on the industry, the EMA, and the FDA summaries of survey results are included in the **Supplemental Material**, followed by individual textual summaries and interpretations of survey results for industry, the FDA, and the EMA. It is highly recommended that these supplemental materials are reviewed to get a full understanding of the underlying viewpoints and proposals, as these are succinctly summarized in the main article.

The following section provides an integrated summary and interpretation of the results by each survey aspect (aspects e and f are discussed jointly to aid interpretation). This integrated summary is based on the survey results, free text comments provided by industry respondents, and the subsequent panel discussion at the associated ACOP8 symposium session titled “Model-Informed Drug Discovery and Development (MID3): Industry Good Practice, Regulatory Expectations, and Technical Gaps” in which the results were

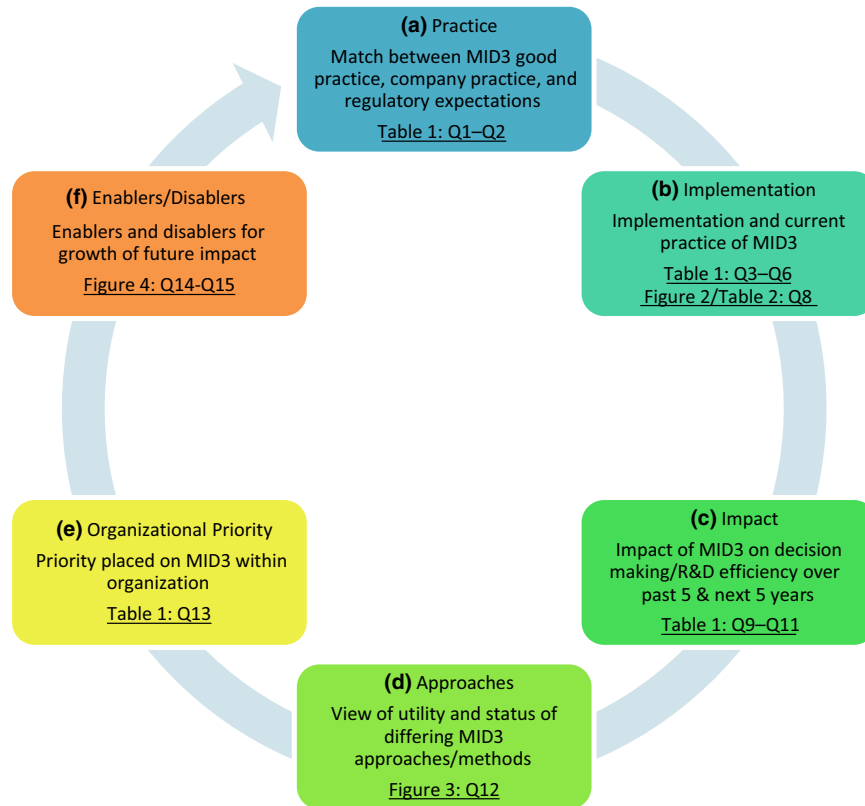


Figure 1 Overview of six aspects ((a) practice, (b) implementation, (c) impact, (d) approaches, (e) organizational priority, and (f) enablers/disablers) that were covered in the questionnaire in support of the American Conference on Pharmacometrics 8 symposium session on “Model-Informed Drug Discovery and Development (MID3): Industry Good Practice, Regulatory Expectations, and Technical Gaps.” References to the specific questions and the result tables and figures are provided. R&D, research and development.

first presented (<http://www.acop7.org/previous-acop8-final-program>).

Integrated industry, FDA, and EMA results and interpretation

Aspect a: match among MID3 good practice, company practice, and regulatory expectations. The authors find it very encouraging that based on the survey results (Table 1, aspect a, industry, the EMA, and the FDA colleagues, in general, agree that the MID3 good practice white paper³ is considered a “good match with some gaps” with respect to regulatory expectations and company practices.

There were a variety of viewpoints with respect to the gaps not addressed by the current white paper or by other references. The EMA colleagues highlighted the need for greater focus on early communication with regulators and “qualification” of specific models with respect to their context of use, especially for high-impact regulatory decisions. Industry respondents have themselves not fully adopted the newer aspects of the good practices (e.g., assumptions and impact assessment) but instead are piloting these approaches where appropriate and/or are waiting to see if this will be requested by regulators. Despite these gaps, the majority opinion across both pharma and EMA respondents was that the white paper was a general guidance document and could be a starting point for developing regulatory

guidelines for industry or could be referenced in future guidelines. The FDA respondents considered the white paper as a good general guidance document, and when appropriate it should be referenced in future regulatory guidelines for industry. However, they also highlight the risk that practices could become too prescriptive and thereby potentially stifle future innovative applications.

As highlighted by some industry respondents, there is a growing need for updates to current regional and global regulatory guidelines, such as population PKs, and exposure response guidelines, and for developing new guidelines focused on emerging specific modeling application types, such as risk benefit assessment and disease modeling. Therefore, the primary discussions focused on whether the community should invest in developing a globally agreed regulatory framework or rather focus on advancing individual guidelines. On one hand, a core global MID3 framework guideline could move forward the understanding and acceptance of these approaches by both technical reviewers and nontechnical regulatory decision makers and in turn foster wider application. It should also help improve the consistency of how technical aspects are covered across specific individual guidelines by providing a common source for terminology and standards. It is also possible that a general MID3 guidance could provide a framework that reduces the immediate need for individual guideline update in some areas as well as providing some coverage for emerging areas

Table 1 Overview of questions and answers to four aspects (a,b,c, & e) of the survey

	Aspect	Question	Industry	FDA	EMA
a	Match between MID3 good practice, company practice, and regulatory expectations	Q1) How close do the recently documented MID3 good practices match with regulatory expectations/company practices? ^a	Good match with some gaps	Good match with some gaps	Good match with some gaps
		Q2) To what extent should the MID3 good practices serve as a regulatory guideline for industry? ^b	Role as a general guidance document and starting point for regulatory guideline development	Good general guidance document and will be/should be referenced in future regulatory guidelines	Role as a general guidance document and starting point for regulatory guideline development/should be referenced in future regulatory guidelines
b	Implementation and current practice of MID3	Q3) How has the degree of implementation of MID3 changed across your organization over the past 5 years in terms of organizational structure with respect to conduct/review of MID3? ^c	Substantial orientation toward these approaches	Modest orientation toward making these approaches more central to organization's business	Modest orientation towards making these approaches more central to organization's business
		Q4) How has the degree of implementation of MID3 changed across your organization over the past 5 years in terms of evolution of resources assigned to conduct/review of MID3? ^d	Substantial increase	Modest increase	Modest increase
		Q5) How has the degree of application of different MID3 approaches changed over the past 5 years? ^d	Substantial increase	Modest increase	Substantial increase
		Q6) How has the degree of implementation of MID3 changed across your organization over the past 5 years in terms of development of MID3 processes?	Substantial increase	No change	Modest increase
c	Impact of MID3 on decision making/R&D efficiency over past 5 and next 5 years	Q9) How has the degree of impact of different and/or integrated MID3 approaches on decision making changed over the past 5 years? ^d	Modest increase	Modest increase	Modest increase
		Q10) What are the expectations for the degree of impact of MID3 on decision making changed over the next 5 years? ^d	Modest increase	Modest increase	Substantial increase
		Q11) How in general is MID3 viewed with respect to being a solution with respect to making R&D and/or regulatory review more efficient? ^e	A growing methodology that is starting to fulfil its promise with respect to advancing R&D efficiency in the years to come	A growing methodology that is starting to fulfil its promise with respect to advancing review efficiency in the years to come	A growing methodology that is starting to fulfil its promise with respect to advancing R&D efficiency in the years to come
e	Priority placed on MID3 within organization	Q13) What priority is placed on MID3 as a solution to making R&D and/or regulatory review more efficient? ^f	Priority set based on expectations set by global regulators ^g	Some priority in order to keep pace with changing expectations and technical advancements	Some priority in order to keep pace with changing expectations and technical advancements

Possible answers and notes: ^aLittle match with many gaps; some match with many gaps; good match with some gaps; very good match with few gaps; other.

^bLimited role as a general guidance document; role as a general guidance document and starting point for regulatory guideline development; good general guidance document and will be/should be referenced in future regulatory guidelines; replace need for equivalent/similar regulatory guideline or could be the reference source. ^cDeclined; no change; modest orientation toward making these approaches more central to organizations' business; substantial orientation toward these approaches. ^dDeclined; no change; modest increase; substantial increase. ^eA mature methodology that will do little to significantly further advance R&D efficiency in the years to come; a mature methodology that is starting to fulfil its promise with respect to advancing R&D efficiency in the years to come; a growing methodology that is expected to do little to significantly further advance R&D efficiency in the years to come; a growing methodology that is starting to fulfil its promise with respect to advancing R&D efficiency in the years to come. ^fNo priority as considered as standard methodology; some priority in order to keep pace with changing expectations and technical advancements; priority set based on expectations set by global regulators; high priority in order to lead the development of high impact MID3 applications with associate evolution of approaches and/or processes. ^gSame number of responses (7) for "some priority in order to keep pace with changing expectations and technical advancements" and "priority set based on expectations set by global regulators" with four voting for "high priority in order to lead the development of high impact MID3 applications with associate evolution of approaches and/or processes." Majority of "priority set based on expectations set by global regulators" responses based on associated comments and those provided under aspect a).

EMA, European Medicines Agency; FDA, US Food and Drug Administration; MID3, Model-Informed Drug Discovery and Development; R&D, research and development.

Table 2 Regulatory response to Q8 (aspect b): What themes are supported by MID3 in the submission you review? Presented as the percentage of submissions that cover the listed MID3 themes

	FDA, %	EMA, %
Medical need	0	0
Pharmacokinetics	81–90	81–90
Efficacy	51–60	51–60
Safety/tolerability	51–60	51–60
Benefit/risk	31–40	1–10
Clinical viability	0	0
Study/program design	21–30	31–40

EMA, European Medicines Agency; FDA, US Food and Drug Administration.

where currently no specific guideline exists (e.g., disease progression modeling). On the other hand, being able to provide sufficient granularity and value could be difficult to do, beyond simply inferring that MID3 can have important value for industry and regulators. Nonetheless, it is evident that regulatory agencies and drug developers already see value of framework type documents (e.g., EMA extrapolation framework document). Similarly, although the diversity and the evolving nature of MID3 methods could make this a bit of a moving target, the provision of general standards, scope, and terminology of this type has also been considered useful in other areas.^{10,21,22} One potential approach for MID3 guidance is through the ICH, where the precedence set by the current ICHE11 addendum (currently at step 2 in the ICH process) can be used as a guide as to what may be possible with respect to global harmonization.

Aspect b: implementation and current practice of MID3. Industry applications of MID3 have been mainly in the domain of PK, followed by efficacy, safety outcomes, study/program design, and benefit-risk assessment in regulatory submissions (Figure 2). This is consistent with what regulators see in submissions (Table 2). In the areas of extrapolation from adults to children, drug-drug

interactions, dose/posology recommendations, corrected QT interval prolongation risk assessment, and medicinal product life cycle management, MID3 approaches play an important role in regulatory decision making. The historical emphasis on PK is consistent with the central role of exposure in drug development and regulatory decision. MID3 is also being used by industry to assess medical need or clinical viability to support internal strategy (Figure 2).

In general, industry respondents have observed a modest to substantial (majority) increase in the implementation, application, resources, and substantial change in organizational structure over the past 5 years (Table 1). In the authors' view, and as supported by some of the associated comments, the heterogeneity here could well be representative of a recent "baseline shift" for organizations that previously had less emphasis on these activities and how they were incorporated into their R&D process. The more modest changes reported by other companies may, therefore, relate to organizations that had already made this step change, achieving partial or full integration into routine R&D practice. For these organizations, subsequent changes in implementation and application may have been more incremental or indeed difficult to maintain given frequent organizational shifts. A key caveat is that the EFPIA/PhRMA industry respondents represent the larger drug development organizations and, thus, are not representative of a large fraction of small and medium biotech and pharmaceutical companies. Some of these organizations may not be aware of the value and/or lack appropriate resources to embed these activities across strategic R&D decision making. Although many more provide MID3 analyses to be in line with regulatory expectations for submissions, often utilizing specialist contract research organization expertise.

The emergence of the Modeling and simulation Working Group and Modeling and simulation working practice translates to a significant shift in structure for the EMA. However, Regulators have, in general, seen a modest orientation toward MID3 with a modest increase in resources (Table 1).

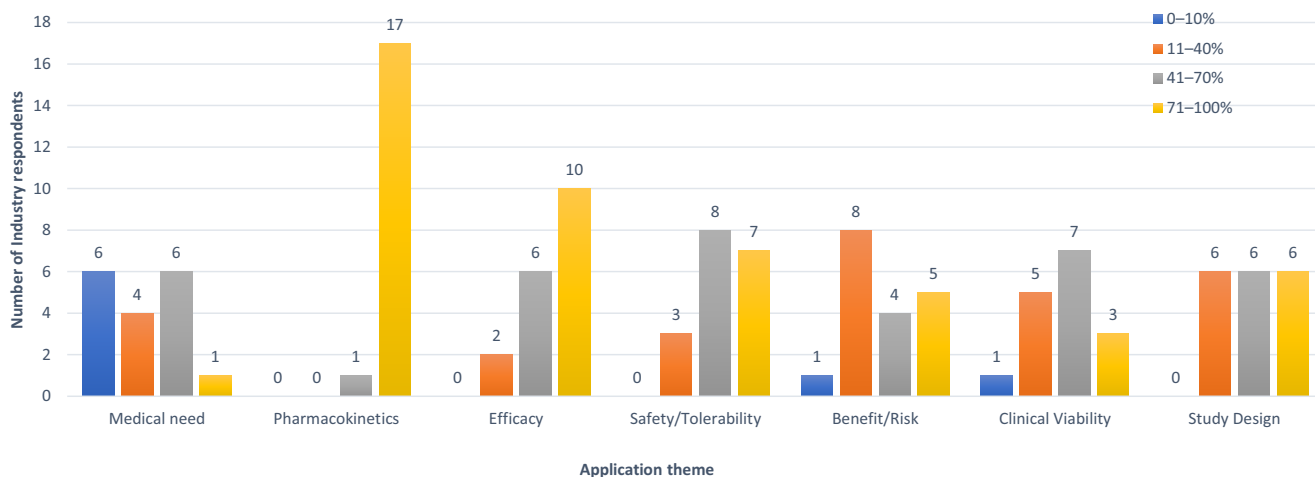


Figure 2 Industry response to Q8 (aspect d): To what extent do the following themes feature in the of strategic plans in your organization? In this overview, the percentage of strategic plans that reference each of the application themes is shown as distribution across the 18 responding companies responding to this question. Compared with other areas, most companies focus on pharmacokinetics in their Model-Informed Drug Discovery and Development strategic plans.

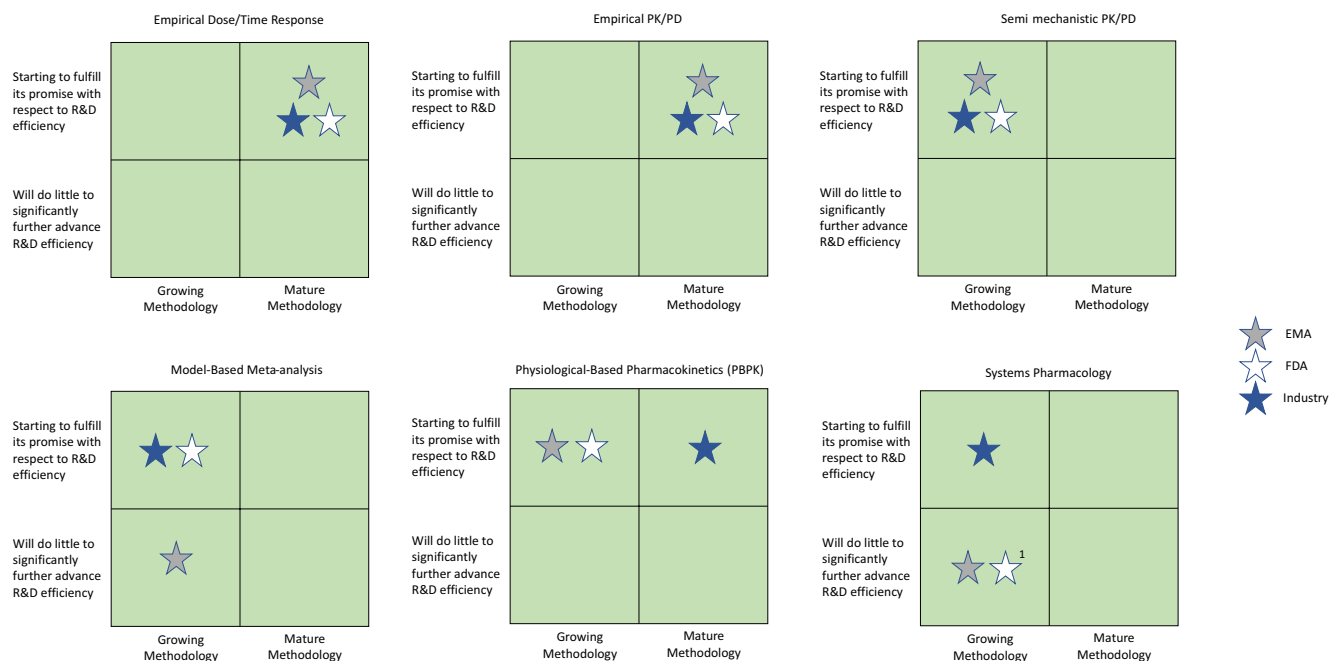


Figure 3 Response to Q12 (aspect d): How are the different approaches viewed with respect to being a solution with respect to making research and development (R&D) and/or regulatory review more efficient? Each modeling approach is assessed with respect to maturity of the methodology and the potential to increase the R&D efficiency. ¹The US Food and Drug Administration (FDA) actual textual response on systems pharmacology was: “this is a growing methodology whose exact potential is unknown at this time and the EMA share this viewpoint.” EMA, European Medicines Agency; PK/PD, pharmacokinetic/pharmacodynamic.

This viewpoint is perceived to be a consequence of several factors: (i) Increased general regulatory expectation and standardization of some MID3 approaches (population PK, exposure-response, concentration-QT analysis) and (ii) increased applications in emerging areas, such as physiologically based PK modeling. There is also recognition that newer areas, such as cheminformatics and systems pharmacology, are emerging, and all these will require establishment of structure and best practices.

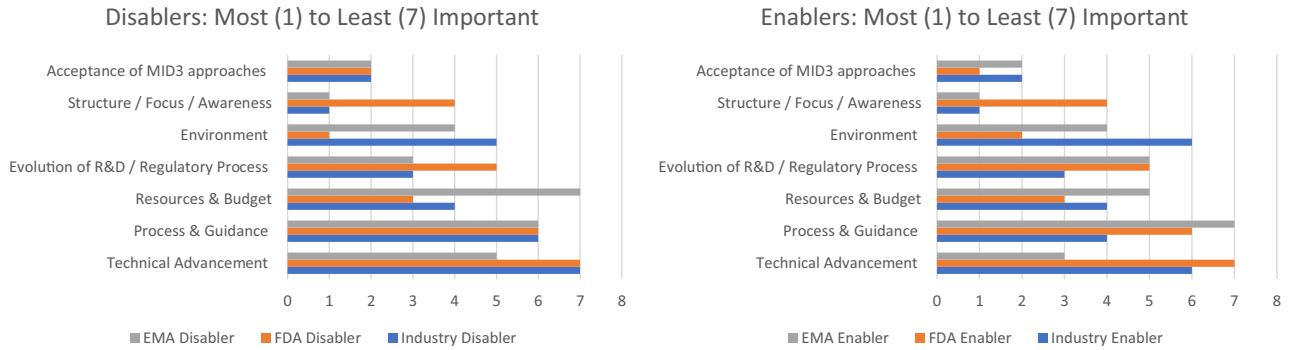
Aspect c: impact of MID3 on decision making/R&D efficiency over past 5 and next 5 years. Across industry and regulators, there has at least been a modest (with some companies reporting a substantial) increase in the degree of impact of MID3 on decision making over the past 5 years (Table 1). There was also consensus across all respondents on MID3 being a growing methodology that is “starting to fulfill” its promise with respect to advancing R&D and regulatory efficiency in the years to come. In addition to the continued growth in the general need for these methods to influence decision making and dose selection, the authors feel that this result is consistent with the increased use in areas where the use of prior knowledge and extrapolation is more often required (e.g., oncology, pediatrics, rare disease, or other special populations).

In terms of the future, most of the EFPIA/PhRMA respondents and the FDA expect at least a modest increase in impact, whereas the EMA and some companies expect a substantial increase in impact of MID3 on decision making over the next 5 years (Table 1). Given the changing nature of our clinical trials, general growth in data science and its

predicted value for R&D,²³ the authors are not surprised by the future expectations for these approaches.

Aspect d: view of utility and status of different MID3 approaches/methods. There was general alignment on the maturity and future promise of individual MID3 approaches, as shown in Figure 3. The exceptions seemed to be regarding the EMA respondents perhaps having less familiarity with model-based meta-analysis (MBMA) approaches and their utility in providing indirect comparative efficacy and safety information, which can be used to underpin dose selection, therapeutic benefit, and facilitate trial design (see **EMA Supplemental Results** for more discussion). This highlights the need for further interaction and education in this area, including greater engagement with statistical colleagues on the merits of using pharmacology principles to maximize the value of MBMA.^{24–26} The mixed viewpoint with respect to quantitative systems pharmacology modeling indicates that, despite application in a regulatory context,²⁷ there is also the need for more engagement in this space to fully explore the potential and the additional complexity of these approaches. The associated sessions at recent conferences^{28–30} in this area and other initiatives³¹ are acknowledged for being important steps in this direction.

Aspects e) priority placed on MID3 within organization and f) disablers/enablers for growth of future impact of MID3. Although the results for the priority of MID3 were mixed between three categories (see footnote g, Table 1), there is a strong viewpoint across many industry respondents that regulatory expectations have a large impact on how



	Guiding Disabler questionnaire text:	Guiding Enabler questionnaire text:
Acceptance of MID3 approaches	Lack of alignment across statisticians, clinical pharmacologist, and clinicians with respect to practice and application. Lack of "Reviewer" confidence in MID3 outputs in lieu of additional evidence	Greater alignment across statisticians, clinical pharmacologist, and clinicians with respect to practice and application. Increases in "Reviewer" confidence in MID3 outputs in lieu of additional evidence
Structure/focus/awareness	Organization focused on speed, study conduct, and trial-based evidence, etc. Lack of alignment of statistical and MID3 approaches and processes. Lack of awareness of value of MID3 approaches among decision-makers	Organization focused on totality of integrated evidence. Good alignment of statistical and MID3 approaches and processes. Increase in awareness among decision makers of MID3 methodologies and the insights each provides
Environment	Lack of availability of disease and system-level data. Lack of Consortia lead development of platform MID3 approaches	Greater availability of disease and system-level data. Consortia lead development of platform MID3 approaches
Evolution of R&D/regulatory process	Lack of focus of new drug development and approval paradigms on the value of MID3. Limited use and acceptance of biomarkers. Lack of alignment of MID3 activities between industry and regulators across the R&D/review life cycle	Increases in the general standards and application of MID3. Clear guidelines that provide a framework for extrapolation. Improved practice against guidelines
Resources/budget	Limited resources assigned to MID3 approaches and/or processes	Focus on MID3 approaches due to cost constraints. Utility to deliver new medicines for smaller populations. Growth in resources assigned to MID3 approaches and/or processes
Process & guidance	Lack of general standards in the application of MID3. Lack of clear guidelines that provide a framework for extrapolation. Poor practice against guidelines	Increases in the general standards and application of MID3. Clear guidelines that provide a framework for extrapolation. Improved practice against guidelines
Technical advancement	Limited development of systems and tools that provide a transparent way to develop, share, and furtherutilize models. Type 1 error inflation where evidence is informed by prior knowledge or obtained via a "learning step"	Improved systems and tools that provide a transparent way to develop, share, and further utilize models. Overcoming the difficulties of Type 1 error inflation where evidence is informed by prior knowledge or obtained via a "learning step"

Figure 4 Graphical representation of disablers and enablers to growth in future impact of Model-Informed Drug Discovery and Development (MID3; aspect f). Left: Q14, What disablers are most likely to hamper the growth in the degree of impact on MID3 on decision making over the next 5 years? Right: Q15, What enablers are most likely to aid the growth in the degree of impact of MID3 on decision making over the next 5 years? EMA, European Medicines Agency; FDA, US Food and Drug Administration; R&D, research and development.

industry prioritizes these approaches. This was highlighted in the associated comments across both practice (aspect a) and priority (aspect e). Moreover, it suggests that in comparison to some “MID3 focused companies” who are looking to lead the way and see inherent value by having MID3 as a central tenet of R&D, many other companies are looking for positive steer and “pull” from the regulatory authorities before further investing in this area. On the other hand, the EMA and the FDA indicated that, in general, some priority should be given to MID3 in their organizations to keep pace with changing expectations, review efficiency, and technical advancements. With respect to the enablers/disablers for growth of future impact of MID3, it should first be noted that the categorical responses show heterogeneity in the rank order of the disablers and enablers across and within organizations, and differences between some of the categories could be smaller than the actual ranking (Figure 4). Nonetheless, it is clear that all organizations place acceptance (or lack of acceptance) of MID3 approaches among statisticians, clinicians, and clinical pharmacologists as an important enabler (disabler). In addition, industry respondents and the EMA emphasize “organizational structure/focus/awareness” as most important to the future of MID3 approaches. In comparison, the FDA survey respondents placed more importance on the potential impact of “environment” (e.g., availability of

disease and system level data; Consortia lead development of platform MID3 approaches). Although the survey did not specifically ask about data flow or curation in general, it is acknowledged, as suggested by a reviewer, that this would also be an important disabler/enabler.

Interestingly, although industry respondents place more emphasis on “process and guidance” as an enabler compared with the FDA and the EMA, it is not a top-ranked priority despite there being significant comments regarding the need for updated and aligned regulatory guidelines. As discussed in more detail in the individual industry results (Supplemental Material); the viewpoint is that updated regulatory guidelines and requests for MID3 in submission help the acceptance, priority and organizational focus on these approaches, as well as the evolution of the R&D paradigm toward predictive sciences in general.

FURTHER CONSIDERATIONS

From the authors’ viewpoint, a common underlying theme is the need to convince “decision makers” across the different organizations of the value of MID3. This issue can be heightened by organizational structures, which may isolate technical experts from each other and the decision-making process. To help address this issue, the authors offer the following considerations:

(i) Educate decision makers in all organizations via workshops and guidelines

A major challenge is decision makers may not be appropriately trained to evaluate MID3 approaches and as a result be more averse to the perceived risk. Therefore, if the uncertainties in any MID3 application are not well understood and translated into associated risks, then the approaches can be discarded altogether. Recent and proposed EMA¹¹⁻¹³ and FDA¹⁹ workshops, etc, are helping to grow awareness and focus on these approaches, and the leadership here is to be commended. Alignment of industry and regulatory decision makers on the acceptance of these approaches is absolutely critical. It is, therefore, important that in addition to expert functions, key stakeholders (decision makers, regulatory affairs, etc.) take part in these or other focused workshops.

An important part of this process is discussion of the aspects and factors that have led to success and failure of MID3 applications from both industry and regulatory perspectives and how greater global consistency can be achieved via early dialogue and parallel interactions with the EMA/FDA. With respect to the former, discussions on their role in bringing novel therapeutics faster to patients without increasing risk may help to convey importance of MID3 to decision makers.⁴ In addition, specific training of key stakeholders in industry and regulatory authorities, so that they can “trust” these approaches and how they are evaluated must be considered. It is clear from the industry perspective, at least, and as discussed earlier, that harmonized global guidelines are seen as part of the solution.

The “communication gap” between modeling scientists and other disciplines and decision makers both within industry and between industry and regulators was one of the original motivating factors for the MID3 good practice white paper.¹¹ The practice of developing a strategic plan covering pertinent R&D questions against key themes (e.g., medical need/commercial viability, PK, efficacy, safety/tolerability, risk-benefit, clinical viability, and study design), associated levels of activity (e.g., compound, mechanism, and disease level), and use of differing but integrated MID3 modeling approaches was proposed and exemplified in this guideline to help aid better alignment. Important here was that these plans are understood by decision makers. Therefore, ensuring that the assumptions, their evaluation, and impact are presented in a transparent manner, as proposed by the MID3 good practice document, is something we must continue to advocate so that it is more widely used and developed.

(ii) Role of modeling scientists in early strategic planning and looking to influence their organizations from an internal perspective

MID3 practitioners in industry have a very important role in ensuring strategic planning is started early and integrated on an ongoing basis and into the general drug discovery and development plan.³ Early “disease level” planning may be required to ensure sufficient up-front thinking is done with respect to the role of MID3 in future trial design and analysis. Procedures to obtain both early and general overarching input from regulators are available (e.g., scientific advice,³² qualification procedure,³³ parallel

EMA-FDA scientific advice,³⁴ type B and C meetings,³⁵ and the FDA pilot program³⁶) to facilitate the endorsement of innovative approaches and alignment with respect to expected “impact” of MID3 applications and the associated assumptions.³

Although the importance of these meetings is clear, the industry believes that more continuous direct interactions between industry and regulatory technical colleagues with respect to MID3 applications could further help efficiency, particularly for higher impact applications and implementation of more technically demanding MID3 approaches (e.g., novel disease progression models), by ensuring technical aspects, such as modeling details, model evaluation, and alignment on the adequate evaluation of assumption occurs more “real time” and outside of these wider meetings. While for the EMA, involvement in “real time” interactions may be challenging due to the nature of the EMA network, this could still be considered.

(iii) Role of professional bodies and consortia

Professional bodies (e.g., PhRMA, EFPIA, ISOP, American Society for Clinical Pharmacology and Therapeutics, European Federation of Pharmaceutical Sciences, Drug Information Association, American Diabetes Association, American Society of Clinical Oncology, American Association for Cancer Research, etc.) have a crucial role in orchestrating industry and regulatory perspectives. They should continue to aid in identifying exemplars of innovative practice, promoting use of MID3 approaches, acting as a sounding board for ideas, and being drivers for good practice development and guideline change. An important role is in facilitating cross-discipline interactions and engagement between industry and regulatory leaders. In addition, consortia from across industry, contract research organizations, academia, and regulators continue to have a fundamental role in driving new directions, knowledge creation, and innovative change. In particular, consortia could act as a “safe harbor” for data sharing and model development, which could then be submitted to regulators for qualification (Alzheimer’s disease³⁷). Both groups have a role in training and facilitating regulator/industry discussions with universities and government bodies on the need for more advanced skillsets in the area of MID3.

SUMMARY

The conducted survey looked at six aspects associated with two overarching questions with respect to both current and future practice and role of MID3. The results affirm that the documented industry good practices (aspect a) are a “good match” to current industry practice and regulatory expectations “with some gaps,” which have been discussed in this article. There is a unified viewpoint across industry and regulators that there has at least been a “modest” step forward in MID3 implementation in terms of organizational structure, resource, and application in the last 5 years and that there is a similar if not greater expectation for the future (aspect b). There is a general increased organizational awareness and expectation that these approaches “are useful” and have and can continue

to impact decision making (aspect c), although there is less familiarity and comfort with some of the “newer” MID3 modeling approaches (such as MBMA, quantitative systems pharmacology, aspect d). A limitation is with respect to how MID3 is being prioritized within organizations (aspects e and f). The discussed approaches to addressing this issue highlight increasing the acceptance of these approaches by industry and regulatory decision makers by having a sustained focus on developing facilitating processes within and across organizations. In this endeavor, modeling scientists, professional bodies, and consortia also have an important role to play in helping this continued evolution. Some approaches include development of an overarching global regulatory guideline encouraging good MID3 practice and development and/or update of existing specific regulatory guidelines to provide more concrete recommendations for industry in areas where there is already significant understanding (e.g., pediatrics, dose finding, etc.). However, it is important to note that the overall goal should not be to “raise the bar for few” but to “shift the baseline” for the whole pharma sector.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website. (www.psp-journal.com)

Supplemental Material S1 Summary.

Supplemental Material S2 Survey responses industry.

Supplemental Material S3 ACOP presentation industry.

Supplemental Material S4 ACOP presentation EMA.

Supplemental Material S5 ACOP presentation FDA.

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