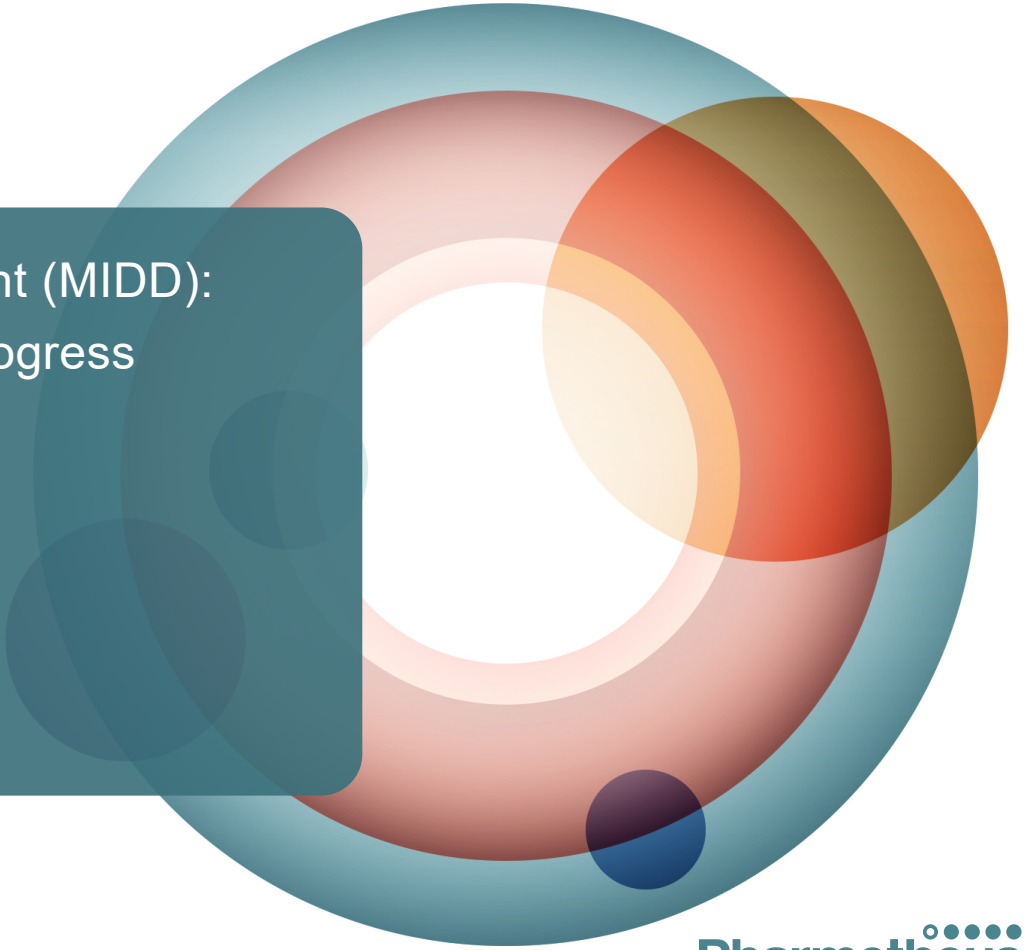
Model Informed Drug Development (MIDD): Challenges, Opportunities and Progress

Peter A Milligan, CEO, Pharmetheus
Richard Anziano, Chief Statistician, Pharmetheus



Pharmetheus

Our experiences and perspectives are informed by (1)

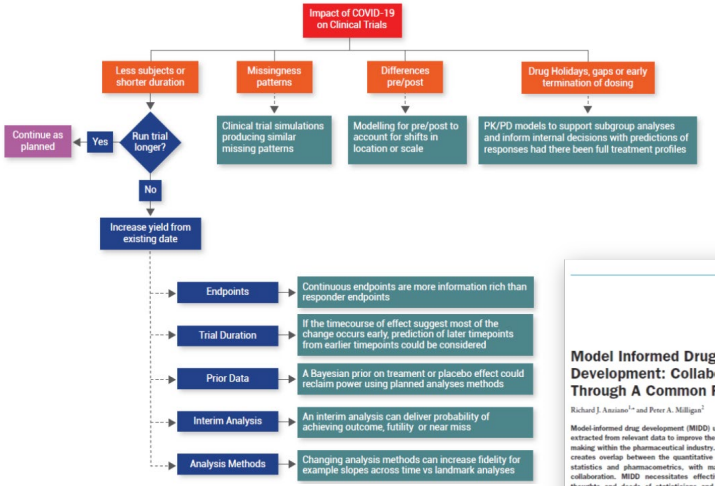
Pfizer (pre 2019)

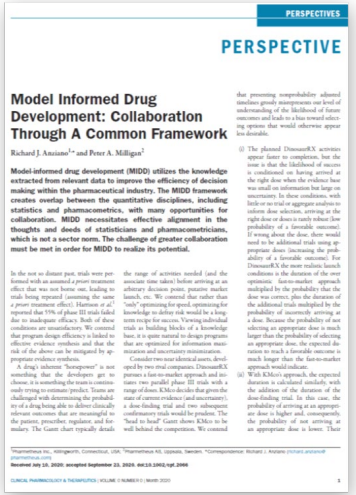
- PM was Head of Global Pharmacometrics and Clinical Pharmacology lead on MIDD implementation for the Pfizer enterprise
- RA was Head of Global Statistics and Statistics lead on MIDD implementation for the Pfizer enterprise

Our experiences and perspectives are informed by (2)

Pharmetheus (since 2019)

- PM is the CEO and acts as a consultant to clients on MIDD implementation and project related matters
- RA is Chief Statistician and acts as a consultant to clients on MIDD implementation and project related matters




PERSPECTIVES

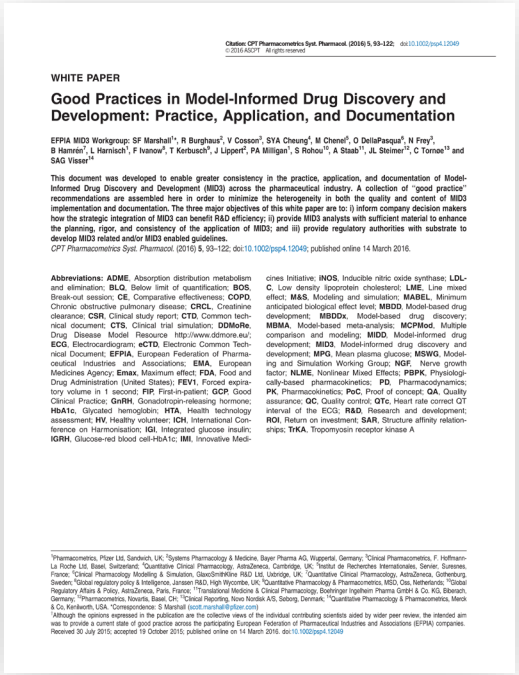
PERSPECTIVE

Model Informed Drug Development: Collaboration Through A Common Framework

Richard J. Anziano[1]* and Peter A. Milligan[2]

Model-informed drug development (MIDD) utilizes the knowledge extracted from relevant data to improve the efficiency of decision making within the pharmaceutical industry. The MIDD framework creates overlap between the quantitative disciplines, including statistics and pharmacometrics, with many opportunities for collaboration. MIDD necessitates effective alignment in the thoughts and deeds of statisticians and pharmacometricians, which is not a sector norm. The challenge of greater collaboration must be met in order for MIDD to realize its potential.

Outline of Presentation



Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122; doi:10.1002/psp4.12049

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[7], B Hamrén[8], L Harnisch[9], F Ivanow[8], T Kerbusch[6], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MID3) across the pharmaceutical industry. A collection of "good practice" recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MID3 implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MID3 can benefit R&D efficiency; ii) provide MID3 analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MID3; and iii) provide regulatory authorities with substrate to develop MID3 related and/or MID3 enabled guidelines.

CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122; doi:10.1002/psp4.12049; published online 14 March 2016.

Abbreviations: ADME, Absorption distribution metabolism and elimination; **BLQ**, Below limit of quantification; **BOS**, Break-out session; **CE**, Comparative effectiveness; **COPD**, Chronic obstructive pulmonary disease; **CRCL**, Creatinine clearance; **CSR**, Clinical study report; **CTD**, Common technical document; **CTS**, Clinical trial simulation; **DDMoRe**, Drug Disease Model Resource http://www.ddmore.eu/; **ECG**, Electrocardiogram; **eCTD**, Electronic Common Technical Document; **EFPIA**, European Federation of Pharmaceutical Industries and Associations; **EMA**, European Medicines Agency; **Emax**, Maximum effect; **FDA**, Food and Drug Administration (United States); **FEV1**, Forced expiratory volume in 1 second; **FIP**, First-in-patient; **GCP**, Good Clinical Practice; **GnRH**, Gonadotropin-releasing hormone; **HbA1c**, Glycated hemoglobin; **HTA**, Health technology assessment; **HV**, Healthy volunteer; **ICH**, International Conference on Harmonisation; **IGI**, Integrated glucose insulin; **IGRH**, Glucose-red blood cell-HbA1c; **IMI**, Innovative Medicines Initiative; **iNOS**, Inducible nitric oxide synthase; **LDL-C**, Low density lipoprotein cholesterol; **LME**, Line mixed effect; **M&S**, Modeling and simulation; **MABEL**, Minimum anticipated biological effect level; **MBDD**, Model-based drug development; **MBDDx**, Model-based drug discovery; **MBMA**, Model-based meta-analysis; **MCPMod**, Multiple comparison and modeling; **MIDD**, Model-informed drug development; **MID3**, Model-informed drug discovery and development; **MPG**, Mean plasma glucose; **MSWG**, Modeling and Simulation Working Group; **NGF**, Nerve growth factor; **NLME**, Nonlinear Mixed Effects; **PBPK**, Physiologically-based pharmacokinetics; **PD**, Pharmacodynamics; **PK**, Pharmacokinetics; **PoC**, Proof of concept; **QA**, Quality assurance; **QC**, Quality control; **QTc**, Heart rate correct QT interval of the ECG; **R&D**, Research and development; **ROI**, Return on investment; **SAR**, Structure affinity relationships; **TrkA**, Tropomyosin receptor kinase A

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[1]Although the opinions expressed in the publication are the collective views of the individual contributing scientists aided by wider peer review, the intended aim was to provide a current state of good practice across the participating European Federation of Pharmaceutical Industries and Associations (EFPIA) companies.

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Pharmaceutical industry sector level influence

Challenge:

"Despite the well-documented sector, associated pressures, and productivity challenges, ***there is a large inconsistency in terms of MIDD utilization across the pharmaceutical industry***. *This is most likely a consequence of* ***the ROI for MIDD not being well understood within the higher echelons of the pharmaceutical industry and health authorities***. *Furthermore, although the current* ***MIDD*** *practice levels have been valuable and influential to a (variable) degree*, ***it is unlikely that the overall sector-associated pressures can be meaningfully impacted if the status quo is maintained***."

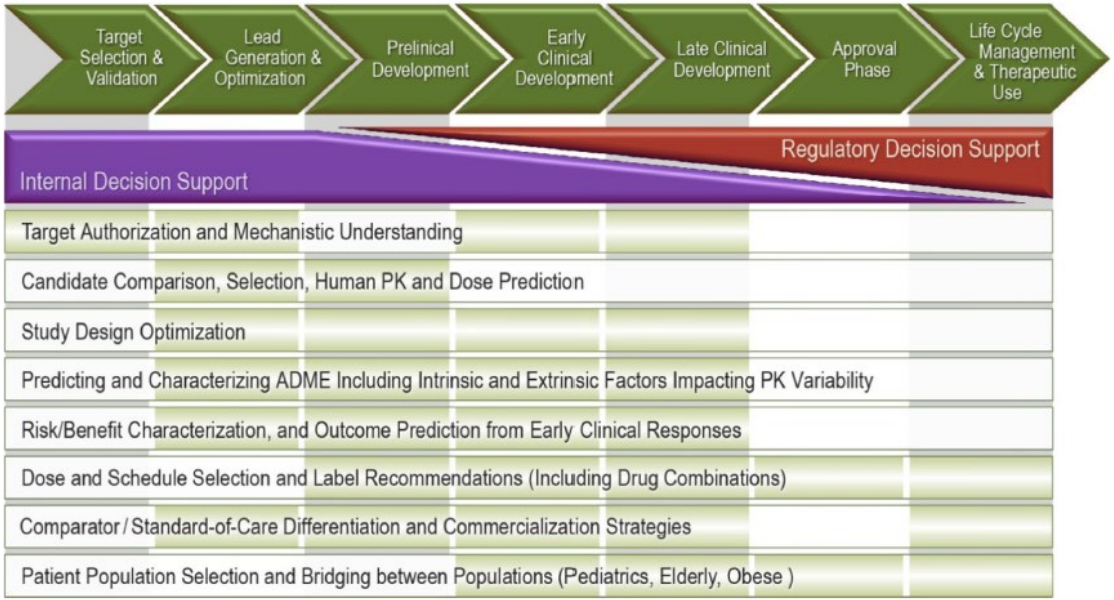
Pharmaceutical industry sector level influence

Opportunity:

"Generating greater awareness among industry and regulatory decision-makers as to ***why and how MIDD can be beneficial is essential****. It is important for increased implementation to* ***shift the balance from the technical advocates "pushing" MIDD to the decision-makers "pulling" MIDD****. In order to support determination of the ROI for* ***MIDD****, sections 3.1 and 3.2* ***illustrated the nature and extent of impacts for a variety of quantitative approaches across a range of relevant R&D scenarios.*** *In addition, in section 4.5 of this document we will introduce an* ***"EFPIA categorization of MIDD value for internal decision-making" that will enable determination of the business value obtained via MIDD."***

Applications of MID3 in the public domain

- About 100 case studies arranged by Application Type and R&D stages
  - ~30 exemplified in document
- Summarised by:
  - Key themes
  - Activities levels
  - Modelling approach
  - R&D questions
  - Internal impact and decision making



Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 416–417; doi:10.1002/psp4.12223

COMMENTARY

Commentary on the MID3 Good Practices Paper

Efthymios Manolis[1,2]*, Jacob Brogren[2,3], Susan Cole[2,4], Justin L. Hay[2,4], Anna Nordmark[2,3], Kristin E. Karlsson[2,3], Frederike Lentz[2,5], Norbert Benda[2,5], Gaby Wangorsch[2,6], Gerard Pons[2,7], Wei Zhao[2,8,9], Valeria Gigante[2,10], Francesca Serone[2,10], Joseph F. Standing[2,11], Aris Dokoumetzidis[2,12], Juha Vakkilainen[2,13], Michiel van den Heuvel[2,14], Victor Mangas Sanjuan[2,15], Johannes Taminiau[2,16], Essam Kerwash[2,4], David Khan[2,3], Flora Tshinanu Musuamba[2,17] and Ine Skottheim Rusten[2,18]; on behalf of the EMA Modelling and Simulation Working Group

To conclude, the MSWG considers that the MID3 white paper can potentiate the utility of modeling and simulation in regulatory review in moving from an *ad-hoc* problem-solving exercise, as it is often perceived, to an important source of evidence generation that influences development and benefit/risk decisions, labeling, risk management, and is crucial for the product lifecycle. The MSWG supports the principles included in the paper and invites other groups developing good practices documents to actively engage in discussions with regulators.

Model-Informed Drug Development: A Regulatory Perspective on Progress

Hao Zhu[1], Shiew Mei Huang[1], Rajanikanth Madabushi[1], David G. Strauss[1], Yaning Wang[1] and Issam Zineh[1,*]

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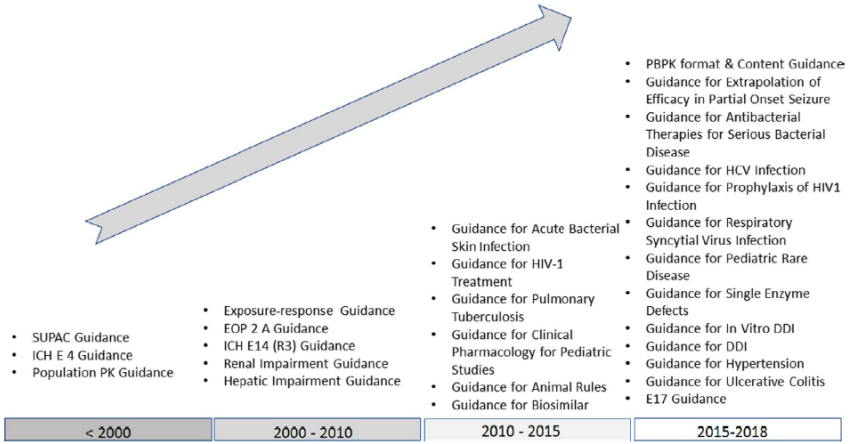


Figure 1 Increased development and incorporation of MIDD approaches in regulatory guidance over time at the FDA. DDI, drug–drug interaction; EOP 2 A, End-of-Phase 2A; FDA, US Food and Drug Administration; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICH, International Conference on Harmonization; MIDD, model-informed drug development; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetics; SUPAC, Scale Up and Post-Approval Changes.

SUMMARY

MIDD has had an eventful history and continues to evolve. Model-based approaches have been shown to improve drug development and enhance regulatory decision making by a variety of metrics. We are on the cusp of exponential growth, application, and acceptance of MIDD. The agency's new MIDD-related programs are creating an environment to facilitate this growth. We foresee an increased demand for MIDD with expanded scope, and believe the community is well positioned to bring these innovations forward for the benefit of patients.

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 87–96; doi:10.1002/psp4.12372

ARTICLE

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

Scott Marshall[1,*], Rajanikanth Madabushi[2], Efthymios Manolis[3], Kevin Krudys[2], Alexander Staab[4], Kevin Dykstra[5] and Sandra A.G. Visser[6]

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. [1]The 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.

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

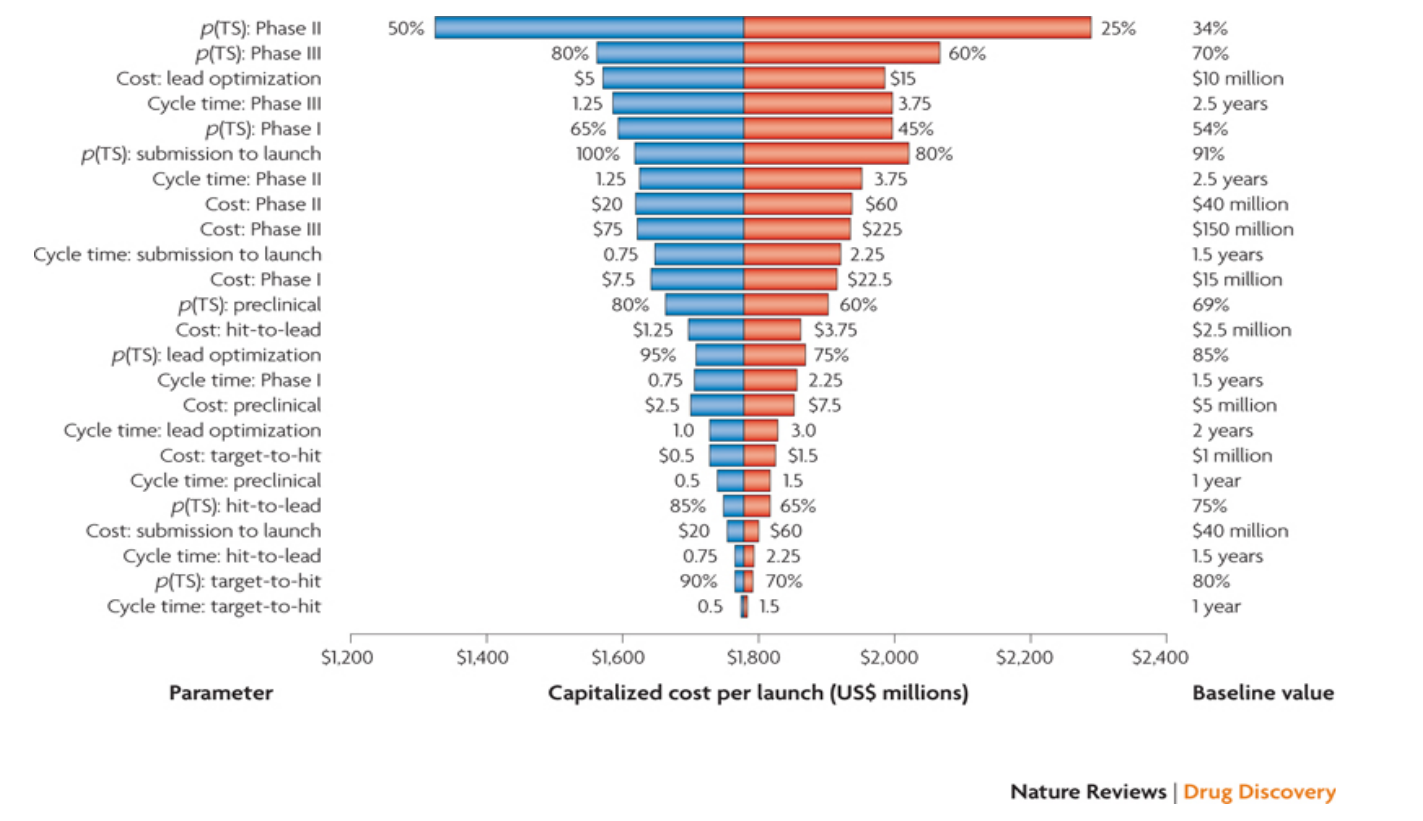
	Aspect	Question	Industry	FDA	EMA
a	Match between MID3 good practice, company practice, and regulatory expectations	Q1) How close do the recently documented MID3 good practices match with regulatory expectations/company practices?[a]	Good match with some gaps	Good match with some gaps	Good match with 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

Survey: further considerations

- Educate decision makers in all organizations via workshops and guidelines
- Role of modeling scientists in early strategic planning and looking to influence their organizations from an internal perspective
- Role of professional bodies and consortia

“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”

Improving Phase 2/3 success is biggest factor to improve R&D productivity



Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 5–8; doi:10.1002/psp4.12365

PERSPECTIVE

PDUFA VI: It Is Time to Unleash the Full Potential of Model-Informed Drug Development

Lokesh Jain[1], Nitin Mehrotra[1], Larissa Wenning[1] and Vikram Sinha[1]*

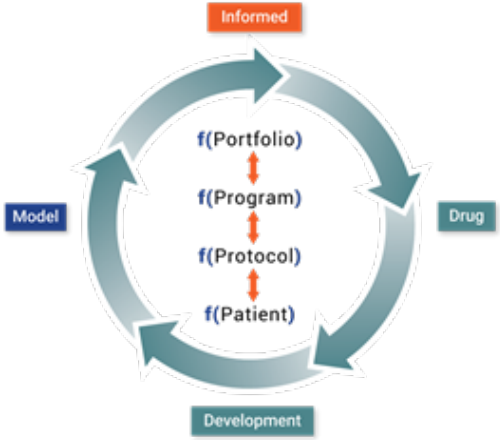
Table 1 Opportunities for application of MIDD-based approaches in clinical drug development

Typical current paradigm	MIDD-based paradigm	Advantages of MIDD paradigm
Sequential phase II– III trial approach	Innovative designs assisted with Clinical Trial Simulations (e.g., seamless phase II–III designs, adaptive designs, and biomarker-based designs)	Better (integrated) use of prior information to make the subsequent steps more efficient
Clinical trials in general population with *post hoc* analysis in subgroups	More targeted clinical trials to fill gaps in evidence for clinical use, based on predictions of benefit–risk in population subgroups	Use of resources to address the relevant questions in a more efficient and timely manner
Primary hypothesis in dose-ranging trials based on pairwise comparison of two doses or a dose and placebo	Primary hypothesis based on demonstration of positive slope in dose–response or exposure–response analysis	• Requires small sample size • Doses other than those tested in clinical study can be proposed
Traditionally designed pediatric studies (e.g., fully powered to demonstrate efficacy and safety end points)	Either replace the need for pediatric studies with evidence from M&S analysis or develop efficient designs to minimize burden on pediatric patients	Fast access to treatments in pediatric population
Specific population labeling based on studies evaluating drug–drug interaction, renal impairment, and hepatic impairment	Leverage integrated understanding of systems and drug PK characteristics to make predictions and evaluate only the extreme scenarios	• Alleviation of specific population trials • More efficient use of resources
Evidence for approval from replicate randomized trials	Evidence of approval from predictions using M&S, which are confirmed with single-efficacy and safety study if necessary	• Faster access to treatments • Lower cost and more efficient use of resources

MIDD, model-informed drug development; M&S, modeling and simulation; PK, pharmacokinetic.

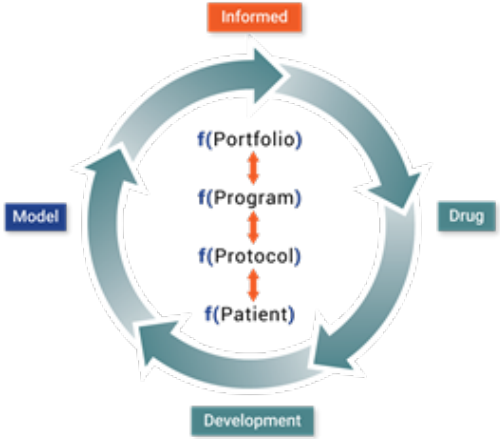
Within companies, it is working organizationally, when:

- The quantitative disciplines have a level of common understanding, and appreciation of, the skills within the other disciplines
  - each discipline brings complementary skills and perspectives/knowledge
  - each is necessary and important for achieving the overall objective efficiently
- The decision makers (and the quantitative disciplines) can frame the “right” questions in a quantitative manner
- The decision makers (and the quantitative disciplines) can quantify, understand and manage uncertainty
  - expressed through **probability considerations** relative to some pre-specified success criteria



Within companies, it is working technically, when:

- The quantitative disciplines adopt an appropriate blend of:
- Modelling components
  - Quantification of greatest compound risks (sources of uncertainty, most important assumptions) informing contingency plans to manage/mitigate risks appropriately
- Knowledge management/evidence synthesis components
  - Generating insights (certainty) around a compound's properties by leveraging accumulated data more effectively
  - Informing the attributes of any “new” data and/or reducing the need for “new” data
- Statistical components
  - Informing the selection of the most efficient study/program designs (optimized to the relevant “success” criteria)



Pharmaceutical industry sector level influence

Comment on Progress:

- Clear advancements have been made – more is being done and showcased
  - Can Model Informed Drug Development → Drug Development?
- Push and pull dynamic has shifted with FDA pilots programs of particular note
  - Client (medium/large) companies experiences are largely favorable
  - Participation promotes considerable internal dialogue
- What does “success” look like?
  - can we gain greater industry alignment?
  - can we have something similar for Regulatory Agencies – an umbrella guidance?

Organizational level influence

Challenges #1:

*"**MIDD** **aims to enhance the extraction of inference** from both existing information and data emanating from ongoing experiments. MIDD is an integrative approach that **can effectively support translation across, and extrapolation beyond**, a given set of experimental conditions.*

*An inherent consequence of this integrative approach is that the necessary source data, information, **expertise will reside across a broad range of personnel, departments, and institutions.** However, **an unintended consequence** can be the potential for "narrower" concerns emanating from infringements of actual or perceived "control," "ownership," "territory," and "domain" **diminishing the likelihood that the "broader" organization can derive the greatest benefit.**"*

Organizational level influence

Challenges #2:

"Another 'integration'' challenge surrounds how well MIDD can fit within R&D planning, processes, and timelines that are designed to service the needs of study level activities. For the potential for ***MIDD*** *to be realized, the associated* ***outputs need to be available for specific R&D decisions and be of a quality consistent with appropriate industry and regulatory standards****. This can present a significant challenge for what are predominately iterative modeling approaches and* ***can also curtail the choice of approach taken because of both data and time constraints."***

Organizational level influence

Opportunities:

*"The desired **technical methodologies for MIDD are established, and companies have colleagues with the appropriate skills** to deliver them. However, most **companies do not fully capitalize on this opportunity** as a result of organizational and/or cultural impediments. Mitigating or **removing these organizational impediments** has been shown to **improve late-stage clinical development productivity.***

*In addition, the adoption of a more realistic assessment of the merits of any given compound can bring productivity dividends to the organization. A cultural **shift toward "truth-seeking" and away from "progression-seeking" across individuals, teams, and governance** can mitigate many if not all of the principal challenges for enhanced MIDD implementation."*

COMMENT

Why is it hard to terminate failing projects in pharmaceutical R&D?

Richard W. Peck[1], Dennis W. Lendrem[2], Iain Grant[3], B. Clare Lendrem[2] and John D. Isaacs[2]

'Quick-kill' strategies in pharmaceutical research and development aim to reduce late-stage attrition by bringing project termination decisions forward, to an earlier point in the process. How can the barriers to implementing such strategies be overcome?

Currently, pharmaceutical research and development (R&D) productivity is low, late-stage attrition rates are high and drug development is costly[1]. Much of this cost is due to spending on molecules that do not complete development. A possible solution has been known for some time: 'quick-kill' strategies that seek to reduce late-stage attrition by bringing forward decisions to terminate projects to an earlier point in the process[2]. There are technical challenges in implementing such strategies to support experimental medicine approaches in early-stage clinical trials, including developing more-sensitive bio-assays for adverse effects and more-specific biomarkers based on clinical pharmacology. However, we consider that the real obstacles to implementation are behavioural, cultural and organizational. Here, we highlight these obstacles and discuss strategies to overcome them.

Obstacles to quick-kill strategies

Progression-seeking behaviours. R&D development milestones are used to manage the flow of products to market. To encourage such flow, R&D leaders usually have targets for the numbers of projects reaching development milestones. Although not without merit, such target setting can be counterproductive for R&D productivity if it leads to a focus on getting projects past a development gate even if that means the molecule fails at the next stage. Until they are terminated, such projects clog the pipeline, incurring additional R&D costs. Furthermore, such targets invite 'gaming' of the system, with decisions based on the need to meet quotas rather than on the viability of projects.

We recommend that such targets be abandoned or, at a minimum, used as part of a framework that takes account of molecule quality — such as the five 'R's described by AstraZeneca[3], or Pfizer's 'three pillars of success' — through which only projects with high chances of success qualify against progression targets. It is important to promote 'truth-seeking' rather than 'progression-seeking' behaviours; at Roche, R&D leadership emphasizes that poor-quality projects will not be progressed to achieve milestone targets.

Individual reward systems also often promote decisions to continue development of projects, with the role models for project teams being those who persist despite the odds. Membership of a team that gets a drug to market brings organizational visibility, higher pay rises, bonuses, invitations to more-promising projects in the future, and can open the door to senior management opportunities. Even when weak projects are eventually terminated, it is accepted as part of the high risk of drug development, and team members may be praised for their perseverance. So, team members have career development incentives to keep pushing their projects even when the evidence suggests that the chances of success are very low.

Drug development decisions are taken by people, and people are subject to powerful cognitive biases. For example, project managers and scientific leaders are often blinded by optimism bias. The value and probability of success is typically overestimated, and the costs and risks grossly underestimated. Such bias may be useful, as the investment required is so high and the chances of success so low that, if the risk were truly understood, perhaps too few people would ever take up the challenge. However, for a sustainable business, this bias needs to be managed, or the organizational and individual incentives described above will simply encourage progression-seeking behaviour.

These biased estimates combine with a 'sunk cost fallacy', in which individuals are loathe to terminate projects if it means 'losing' monies already spent. Decision makers seem to prefer the uncertain value of further development and the marginal costs associated with the progression of a molecule to the next decision point over project termination, no matter how unlikely the future success. This fallacy is exacerbated by a lack of understanding of the opportunity cost of such decisions.

The language of failure. Most organizations struggle to separate project decisions from the language of success and failure. Terminations are viewed as 'failures' even though decisions not to progress ineffective projects that would otherwise have consumed more resources should

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21 August 2015

- **Confirmation Bias:**
  - Ignore evidence that contradicts their preconceived notions (conclude bad data v null drug effect)
- **Anchoring:**
  - Weigh one piece of information too heavily in making decisions (focus on the one positive trial….but of how many?)
- **Loss aversion:**
  - Too cautious (continue project - sunk costs or don't want to accept the project isn't going to yield a drug)

Bias in Decision Making

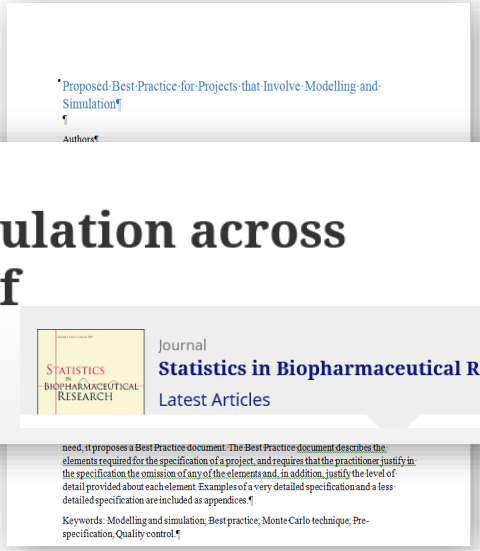
Daniel Kahneman

Harvard Business Review – June 2011

Interaction with PSI/ EFSPI (Statisticians in the Pharmaceutical Industry) Special Interest Group for M&S workshop May 2016


WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation


Proposed Best Practice for Projects that Involve Modelling and Simulation

Authors

need, it proposes a Best Practice document. The Best Practice document describes the elements required for the specification of a project, and requires that the practitioner justify in the specification the omission of any of the elements and, in addition, justify the level of detail provided about each element. Examples of a very detailed specification and a less detailed specification are included as appendices.

Keywords: Modelling and simulation; Best practice; Monte Carlo technique; Pre-specification, Quality control.

Original Articles

Common Best Practice in Modeling & Simulation across Quantitative Disciplines: A Comparison of independently emerging Proposals

Sandra A.G. Visser, Jonathan D. Norton, Scott Marshall & Michael O'Kelly

Page 00 | Received 30 Nov 2016, Accepted 20 Sep 2017, Accepted author version posted online: 29 Sep 2017

Journal

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- Risk Based QC/verification
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- Pre-specification of assumptions

PERSPECTIVE

Model Informed Drug Development: Collaboration Through A Common Framework

Richard J. Anziano[1,*] and Peter A. Milligan[2]

Model-informed drug development (MIDD) utilizes the knowledge extracted from relevant data to improve the efficiency of decision making within the pharmaceutical industry. The MIDD framework creates overlap between the quantitative disciplines, including statistics and pharmacometrics, with many opportunities for collaboration. MIDD necessitates effective alignment in the thoughts and deeds of statisticians and pharmacometricians, which is not a sector norm. The challenge of greater collaboration must be met in order for MIDD to realize its potential.

In the not so distant past, trials were performed with an assumed *a priori* treatment effect that was not borne out, leading to trials being repeated (assuming the same *a priori* treatment effect). Harrison *et al.*[1] reported that 55% of phase III trials failed due to inadequate efficacy. Both of these conditions are unsatisfactory. We contend that program design efficiency is linked to effective evidence synthesis and that the risk of the above can be mitigated by appropriate evidence synthesis.

A drug's inherent "horsepower" is not something that the developers get to choose, it is something the team is continuously trying to estimate/predict. Teams are challenged with determining the probability of a drug being able to deliver clinically relevant outcomes that are meaningful to the patient, prescriber, regulator, and formulary. The Gantt chart typically details the range of activities needed (and the associate time taken) before arriving at an arbitrary decision point, putative market launch, etc. We contend that rather than "only" optimizing for speed, optimizing for knowledge to defray risk would be a long-term recipe for success. Viewing individual trials as building blocks of a knowledge base, it is quite natural to design programs that are optimized for information maximization and uncertainty minimization.

Consider two near identical assets, developed by two rival companies. DinosaurRX pursues a fast-to-market approach and initiates two parallel phase III trials with a range of doses. KMco decides that given the state of current evidence (and uncertainty), a dose-finding trial and two subsequent confirmatory trials would be prudent. The "head to head" Gantt shows KMco to be well behind the competition. We contend that presenting nonprobability adjusted timelines grossly misrepresents our level of understanding of the likelihood of future outcomes and leads to a bias toward selecting options that would otherwise appear less desirable.

(i) The planned DinosaurRX activities appear faster to completion, but the issue is that the likelihood of success is conditioned on having arrived at the right dose when the evidence base was small on information but large on uncertainty. In these conditions, with little or no trial or aggregate analysis to inform dose selection, arriving at the right dose or doses is rarely robust (low probability of a favorable outcome). If wrong about the dose, there would need to be additional trials using appropriate doses (increasing the probability of a favorable outcome). For DinosaurRX the more realistic launch conditions is the duration of the over optimistic fast-to-market approach multiplied by the probability that the dose was correct, plus the duration of the additional trials multiplied by the probability of incorrectly arriving at a dose. Because the probability of not selecting an appropriate dose is much larger than the probability of selecting an appropriate dose, the expected duration to reach a favorable outcome is much longer than the fast-to-market approach would indicate.

(ii) With KMco's approach, the expected duration is calculated similarly, with the addition of the duration of the dose-finding trial. In this case, the probability of arriving at an appropriate dose is higher and, consequently, the probability of not arriving at an appropriate dose is lower. Their

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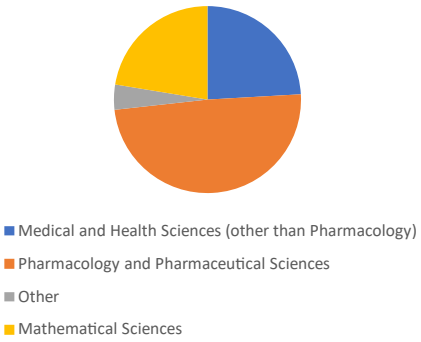
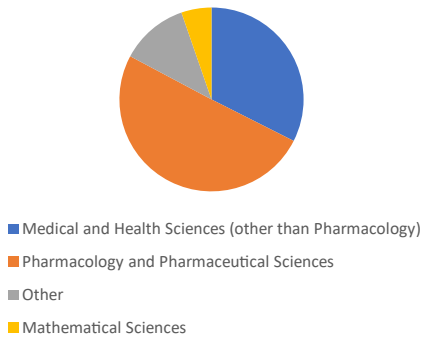
Publications by Journal type: MIDD distributions

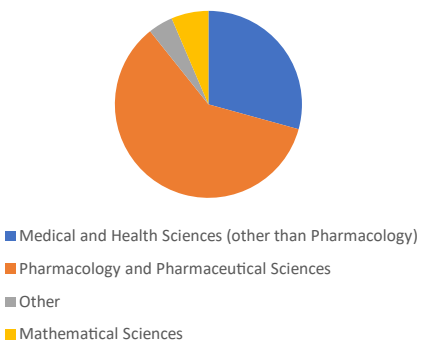
Lalonde (2007) (N=415)



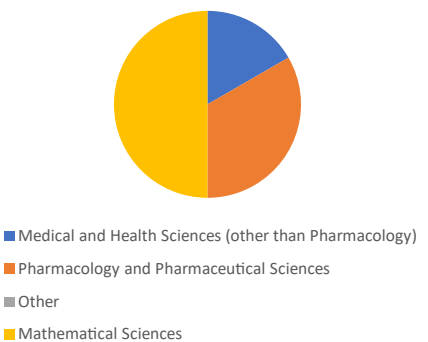
Milligan (2013) N=145



Marshall (2016) N=140



Visser (2018) N=6

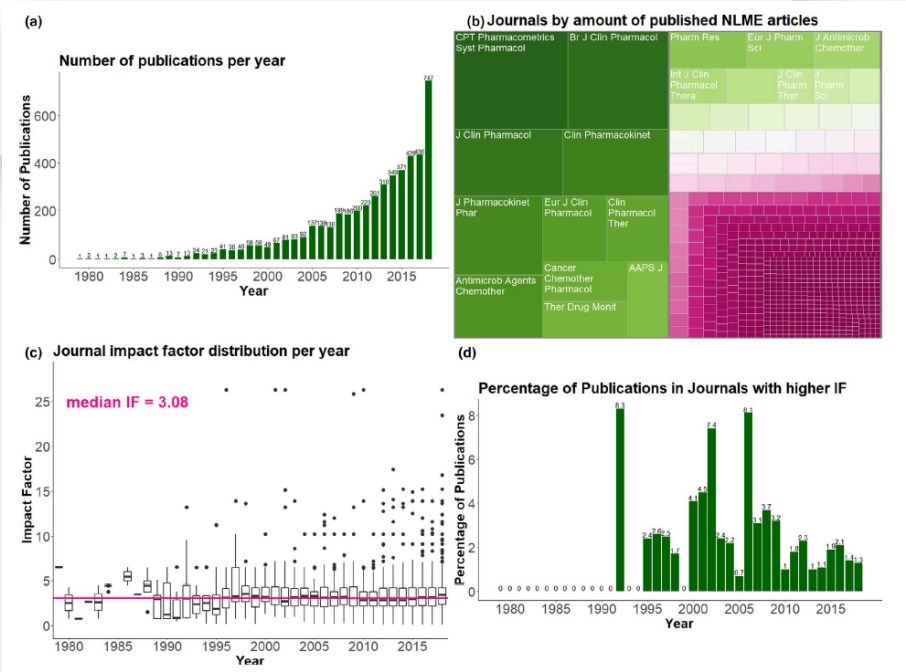


Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 191–194; doi:10.1002/psp4.12501

PERSPECTIVE

What "Impact" Do NLME Publications Have Outside Our Community?

Stefanie Hennig[1,2,3,*], Julia Fischer[4] and Charlotte Kloft[2]



Model Informed Drug Development, in words

Lalonde et al:

*"Development and application of **pharmaco-statistical models of drug efficacy and safety** from **pre-clinical data** to **improve drug development knowledge management and decision making**"*

Marshall et al:

*"A **quantitative framework** for prediction and extrapolation centered on knowledge and inference generated from **integrated models** of **compound, mechanism and disease level data** aimed at **improving the quality, efficiency and cost effectiveness of decision making**"*

PDUFA VI Goals Letter:

*"Development and application of **exposure-based, biological, and statistical models** derived from **pre-clinical and clinical sources** to **address drug development or regulatory issues**"*

ICH MIDD Proposal

*"the use of **quantitative models** for prediction and extrapolation, centered on knowledge and inference from **integrated model-informed representations** of **compound, mechanism, patient population, and disease-level data** derived from appropriate pre-clinical, clinical, and real-world data sources with the aim to **reduce uncertainty about safety and efficacy of investigational drugs and increase transparency in regulatory standards to improve drug development efficiency"***

Organizational level influence

Comment on Progress:

- Top-down – leadership buy-in as to what “success” looks like, focus on stakeholders
  - Fosters gap analysis approach, supporting choice of route to advance, based on the level of ambition within the organization
- Top-down – Clinical Pharmacology/Pharmacometrics leaders perform development team leader roles
- Bottom-up - “we” read “our” journals, focus on the statisticians
  - (MIDD) Regulatory publications appearing in statistical journals
  - (MIDD) Academic/methods publications appearing in statistical journals
  - More MIDD presentations at statistical conferences
- Bottom-up - “we” read “our” journals, focus on the clinician
  - (MIDD) Application publications appearing in medical journals
  - More MIDD presentations at therapeutic area conferences

Plan level influence

Challenges:

"Clinical development ***plans emanating from a*** *rigid* ***"confirmatory mind-set,"*** *which can* ***lead to an overreliance on empirical evidence*** *to address clinically important questions. This* ***can be the result of a narrow interpretation of*** *the validity of* ***alternative approaches to the randomized clinical trial*** *in generating a robust evidence base* ***from which to draw clinical inference."***

Plan level influence

Opportunities:

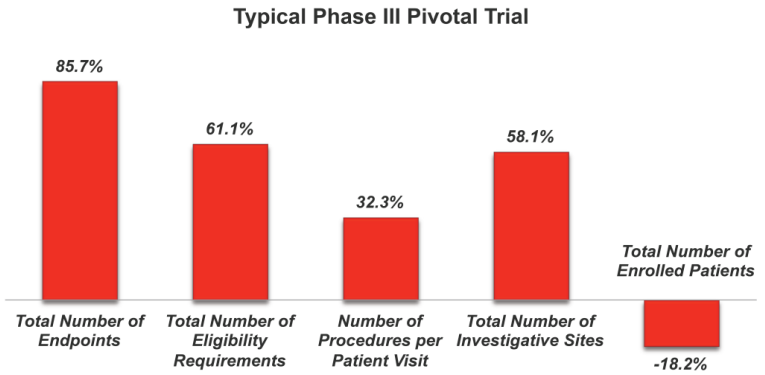
*"There should be more effective dialog during **plan creation**. Consideration should be made of the following qualifying questions in order to gain greater alignment and consensus across stakeholders and the multiple disciplines contributing to the plan construction and implementation."*

- *Determine what information will be generated and how will these activities inform the decision(s).*
- *Check that the proposed activity can provide answers to the identified questions and that the questions are pertinent.*
- *Check that there is an efficient balance between study-based activities vs. broader compound, mechanism, and disease-based activities.*
- *Determine what are the technical and resource interdependencies and time sequences between each activity in the **MIDD** plan.*
- *Determine what the most impactful assumptions are.*
- *Determine what the most likely limitations are.*
- *Determine what will be done to ensure availability of deliverables in sufficient time to inform the decision.*
- *Determine what would be the impact of not performing these activities."*

Drivers of high development costs

- Preclinical screens and predictive model performance
- Chronic and complex indications
- Clinical trial size
- Patient recruitment and retention
- Increased protocol complexity
- Regulatory demands
- Commercial demands

Typical Phase III Protocol	*2001-2005*	*2011-2015*
Total Number of Endpoints	7	13
Total Number of Eligibility Criteria	31	50
Total Number of Procedures	110	187
Total Number of Procedures per Visit	10	13
Proportion of Procedures that are 'Non Core'	18%	31%
Total Number of Data Points Collected*	494,236	929,203



PDUFA VI: Janet Woodcock* perspectives**

- Additional tools beyond RCT will “come into play”
  - Extreme heterogeneity in disease manifestation and rare diseases compromise RCT efficiency
  - More questions rather than “does the drug work”?
    - re-position the (over) emphasis on preserving α
  - Largely becomes a set of Clinical Pharmacology questions
    - coupled with statistics and medicine…
    - greater collaboration across the 3 disciplines within FDA needed during policy/guidance development and review cycle …..

* Director of the Center for Drug Evaluation and Research (CDER)
** Presented at DIA/FDA Statistics Forum 24th April 2017, North Bethesda, MD

PDUFA VI: Janet Woodcock* perspectives**

- New methodological approaches that can answer more than one question at a time “are the future”
  - Platform trials with disease centric Master Protocols***
    - consider regimen improvement benefits as well as NCE benefits
    - “inherently adaptive” in design
  - Quantitative benefit: risk analysis and move away from current “pseudo-qualitative” approach
    - Explicit assumptions - particularly relative weighting
  - Patient focussed drug development will require “a significant shift in how development is implemented”
    - PRO instruments to characterise “what matters to patients” – the burden of treatment

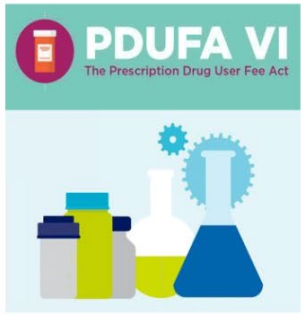
* Director of the Center for Drug Evaluation and Research (CDER)
** Presented at DIA/FDA Statistics Forum 24th April 2017, North Bethesda, MD
***Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017; 377:62-70.

PDUFA VI: Janet Woodcock* perspectives**

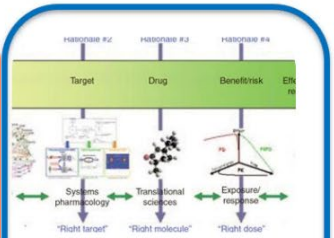
- Trend towards (mechanistically plausible) targeted therapies
  - Necessitates different development programme design
  - Genetic predisposition implications for interventions
  - Use of natural history comparative data should be fit for purpose
    - Greater emphasis on outcomes rather than heterogeneity
- Qualification of clinical outcomes to become more robust and move beyond clinician “face validity”
  - What is the “minimally significant” clinical benefit level?
- Qualification of biomarkers codified as “fit for purpose within a context of use”

* Director of the Center for Drug Evaluation and Research (CDER)
** Presented at DIA/FDA Statistics Forum 24th April 2017, North Bethesda, MD

PDUFA VI: Regulatory Decision Tools



Complex Innovative Trial Designs



Model-informed Drug Development

Biomarker Qualification

Real World Evidence

Benefit/Risk Assessment

Patient Voice

CID and MIDD Pilot Programs

- Jointly administered by statisticians from
  - Center for Drug Evaluation and Research (CDER)
  - Center for Biologics Evaluation and Research (CBER)
- Enhancing regulatory decision tools to support drug development and review
  - includes designs involving complex adaptations, Bayesian methods, or other features requiring simulations to determine statistical properties (e.g., type I error)
- To facilitate the advancement and use of CIDs
  - Develop staff capacity
  - Conduct a pilot meeting program
  - Develop or revise relevant Manuals of Policies and Procedures (MAPPs), Standard Operating Policy and Procedures (SOPPs), and/or review templates
  - Publish draft guidance
  - Convene a public workshop

- Jointly administered by
  - CDERs Office of Clinical Pharmacology
  - CBERs Office of Biostatistics and Epidemiology
- Conduct a pilot program with a priority for requests on:
  - Dose selection or estimation (e.g., for dose/dosing regimen selection or refinement)
  - Clinical trial simulation (e.g., based on drug-trial-disease models to inform the duration of a trial, select appropriate response measures, predict outcomes, etc.)
  - Predictive or mechanistic safety evaluation (e.g., use of systems pharmacology/mechanistic models for predicting safety or identifying critical biomarkers of interest)
- Develop or revise MAPPs, SOPPs, review templates and training, to incorporate MIDD guidelines
- Publish draft guidance, or revise relevant existing guidance, on MIDD

https://www.fda.gov/CIDpilot and https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?

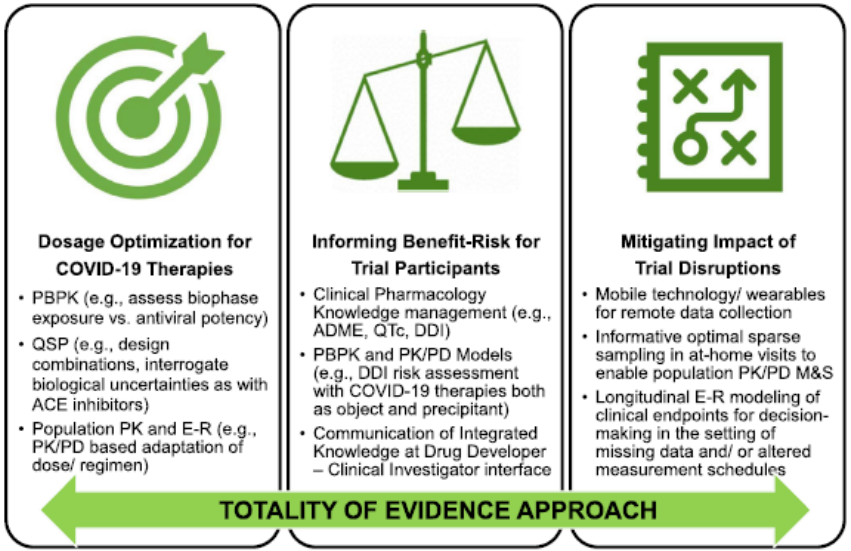
Hans-Georg Eichler[1,2,*], Marco Cavaleri[1], Harald Enzmann[3,4], Francesca Scotti[1], Bruno Sepodes[4,5], Fergus Sweeney[1], Spiros Vamvakas[1] and Guido Rasi[1,6]

COVID-19: A Defining Moment for Clinical Pharmacology?

Piet H. van der Graaf[1,2,*] and Kathleen M. Giacomini[3]

Challenges in Drug Development Posed by the COVID-19 Pandemic: An Opportunity for Clinical Pharmacology

Karthik Venkatakrishnan[1,2,*], Oezkan Yalkinoglu[3], Jennifer Q. Dong[1,2] and Lisa J. Benincosa[1,2]

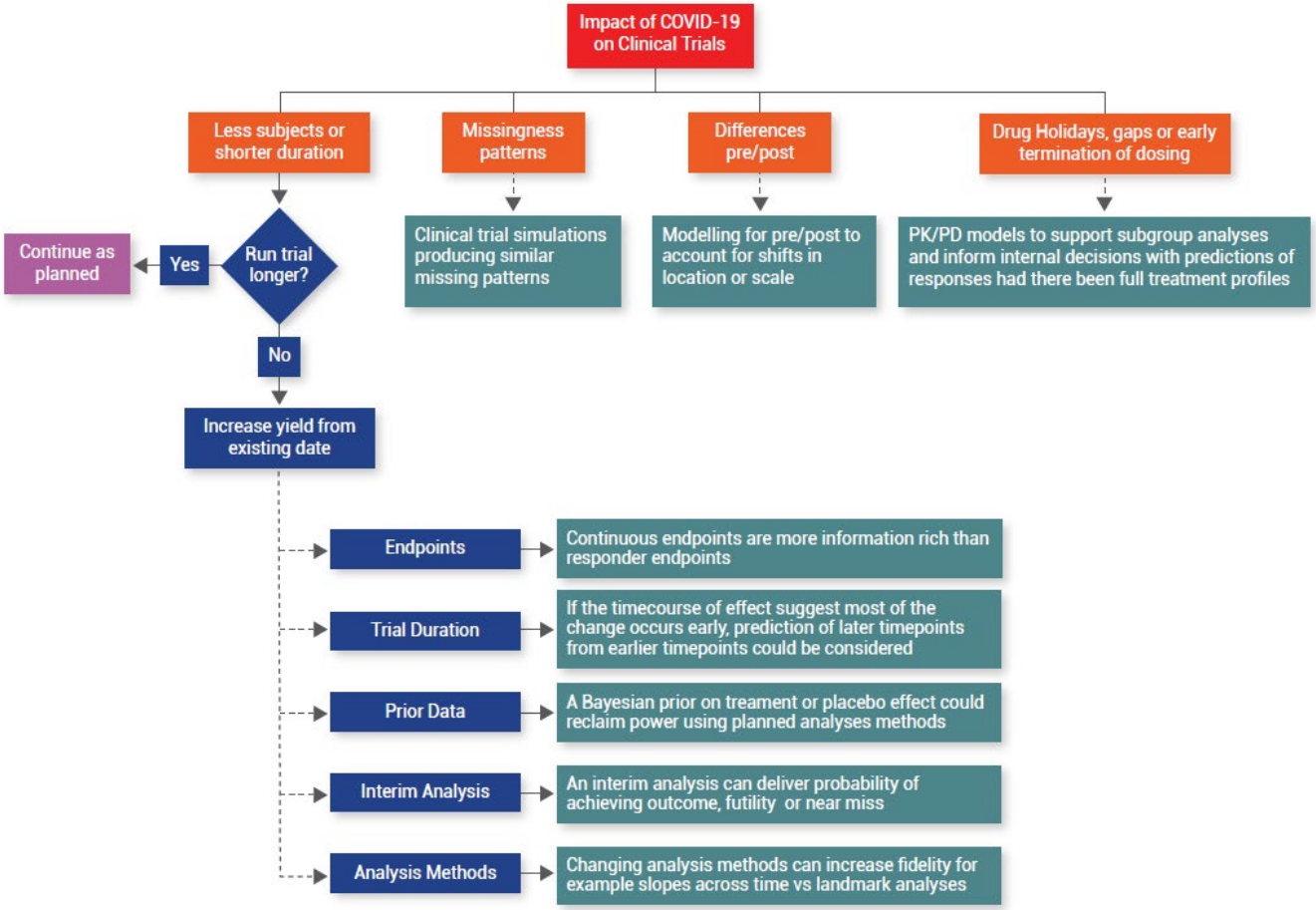


Oncology Treatment In the Era of COVID-19: We Cannot Afford to Hlt the Pause Button

Sarah A. Holstein[1,*] and Julie M. Vose[1]

Table 1 Summary of changes in oncology clinical trial conduct

Action	Pre-COVID-19 era	Current COVID-19 era	Potential future
Informed consent	In-person visits	Institution-dependent; some allow electronic/phone consents	In-person, secure online or phone consents
Clinic visit	In-person visits	Maximize telehealth visits; minimize in-person visits	Mix of in-person and telehealth visits
Vital signs	In-person visits	Subjects report some vital sign information during telehealth visit	Provide in-home access to temperature, blood pressure, heart rate, pulse oximetry monitoring, wearable sensors
Toxicity reporting	In-person visits, paper questionnaires	Telehealth visits; questionnaires may not be collected	In person-visits, online questionnaires, telehealth visits
Drug administration	Study drug (i.v., s.c., p.o.) administered at study center	Minimize administration of i.v./s.c. study medications; ship oral medications to patient	Utilize both local and study infusion centers; option of mailing oral medications
Safety labs	Study center only	May not be done or exceptions required to use local facilities	Protocols allow labs to be drawn at study center, local facilities or via home health care
Study-specific labs	Study center only	May not be done	Protocols allow labs to be drawn at study center, local facilities or via home health care
Radiology assessment	Study center only	Scans may not be done or exceptions required to use local facilities	Protocols allow scans to be performed at study center or local facilities
Biopsies for correlative studies	Study center only	May not be done	Protocols allow biopsies to be performed at study center or local facilities
Site monitoring	In-person visits	Postponed or via remote	Increased utilization of secure remote monitoring
COVID-19 testing	Not applicable	Inconsistent use	Protocol-specified testing for active infection, serology status, or immunization status



https://pharmetheus.com/covid-19-impact-on-clinical-trials

Plan level influence

Comment on Progress:

- If an MIDD plan exists is it core to the Development Plan?
  - Model Informed Drug Development → Drug Development
- We have for some time been developing drugs “differently” due to
  - the nature of the compound, the modality of medicine, the diseases studied, the data generated, the basis upon which decisions are made etc. which have effected drug development conduct ……
  - *then the SARS-CoV-2 virus appeared…..*
- What role will MIDD have in the new norm?
  - Fail to plan, plan to fail

Activity level influence

Challenges #1:

*"Approaches that are **precedented and conservative** can be **considered** in some quarters to be the most **robust and trustworthy**. In line with good clinical practice and International Conference on Harmonization guidelines, **primary data analyses are defined** in clinical study protocols and statistical analysis plans **in advance** of study initiation and conduct. Although this approach fulfils a requirement for both statistical rigor and integrity, which is of particular importance within a confirmatory setting, **pre-specification** will often lead to the adoption of more **straightforward "assumption-light" analysis methods."***

Activity level influence

Challenges #2:

*"Within a **confirmatory setting**, MIDD approaches are often conducted as **secondary** or exploratory analyses **after the primary analysis has been conducted and communicated**, limiting the potential for MIDD approaches to effectively influence R&D decision-making and regulatory assessment. Another challenge is **the degree of inconsistency in the format and detail of MIDD application that exist across the range of reports submitted to regulators** (e.g., clinical overview or SmPC both across companies and between regulatory reviewers). Important elements, such as **questions to be addressed by particular analyses, resultant conclusions, and recommendations, are not always clearly and effectively communicated.** There is a tendency for sponsors and regulators to **focus on the technical** aspects of MIDD, such as individual parameter uncertainty and variability **rather than on the "bigger picture"** joint/integrated uncertainties manifest in, for example, an exposure-response curve and the resultant influence on dosing and labeling recommendations."*

Activity level influence

Challenges #3:

*"From the perspective of the regulatory assessor, there is **often insufficient information provided** to be able to effectively judge the appropriateness of the model for estimation and/or prediction/simulation. The 2011 EMA/EFPIA M&S workshop identified two common limitations of analysis documentation submitted for regulatory review: **a lack of transparent description of influential assumptions, and an ineffective evaluation or reporting of the impact of potentially erroneous assumptions (i.e., sensitivity analyses)** on the resultant conclusions and recommendations. These limitations were considered to be **an unequivocal barrier to the wider acceptance of MIDD approaches within the regulatory agencies (and industry).**"*

Activity level influence

Opportunities #1:

*"There is a **growth** in the use of analysis methodologies, such as **systematic reviews to complement, and in many aspects enhance,** the level of information derived from **traditional randomized controlled studies.** There is a greater recognition that **fit-for-purpose** approaches derived from a broader set of analysis methods **can efficiently inform clinical and regulatory decision making."***

Activity level influence

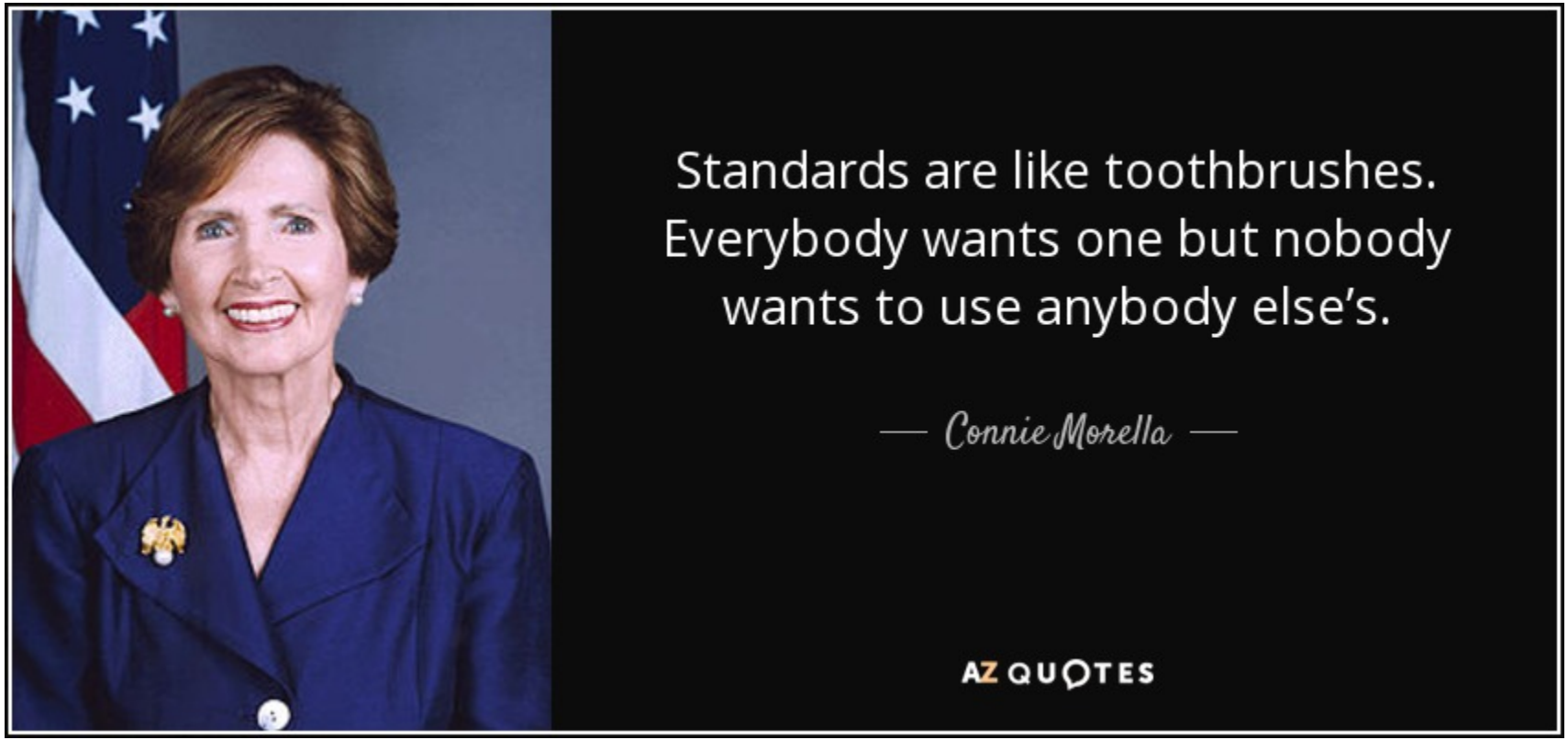
Opportunities #2:

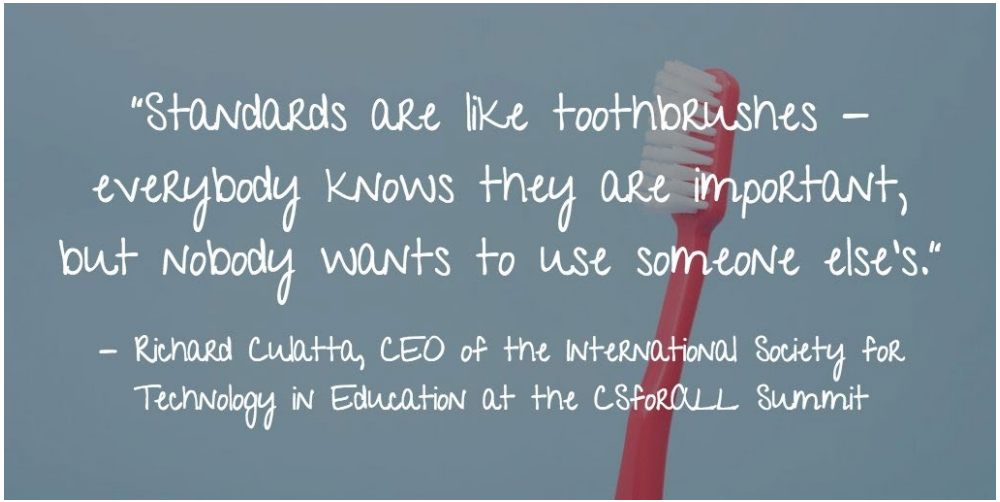
*"Of particular importance to **MIDD** capability and capacity will be the **Drug Disease Model Resources consortium.** This Innovative Medicines Initiative call will enable a **continuous integration of available information related to a drug or disease** into constantly evolving mathematical models. The models will be capable of describing and predicting the behavior of studied systems to address the questions of researchers, regulators, and public health care bodies. This will be achieved through the **generation of a common definition language for data, models, and workflows, along with an ontology-based standard for storage and transfer of models.** All drug and disease model libraries developed will be made **available as a public resource and an opensource interoperability framework** will be the backbone for the integration of modeling applications."*

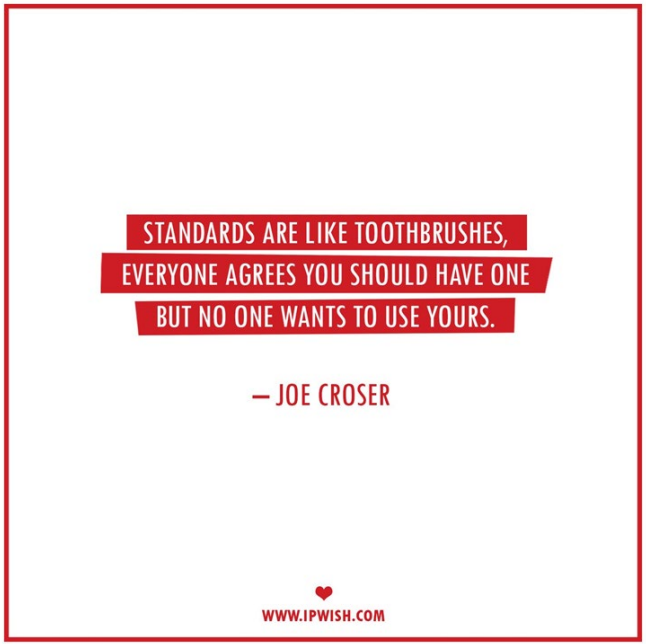
Activity level influence

Opportunities #3:

"With respect to the second challenge, this document ***aims to establish de facto standards and good practices.*** *As stated earlier,* ***greater transparency with respect to the chosen data, methodologies used, key assumptions, model assessment, and pre-specification (when appropriate)*** *have been highlighted as important issues to address. The EFPIA workgroup proposal with respect to good practices and documentation for MIDD is addressed in section 5."*


Standards are like toothbrushes. Everybody wants one but nobody wants to use anybody else's.
— Connie Morella —
AZ QUOTES


"Standards are like toothbrushes –
everybody knows they are important,
but nobody wants to use someone else's."
– Richard Culatta, CEO of the International Society for
Technology in Education at the CSforALL Summit


STANDARDS ARE LIKE TOOTHBRUSHES,
EVERYONE AGREES YOU SHOULD HAVE ONE
BUT NO ONE WANTS TO USE YOURS.
– JOE CROSER
WWW.IPWISH.COM

International Society of Pharmacometrics (ISOP): dataset standards

CDISC: Study Data Tabulation Model (SDTM)

- CDISC formed 1997
- Limited uptake, each company had own standards and limited motivation to change without assurance that the standard would be universal
- Precipitating event in 2004, this standard referenced in the eCTD Guidance
- Within two years becomes standard practice for companies

ISOP: Standards for Pharmacometrics Datasets

- Builds on CDISC, but specific for Pharmacometric datasets
- Established 2015
- Version 1 of standards Nov 2020
- Limited uptake so - similar reasons to CDISC at first?
- Does this need a similar precipitating event galvanize support and drive compliance?
- Could/should this fall under CDISC?

Open Models for Clinical Pharmacology

Daniel C. Kirouac[1,*]

Computational models incorporating molecular, cellular, and physiological mechanisms (i.e., quantitative systems pharmacology (QSP)) are gaining traction as predictive tools in drug development. To significantly impact clinical pharmacology, the methods need to be transparent and reproducible. This is often not the case. If QSP is to reach to the same level of acceptance as more established pharmacometrics approaches, what steps are necessary to bring this to fruition?

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 107 NUMBER 4 | April 2020

Open Data for Clinical Pharmacology

Jackson Burton[1], Sanchita Bhattacharya[2,3], Klaus Romero[1] and Daniela J. Conrado[4,*]

The term open data typically refers to data that are completely unrestricted in terms of access, redistribution, and intended use. The aim of open data in clinical pharmacology (ODCP) is to transform data into knowledge to facilitate innovation and solutions for unmet medical needs. Although open data in clinical settings has been traditionally uncommon, significant progress has been made for sharing anonymized patient-level data with the purpose of increasing the likelihood of developing novel treatments.

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REVIEW

Challenges in Alzheimer's Disease Drug Discovery and Development: The Role of Modeling, Simulation, and Open Data

Daniela J. Conrado[1,*], Sridhar Duvvuri[2], Hugo Geerts[3], Jackson Burton[4], Carla Biesdorf[5], Malidi Ahamadi[6], Sreeraj Macha[7], Gregory Hather[8], Juan Francisco Morales[9], Jagdeep Podichetty[4], Timothy Nicholas[10], Diane Stephenson[4], Mirjam Trame[11], Klaus Romero[4] and Brian Corrigan[10] on behalf of the Drug Development Tools in the Alzheimer Disease Continuum (DDT-AD) Working Group

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 107 NUMBER 4 | April 2020

Scientific and Regulatory Considerations for an Ontogeny Knowledge Base for Pediatric Clinical Pharmacology

Gilbert J. Burckart[1,*], Shirley Seo[1], Aaron C. Pawlyk[2], Susan K. McCune[3], Lynne P. Yao[4], George P. Giacoia[2], Yaning Wang[1] and Issam Zineh[1]

Understanding all aspects of developmental biology, or pediatric ontogeny, that affect drug therapy from the fetus to the adolescent child is the holy grail of pediatric scientists and clinical pharmacologists. The scientific community is now close to being able to tie together the vast amount of information collected on pediatric ontogeny over the past 60 years. An organized knowledge base and new tools would allow us to utilize this information effectively in pediatric drug development.

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Activity level influence

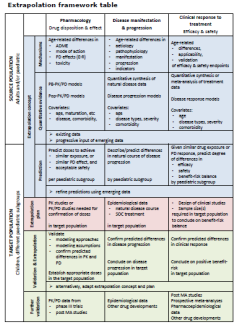
Comment on Progress:

- We (still) have variability in practice levels across our community
- Our community's approach to standards creation and utilization is rate limiting
- We recognize the need greater consistency in practice levels, we express a desire to follow standards, but we have difficulties to create "community norms"
  - What is the MIDD "carrot and stick"?

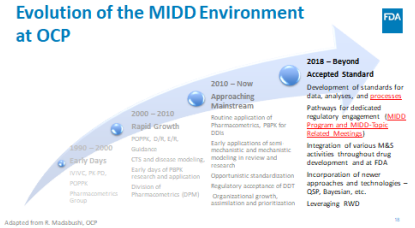
Global Regulators are actively embracing MIDD

EMA

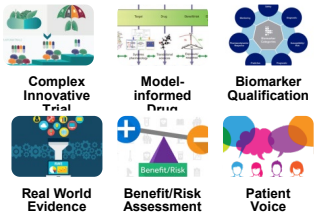
Extrapolation Framework



FDA



PDUFA VI



Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 550–552; doi:10.1002/psp4.12554

PERSPECTIVE

Meeting Report: PMDA Public Workshop on Pharmacometrics at Japan

Shinichi Kijima[1,*], Yoshinori Ochiai[1] and Akihiro Ishiguro[1]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 413–415; doi:10.1002/psp4.12203

PERSPECTIVE

Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

M Sato*, Y Ochiai, S Kijima, N Nagai, Y Ando, M Shikano and Y Nomura

In Japan in October 2016, the Pharmaceuticals and Medical Devices Agency (PMDA) began to receive electronic data in new drug applications (NDAs). These electronic data are useful to conduct regulatory assessment of sponsors' submissions and contribute to the PMDA's research. In this article, we summarize the number of submissions of quantitative modeling and simulation (M&S) documents in NDAs in Japan, and we describe our current thinking and activities about quantitative M&S in PMDA.

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PERSPECTIVE

Model Informed Drug Development and Regulation in China: Challenges and Opportunities

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REVIEW

Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other?

Tania Teixeira[1,*], Sandra L. Kweder[2] and Agnes Saint-Raymond[1]

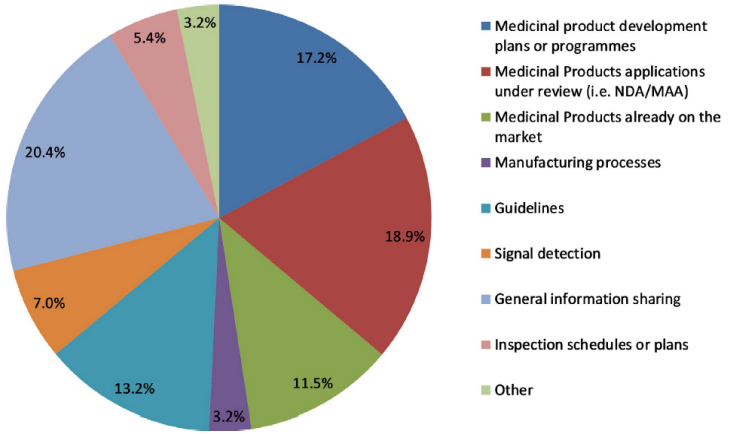

Figure 1 Top topic areas discussed in clusters. Values shown are from aggregate results from a compiled list of the topic areas identified for all clusters. MAA, Marketing Authorisation Application; NDA, New Drug Application.

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Table 1 Clusters and participating agencies

Name	Short description of discussion areas	Meeting frequency[a]	Participating agencies	Surveyed cluster/ comment
Advanced therapies/ regenerative medicines (ATRM)	Development programs and challenges in regulation of advance therapy medicinal products, such as cell and gene therapies	5–6 times/ year	EMA, FDA, HC, PMDA/ MHLW	Yes
Anti-infectives	Development of medicinal products for this therapeutic area	Monthly	EMA, FDA, HC, PMDA	No
Antivirals	Development of medicinal products for this therapeutic area	2–4 times/ year	EMA, FDA	No
Active Pharmaceutical Ingredients International Inspection Program (API)	Collaboration toward the efficient use of inspection resources and the gain of confidence in each other's inspection outcomes	Monthly	EMA, FDA, PMDA, HC, TGA, EDQM, WHO, MS: France, Denmark, United Kingdom, Italy	Yes
Bioequivalence collaboration (BE)	Collaboration toward the efficient use of inspection resources and the gain of confidence in each other's inspection outcomes	4 times/ year	EMA, FDA, MS: Austria, France, Germany (BfArM), Italy, The Netherlands, Spain, United Kingdom	Yes
Biomarkers qualification (QBiom)	Activities related to biomarker qualification, parallel Qualification Advice/Opinion procedures	4 times/ year	EMA, FDA	No
Biosimilars (Biosim)	Development programs and medicinal products that are biosimilars	3 times/ year	EMA, FDA, PMDA/ MHLW, HC, Swissmedic	Yes
Biostatistics (Biostats)	Regulatory science and challenges related to biostatistics	2 times/ year	EMA, FDA	No
Blood products	Development programs and medicinal products for this therapeutic area	4 times/ year	EMA, FDA, HC	Yes
Breakthrough/PRIME	Information sharing on designation decisions for proposals submitted to both agencies (post decision only)	4 times/ year	EMA, FDA	Yes
Cardiovascular medicinal products	Development programs and medicinal products for this therapeutic area	4 times/ year	EMA, FDA	Yes
Clinical outcome assessment (COA)	Activities related to qualification of novel methodologies in both agencies, parallel Qualification Advice/Opinion procedures	4 times/ year	EMA, FDA	No
GCP Initiative (GCP)	Collaboration toward the efficient use of inspection resources and the gain of confidence in each other's inspection outcomes	Every 2 months	EMA, FDA, PMDA/ MHLW	Yes
Mutual Recognition Agreement (MRA)	Collaboration toward implementation of the MRA	Every 2 months	EMA, FDA	No
Psychiatry (Psych)	Development programs and medicinal products for this therapeutic area	Every 2 months	EMA, FDA	No
Nonclinical Oncology (Pharm Tox)	Nonclinical aspects of oncology product development	Quarterly	EMA, FDA	Yes
Oncology-Hematology medicinal products	Development programs and ongoing assessments of medicinal products for this therapeutic area	Monthly	EMA, FDA, HC, PMDA/MHLW, TGA, Swissmedic	Yes
Orphan medicines	Challenges in assessing for orphan designation and product development	4 times/ year	EMA, FDA	Yes
Pediatric medicines	Discussion of development programs—pediatric investigation plans—and medicinal products for this patient population	Monthly	EMA, FDA, HC, PMDA/ MHLW, TGA	Yes
Patient engagement (PE)	Sharing best practices on patient involvement in medicines' lifecycle	2 times/ year	EMA, FDA, HC	Yes
Pharmacogenomics	Challenges and regulatory science related to using pharmacogenomic tools in drug development	2 times/ year	EMA, FDA, PMDA/ MHLW	Yes

Table 1 (Continued)

Name	Short description of discussion areas	Meeting frequency[a]	Participating agencies	Surveyed cluster/ comment
Pharmacometrics (Modeling and Simulation)	Challenges and regulatory science of pharmacometrics and modeling in drug development	4 times/ year	EMA, FDA, PMDA/ MHLW, HC	Yes
Pharmacovigilance (PhV)	Sharing of information on drug safety issues for human medicinal products and advance notice of regulatory action, public information, and communication	Monthly	EMA, FDA, PMDA/ MHLW, HC	Yes
Pharmacovigilance Strategy (PhV Strategic call)	Strategic regulatory science topics that are not product specific	4 times/ year	EMA FDA	No
Rare diseases	Development programs and medicinal products being studied for rare diseases	Monthly	EMA, FDA	Yes
Real-World Evidence – Big data (RWE)	Platform to foster consistency of approach, address common challenges, leverage data, network and expertise available to facilitate advances in regulatory science	4 times/ year	EMA, FDA	No Established in 2018
(Medicines) Shortages	Information on drug shortages across regions and shared efforts to mitigate them	4 times/ year	EMA, FDA, HC, TGA	Yes
Vaccines (Vacc)	Development programs and medicinal products for this therapeutic area	4 times/ year	EMA, FDA, HC	Yes
Veterinary medicines (Vets)	Development programs and challenges related to multiple aspects of veterinary medicinal products	4 times/ year	EMA, FDA	Yes
Veterinary Novel therapies (Vets Novel T)	Information exchange on activities related to facilitating development of novel therapies for veterinary use	4 times/ year	EMA, FDA	No
Veterinary Pharmacovigilance (Vets PhV)	Sharing of information on drug safety issues for veterinary medicinal products and advance notice of regulatory action, public information, and communication	2 times/ year	EMA, FDA, HC	Yes

EDQM, European Directorate for the Quality of Medicines; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HC, Health Canada; MHLW, Japanese Ministry of Health, Labour, and Welfare; MS, member state; PMDA, Pharmaceuticals and Medical Devices Agency; TGA, Australian Therapeutic Goods Administration; WHO, World Health Organization.

[a]Meeting frequency is averaged and some have been reduced due to Brexit resource constraints in 2018/19. Frequency of *ad hoc* calls for emerging topics not shown.

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COMMENTARY

A Holistic and Integrative Approach for Advancing Model-Informed Drug Development

Rajanikanth Madabushi[1]*, Yaning Wang[1] and Issam Zineh[1]

We are approaching nearly 2 decades of experience in demonstrating the relevance and value of MIDD. With exciting innovations on the horizon and institutional support for MIDD across many sectors, we are at an important moment in which synergies can be brought to bear to achieve consistent and relevant application of MIDD for patient and societal benefit.

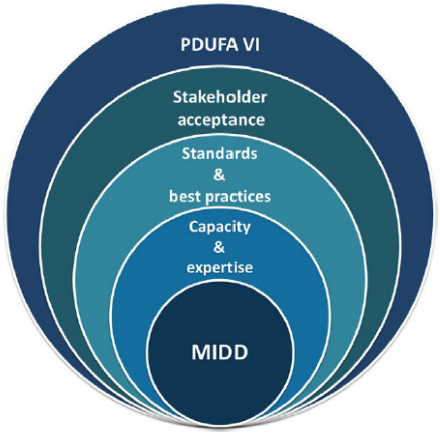

Figure 1 An integrative approach for advancing model-informed drug development (MIDD) under Prescription Drug User Fee Act (PDUFA) VI. MIDD can be seen as foundational to efficient and effective drug development and regulatory evaluation of small molecule drugs and biological products. To advance more widespread and predictable application, MIDD requires an adequate staff capacity and expertise, community-accepted standards and best practices, and multistakeholder acceptance eyond technical experts. The commitments laid out under PDUFA VI provide an opportunity to achieve these goals in a holistic and integrated manner.

STATE OF THE ART

Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang[1]*, Hao Zhu[1], Rajanikanth Madabushi[1], Qi Liu[1], Shiew-Mei Huang[1] and Issam Zineh[1]

Current Applications

Dose Optimization

Dose Optimization for the general patient population prior to drug approval

Dose Optimization for subgroups

Dose Optimization post approval

Supportive evidence of efficacy Informing clinical trial designs

Policy development

Future trends and considerations

MIDD under PDUFA VI

Mechanistic models

Models to analyze medical images

Real world data/ real world evidence

Table 3 Guidances endorsing model-informed drug development strategies in drug development and regulatory evaluation

Guidance name
Guidance for Industry: Population Pharmacokinetics
Guidance for Industry: Exposure-response Relationships-Study Design, Data Analysis, and Regulatory Applications
Physiologically Based Pharmacokinetic Analyses—Format and Content Guidance for Industry
Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry
ICH E4 Dose-Response Information to Support Drug Registration
Guidance for Industry: End-of-Phase 2A Meetings
Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations
ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs—Questions and Answers (R3)
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment
Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases
Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment
Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis
Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment
Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment
Pulmonary Tuberculosis: Developing Drugs for Treatment
Pediatric Rare Diseases—A Collaborative Approach for Drug Development Using Gaucher Disease as a Model
General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
Product Development Under the Animal Rule
Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies
In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies
Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
Hypertension: Developing Fixed Dose Combination Drugs for Treatment
Ulcerative Colitis: Clinical Trial Endpoints
Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling
E17 General Principles for Planning and Design of Multiregional Clinical Trials

Closing comments

Model Informed Drug Development → Drug Development

- We have a shared ambition to realize the potential of MIDD
- We seek greater normalization of quantitative activities towards company and regulatory decision making
- We seek a shift in our practitioners from solution provider to problem owner
- We seek an improved integration with related quantitative disciplines
- We posses the technical foundations and we have the ability to grow technically to meet increased challenges
- We need to do better with our practice standards and our collective norms

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- My legacy Pfizer colleagues/experiences
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