Utilizing a Quantitative Framework to support Extrapolation

Peter A Milligan
Head of Pharmacometrics
Global Clinical Pharmacology, Pfizer

Acknowledging the EFPIA MID3 Working Group
PSI One Day Meeting: Extrapolation, GSK, November 22nd 2017

Presentation Outline

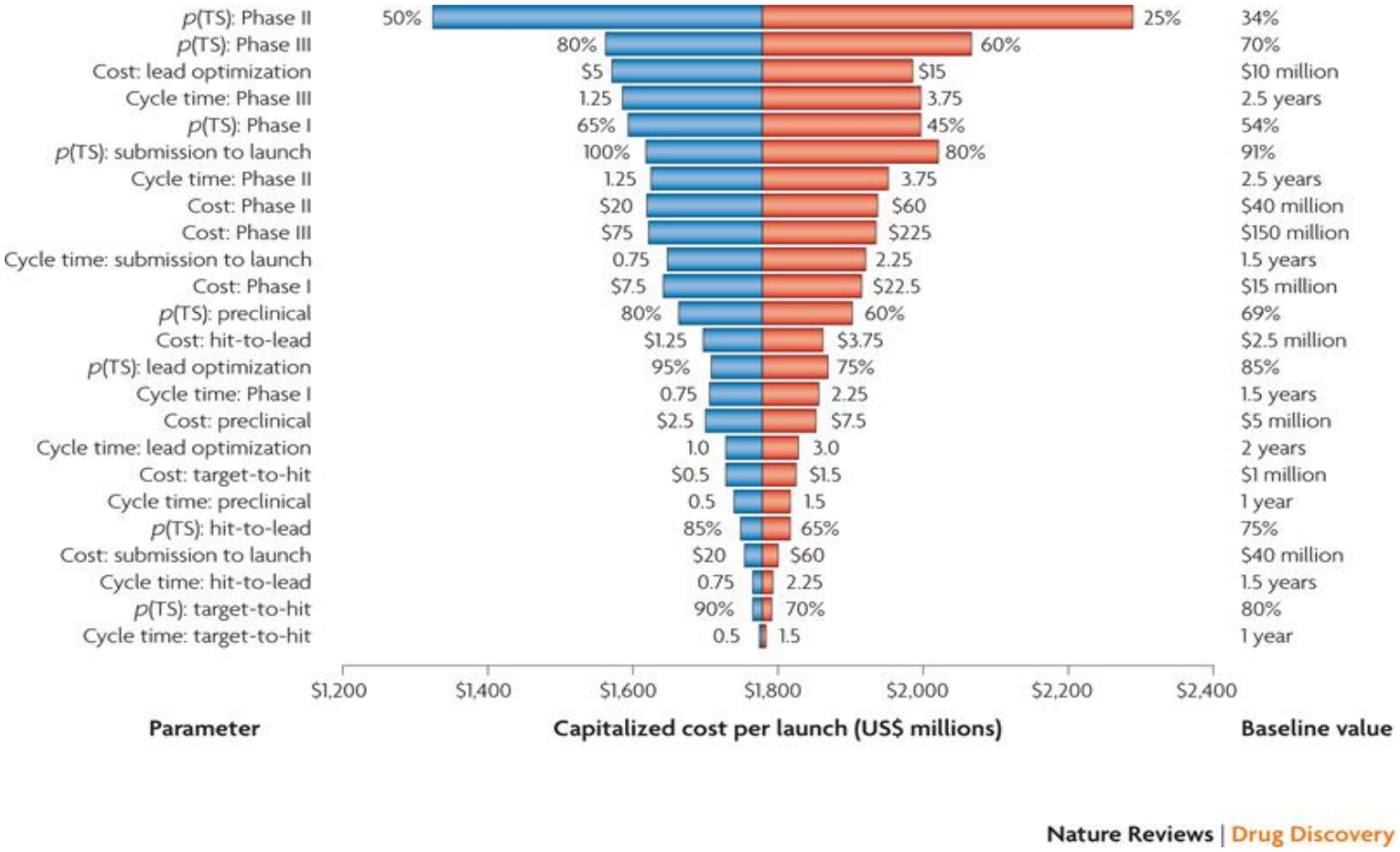
- ***Why*** Extrapolation
  - Personal (Clinical Pharmacology/Pharmacometrics) perspective
- ***What*** does it look like (from the above perspective)
  - The "Quantitative Framework"
- ***How*** could it be performed
  - Bulk of the presentation
- ***Why now…..***

Why

Many Sources of Study/Compound Uncertainties

- Changing formulations/dosing frequency
  - PK/PD models
- Changing duration of treatment
  - longitudinal models
- Changing study "success" criteria
  - design & trial execution models
- Changing endpoint of interest
  - translation models
- Changing sequence, schedule, combinations
  - disease and system models
- Changing populations
  - disease and (multiscale) system models
- Changing indication dynamics
  - (model based) meta analytic models
- Changing differentiation/transition criteria to progress through research/ discovery/ development/ registration/ reimbursement…….
  - decision theoretic models

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



Paul et al. Nat Rev Drug Discov 2010;9:203-14

Pharmacostatistical Perspective

The intellectual health of clinical drug evaluation

Lewis B. Sheiner, MD *San Francisco, Calif.*

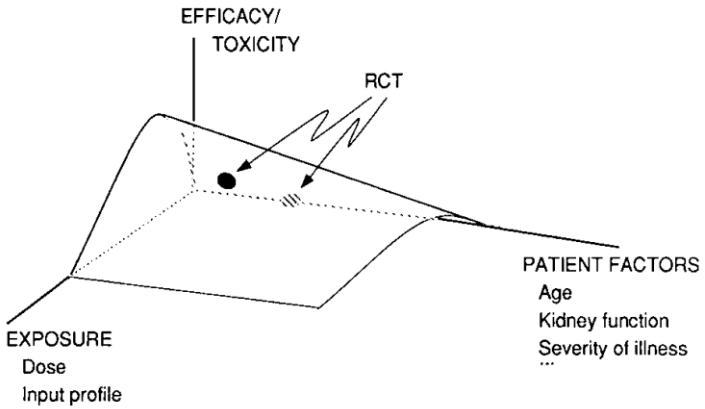


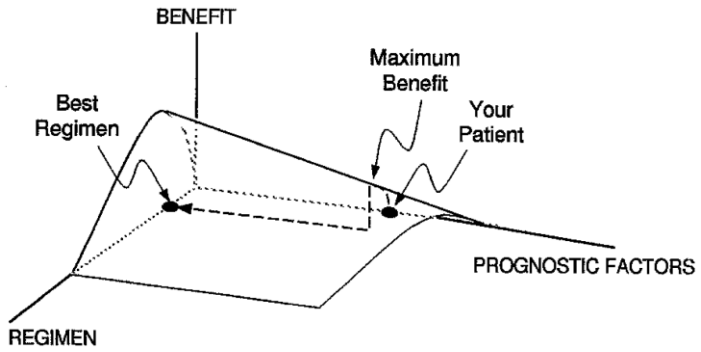
Fig. 3. The therapeutic response surface.

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 61 NUMBER 3 MARCH 1997

COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

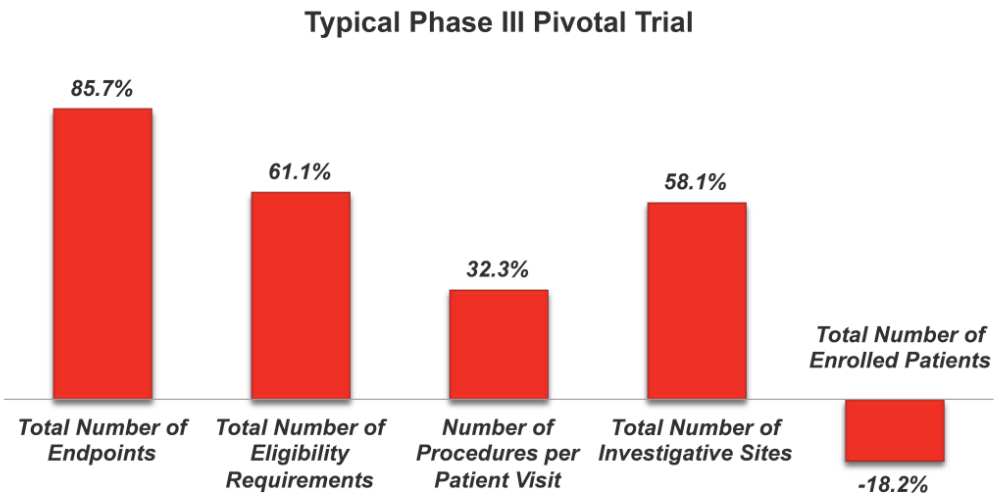


Drivers of High Development Costs

- 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



Source: Tufts CSDD, 2017; *Medidata Solutions

What

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; 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[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

Objectives:
- To promote "Good Practices" with regards to the planning conduct & documentation
- To include illustrative examples to demonstrate their use, impact & value
- To promote Model Informed Drug Discovery & Development (MID3)

Review and Input from MSWG:
- Efthymios Manolis (EMA/MSWG)
- Terry Shepard (MHRA/MSWG))
- Ine Skottheim-Rusten (NMA/MSWG/PDCO)

CHMP Sponsors:
- Tomas Salmonson (MPA/CHMP chair)
- Rob Hemmings (MHRA/CHMP/SAWP)

Abstract:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/abstract
Paper:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf
Supplemental info:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/suppinfo
Podcast:
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2163-8306/homepage/podcasts.htm

EMA/EFPIA M&S Workshop (Dec. 2011)

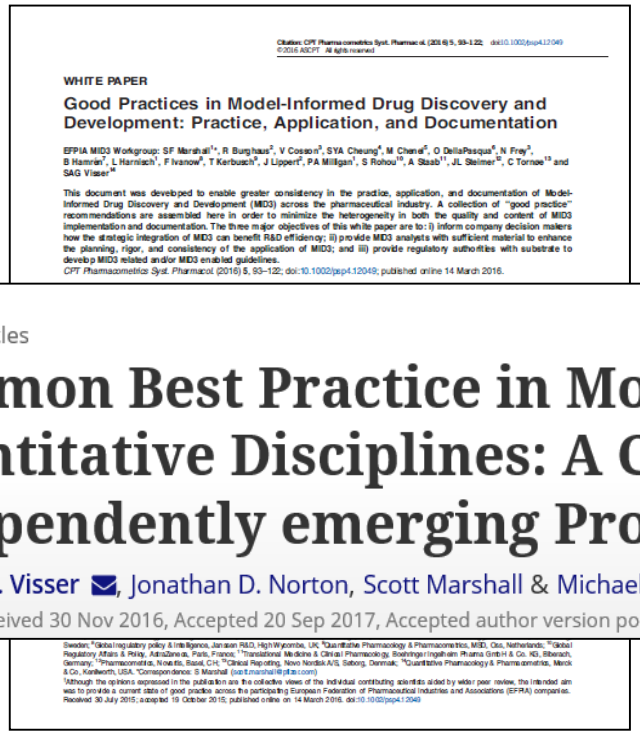
Objectives

- Discuss the role and scope of M&S in drug-development from both the developer's and the regulator's perspectives.
- An opportunity for industry, academia and regulators:
  - To learn from each other
  - Create greater awareness
  - Share experiences
  - Identify gaps and future opportunities

Outputs

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

MID3



WHITE PAPER

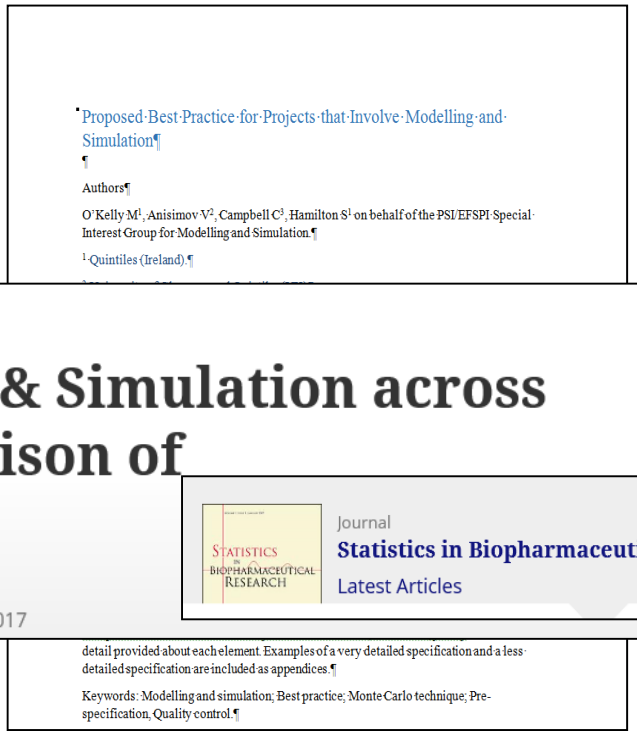
Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

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[1], F Ivanow[9], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornoe[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.

M&S



Proposed Best Practice for Projects that Involve Modelling and Simulation

Authors

O'Kelly M[1], Anisimov V[2], Campbell C[3], Hamilton S[1] on behalf of the PSI/EFSPI Special Interest Group for Modelling and Simulation.

[1] Quintiles (Ireland).

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

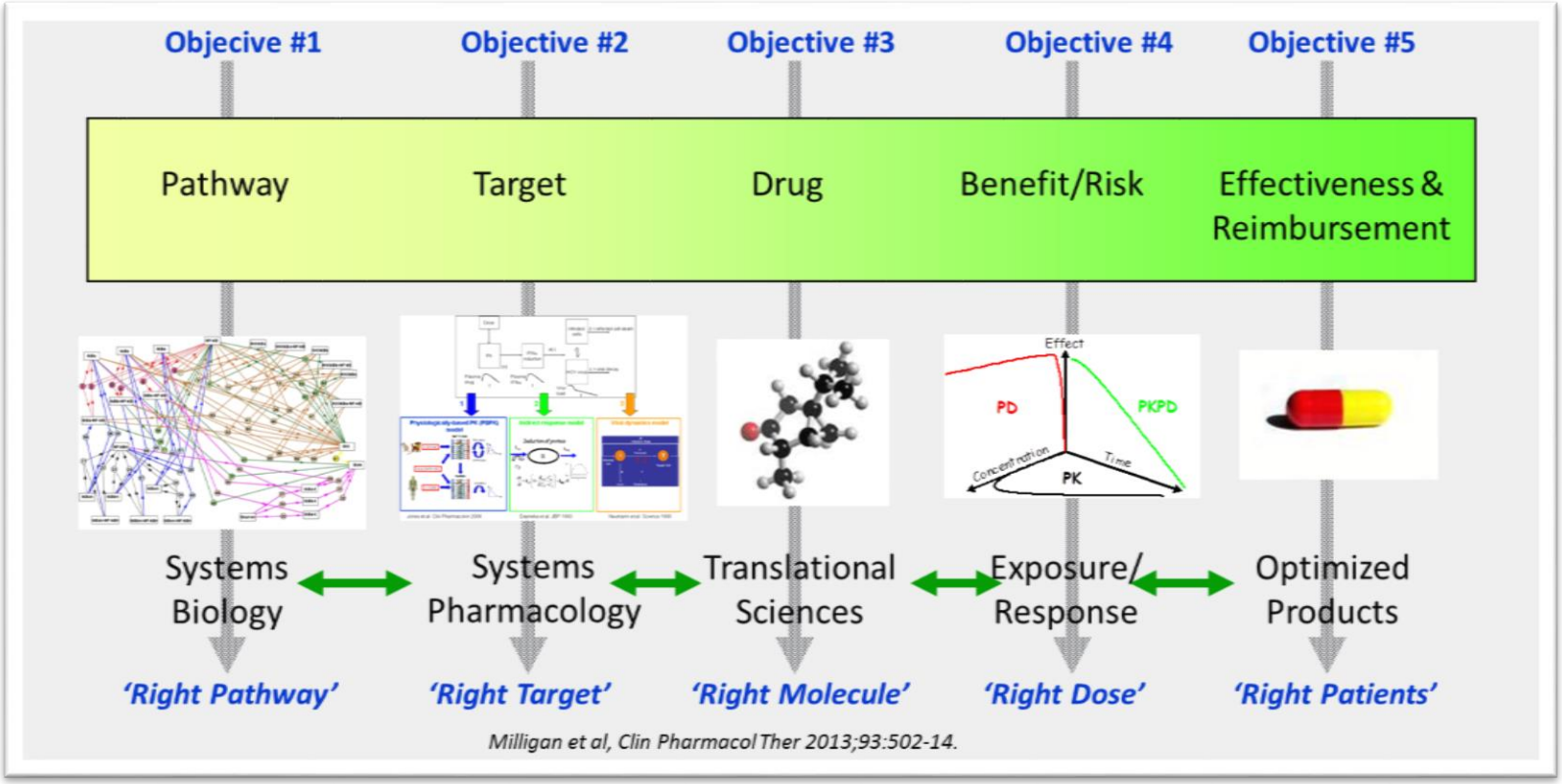
How

- Basic standards in planning & reporting for MID3 activities
- Risk Based QC/verification
- Documentation of assumptions, evaluation & impact assessment of MID3 activities

- Basic standards in planning & reporting M&S related to trial design
- M&S plans templates proposed
- Sensitivity analyses and operating characteristics
- Pre-specification of assumptions

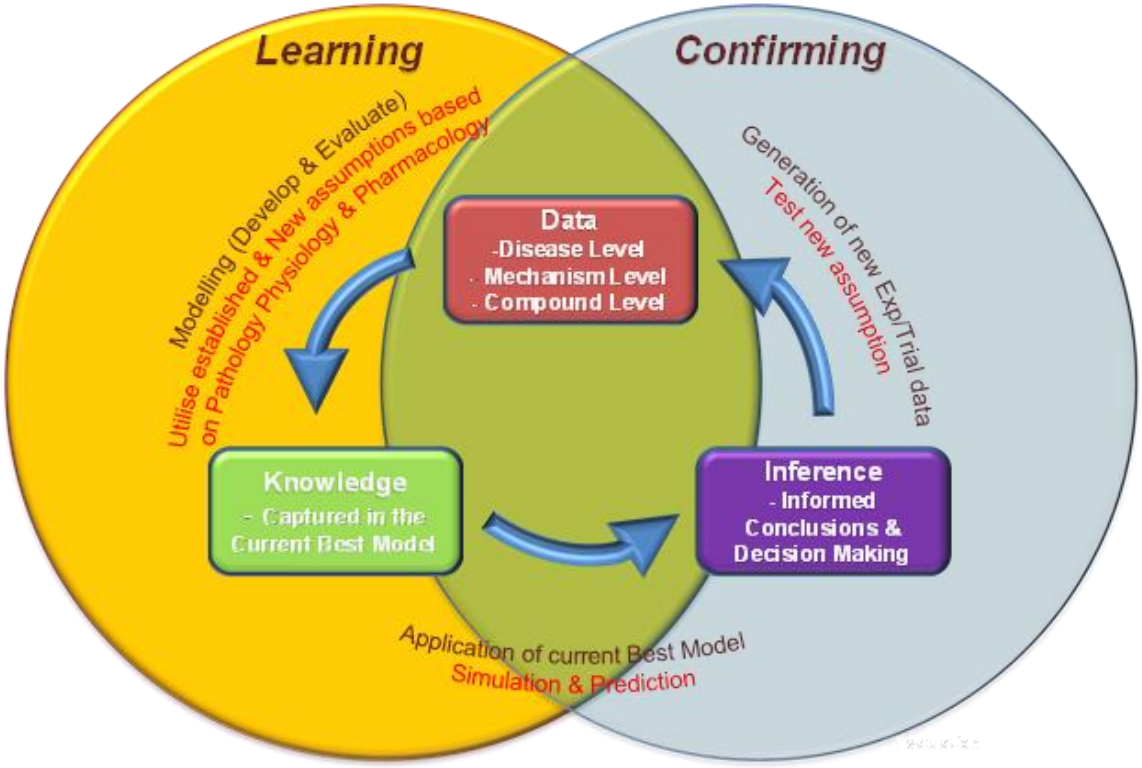
Note: Model informed approaches were discussed EFSPI Nov 2015 Dose finding WS

Constructing the Quantitative Framework



Model-Informed Drug Discovery & Development - **MID3**:
"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"

Importance for Decision Makers



Key:
Boxes: Steps in the "Learn and Confirm Cycle".
Arrows: Processes that link these key steps

- **Informing R&D questions and decisions at both project and portfolio levels**
- **Supporting translation across, and extrapolation beyond, the direct inference**
- **Aiding industry and regulatory acceptance of inferences obtained from clinical scenarios that are impractical/difficult to fully resolve through individual studies**
- **Impact and Return of Investment**
  - **Increased confidence**
  - **Cost savings**
  - **Unnecessary cost avoidance**
  - **Increased efficiency**

Milligan et al., 2013
Allerheiligen, 2014

Sheiner, L.B. Learning versus confirming in clinical drug development. CPT. 61, 275–291 (1997).

How

MID3 Framework: Key Elements

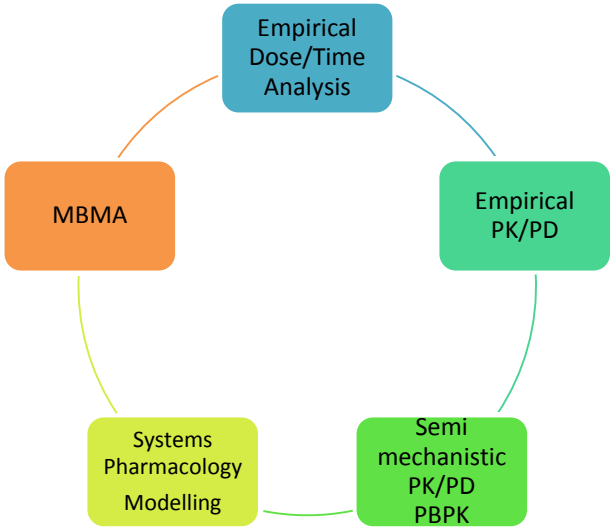
✱ Strategic Questions & Planning

- Medical Need / Commercial viability
- Pharmacokinetics
- Efficacy
- Safety/Tolerability
- Benefit/Risk
- Clinical viability
- Study and Program design

✱ Level(s) of activities

- **Compound Level**
- **Mechanism Level**
- **Disease Level**

✱ MID3 Approach(es)



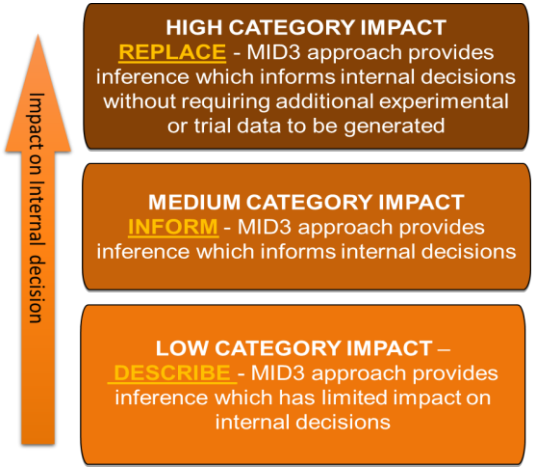
✱ Documentation :

Analysis plan	Simulation plan	Report
• Introduction	• Introduction	• Synopsis
• Objectives	• Objectives	• Introduction
• Data plan	• Additional information	• Objectives
• Data exploration	• Methods	• Data
• Methods	• Assumptions	• Methods
• Assumptions		• Assumptions
		• Results
		• Applications (prediction/simulation)
		• Discussion
		• Conclusions
		• Appendix

✱ Assumptions:

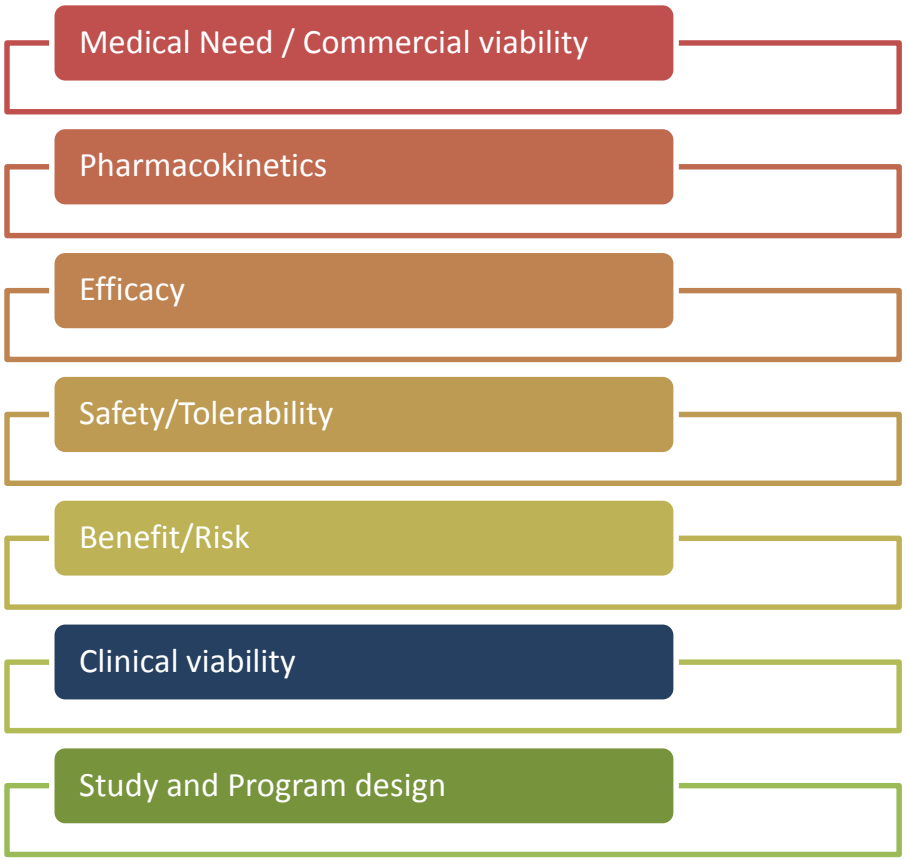
Type of Assumptions
• Pharmacological
• Physiological
• Disease
• Data
• Mathematical and statistical

✱ Impact :

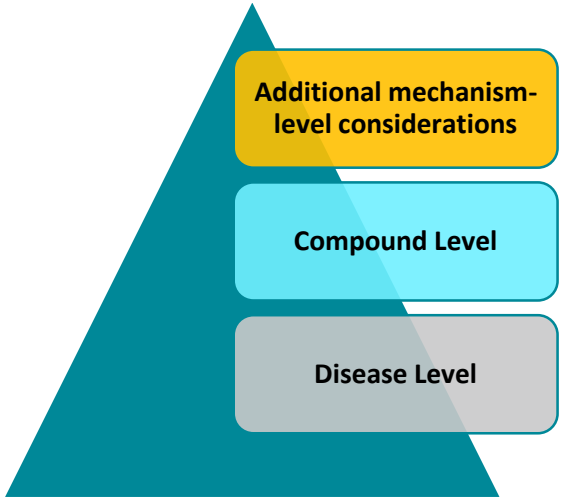


Categorizing Key Questions into MID3 Strategic Plan

- 7 key themes:



- 3 key levels



Additional mechanism-level considerations: compound-level or disease-level questions & activities where there is a focus on the MoA and knowledge gained from other compounds with a similar MoA

Compound Level: questions & activities that focus on the data associated with a compound of interest

Disease Level: questions & activities that can be answered in advance of development of any particular compound

See Table 1 in white paper: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf

EFPIA Classification of MID3 Internal Impact

Impact on Internal decision

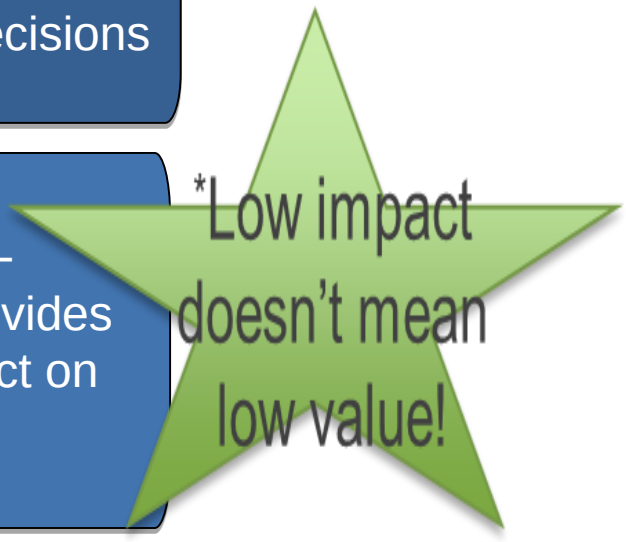
HIGH CATEGORY IMPACT
REPLACE - MID3 approach provides inference which informs internal decisions without requiring additional experimental or trial data to be generated

MEDIUM CATEGORY IMPACT
INFORM - MID3 approach provides inference which informs internal decisions

LOW CATEGORY IMPACT –
DESCRIBE - MID3 approach provides inference which has limited impact on internal decisions

The aim is:

- to provide a starting point for the discussion on impact on internal decision making
- to enable greater clarity in the level of impact of existing literature examples



Planning, Conduct and Documentation of MID3

Components of Good practice Plans: “Fit for Purpose”

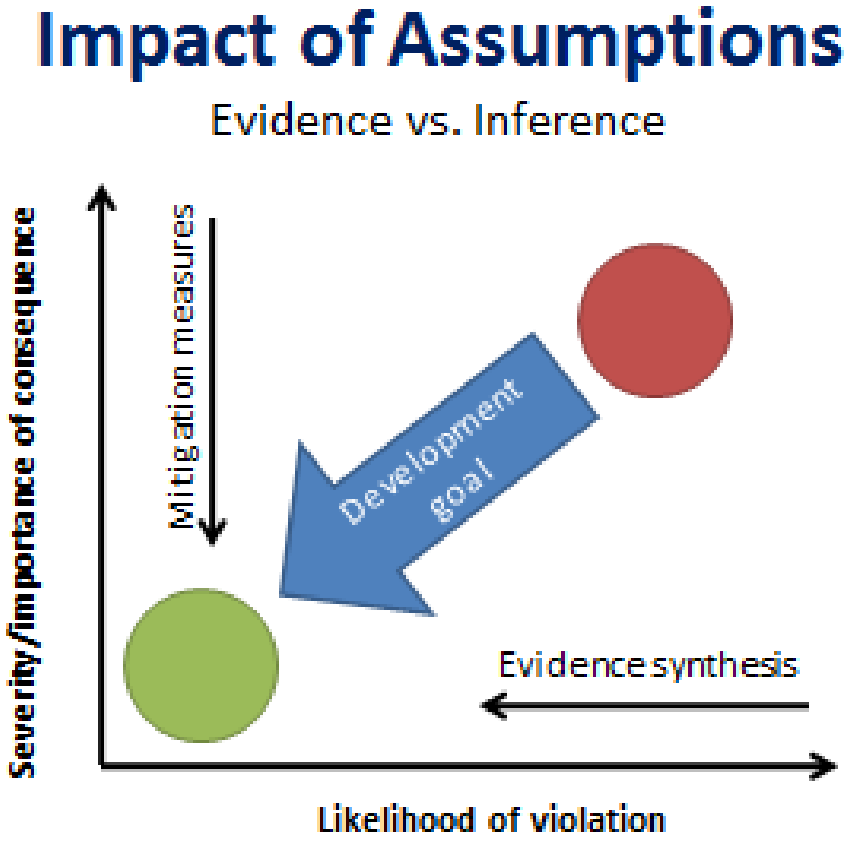
Good Practice

- Clarity on the key questions & Objectives
- Transparency of Assumptions & their Evaluation
- Simulations to Integrate the necessary Levels of Uncertainty
- Reproducible Research - Utilize QA/QC Risk Based Guideline:
  - QA - Audit Trail
  - Scientific Review
  - Risk assessment to determine the extent of the QC required
- Sufficient Information to judge the model
- Documentation orientated to satisfy all end-users
- “Fit for Purpose” Use Adequate Graphical and/or Tabulated display of Key Data features, Model and Simulation Results.
- Good practice proposal on Inclusion of MID3 Analyses and Conclusions in CTD

Table 4 The common general structure of documents describing MID3 analyses

Analysis plan	Simulation plan	Report
• Introduction	• Introduction	• Synopsis
• Objectives	• Objectives	• Introduction
• Data plan	• Additional information	• Objectives
• Data exploration	• Methods	• Data
• Methods	• Assumptions	• Methods
• Assumptions		• Assumptions
		• Results
		• Applications (prediction/simulation)
		• Discussion
		• Conclusions
		• Appendix

Table to Categorize Assumptions



Type of Assumptions
Pharmacological
Physiological
Disease
Data
Mathematical and statistical

Assumption Evaluation Approach

- Pharmacology – consider the nature and extent of ***drug treatment*** effects on endpoints of interest
  - E.g. shape and time course of exposure/dose response, covariates, mechanisms, combinations
- Physiology – consider the nature and extent of ***population*** effects on endpoints of interest
  - E.g. depression patients are "HV-like", ethnic differences, age, gender
- Pathology – consider the nature and extent of ***disease process*** effects on endpoints of interest
  - E.g. disease progression, prognostic factors,
- Data – consider the nature and extent of ***interpolation and extrapolation*** effects on endpoints of interest
  - E.g. contrasts from NMA, linking of endpoints, missing data imputation
- Mathematical and/or Statistical – consider the nature and extent of ***the numerical property*** effects on endpoints of interest
  - E.g. normality assumptions, mean response, CI bounds, variances

Assumption Evaluation Approach

Important assumptions should be evaluated as to whether:

- *They are currently accepted (established versus new)*
- *They can be prospectively verified*
- *They are testable based on the a) data used for developing the model (or otherwise available data) or b) based on data that will be obtained in future studies*
  - *In this case, the proposed approach used to test and confirm the assumption should be detailed.*
- *Assumptions are not testable.*
  - *In this case, the impact of an erroneous supposition and therefore the validity with respect to its intended application should be evaluated with an appropriate sensitivity analyses*

Working Example of an Assumption Table: COPD

Examples of important assumptions	Examples of important assumptions	Justification	New/Established?	Testable/Non-Testable?	Testable/Non-Testable Rationale	Test/approach to assess impact	Evaluation
Principally concerning Pathology	In COPD the FEV1 response predicts ER	Can evaluate FEV1 in small, short duration studies unlike ER. Scientifically plausible association between two endpoints.	Established	Not testable	Not testable with the current dataset	Cannot be estimated directly from current dataset, but informed by available literature evidence (MBMA)	
Principally concerning Pharmacology	PD effect on FEV1 of 75ml is an appropriate target value	KOLs are most comfortable with this figure	New	Not testable	Not testable with the current dataset	Sensitivity analysis changing the target value	
Principally concerning Pharmacology	PD effect on FEV1 at week 6 is an appropriate endpoint to predict ER	KOLs are most comfortable with end of treatment phase (landmark) analysis	Established	Testable	Testable with a wider range of time points	Change the value of time points and/or assess longitudinal response	
Principally concerning Pharmacology	PD effect on FEV1 to ER is consistent across mechanisms	Change in FEV1 drives ER and different mechanisms share same underlying FEV1:ER relationship	Established	Testable	Testable with a wider range of doses and mechanisms	Sensitivity analysis changing this assumption In absence of sufficient data to support/refute	
Principally concerning Pharmacology	PD effect on FEV1 is additive across mechanisms	Change in FEV1 drives ER and different mechanisms share same underlying FEV1:ER relationship	New	Not testable	Not testable with the current dataset	Sensitivity analysis changing this assumption In absence of sufficient data to support/refute	
Principally concerning Pharmacology	PD effect on FEV1 is non-monotonic	Empirical evidence from available data	New	Testable	Testable with a wider range of concentrations	Comparison of simulated metrics of interest across boarder exposure range	
Principally concerning maths and/or stats	NDLM is an appropriate data analytic	Empirical evidence from available data	New	Testable	Testable with a wider range of data analytics	Comparison of simulated metrics of interest between the different data analytics	
Principally concerning maths and/or stats	Mean responses are appropriate descriptors	NDLM requires normal distributed data	Established	Testable	Testable as can visualize data distributions	If non-normal data perform transformation	

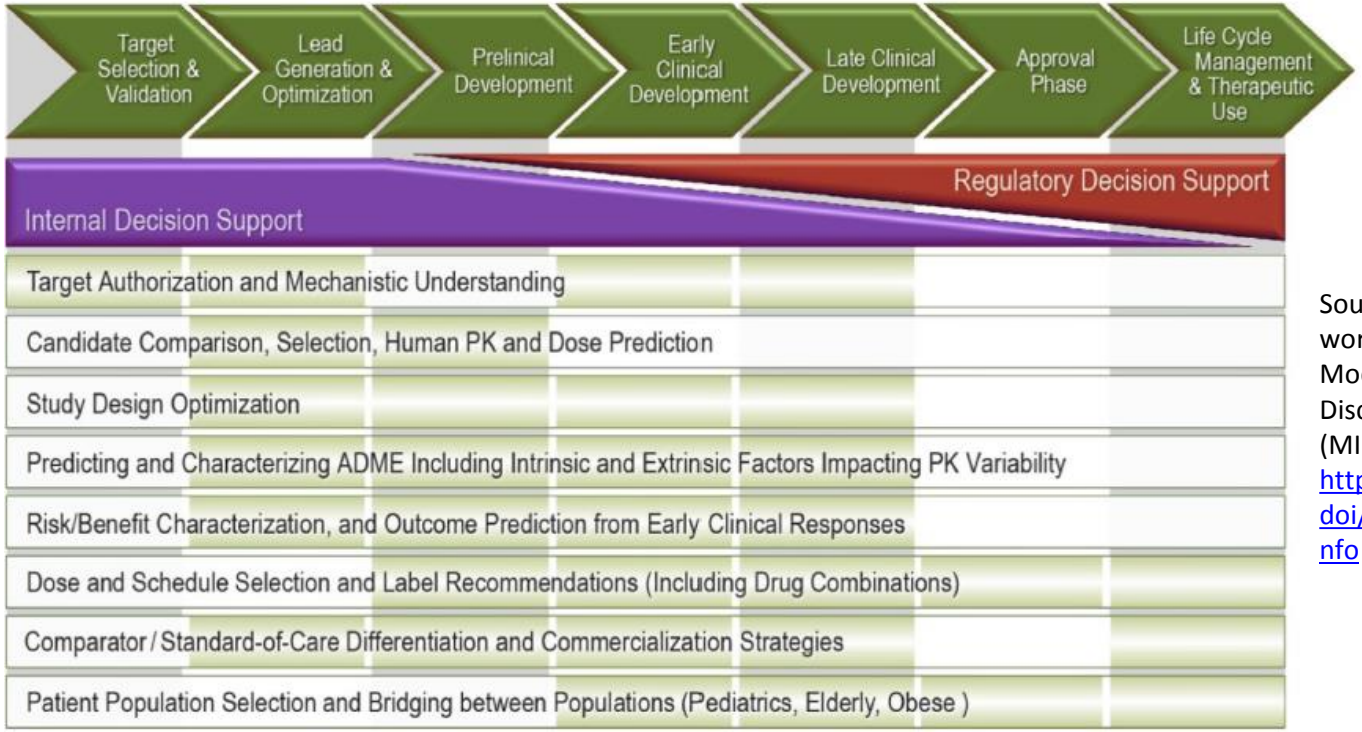
And so on……

1. Duration of trial
2. Population studied is relevant to Phase 3 population
3. Countries in which Phase 3 studies will be conducted do not present any important differences in epidemiology, diagnosis, standards of care and patient management compared with those studied in Phase 2.

Applications of MID3 in 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

- Sourced from PUBMED and the EMA/EFPIA M&S workshop
- Does not pretend to be an exhaustive overview of each application



Source: EFPIA MID3 workgroup: Good Practices in Model-Informed Drug Discovery and Development (MID3) http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/suppinfo

Why Now

Regulatory Focus on Paediatrics

Original Article

DIA

Therapeutic Innovation
& Regulatory Science
1-7

Extrapolation of Efficacy in Pediatric Drug Development and Evidence-based Medicine: Progress and Lessons Learned

**Haihao Sun, MD, PhD[1], Jean W. Temeck, MD[1], Wiley Chambers, M
Ginger Perkins, AAS[1], Renan Bonnel, PharmD, MPH[1], and
Dianne Murphy, MD[1]**

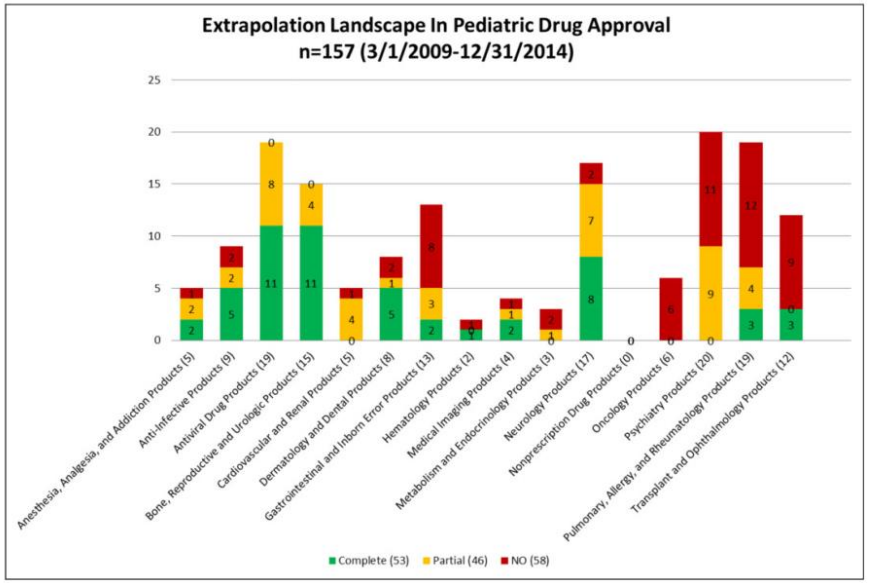


Figure 1. Extrapolation Landscape In Pediatric Drug Approval.

Drug Development: The Use of Unlicensed/Off-label Medicines in Pediatrics

[*]Yuichiro Yamashiro, [†]Jennifer Martin, [‡]Madlen Gazarian, [§]Sharon Kling, [||]Hidefumi Nakamura, [||]Akira Matsui, [¶]Salvatore Cucchiara, [¶]Marina Aloi, [#]Erica L. Wynn, and [#]Andrew E. Mulberg

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/199678/2016

Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Draft

Draft agreed by Biostatistics Working Party	September 2017
Draft agreed by Modelling and simulation group	September 2017
Draft agreed by PKWP	September 2017
Draft agreed by Scientific Advice Working Party	September 2017
Draft Adopted by PRAC	29 September 2017
Draft Adopted by PDCO	12 October 2017
Draft Adopted by CHMP	12 October 2017
Start of public consultation	13 October 2017
End of consultation (deadline for comments)	14 January 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Template for scientific document (part B-E)

for an application for a <Paediatric Investigation Plan> <including> <a deferral> <and> <a> <waiver>

<Active substance> *or* <INN>- *(Only when INN is at least recommended)*

<Trade name> <and associated trade names>- *(Only in case of authorised products)*

<Applicant's name>

<EMEA-xxxxxx-PIPxx-xx>

Guidance text is in green italics. You may print a copy of this template with the drafting note, then delete them all in one:

Click on Ctrl-Alt-Shift-S to view the "styles" window. Select "Drafting notes (Agency)" and click on the icon on the right, chose "Select all XXX instances", press the "Delete" key on the keyboard.

Do not change or delete the titles and the numbering style. (Add "Not applicable" if necessary)

Do not delete the comment boxes.

Suggested font: Verdana 9.

Paragraph tab: alignment: left, outline level: body text, indentation: 0, spacing before: 0pt and after: 7pt; line spacing: at least, at: 14pt.

ICH harmonisation for better health

Concept Paper Outline

Pediatric Extrapolation

Endorsed by the Assembly on [day/Month/Year]

Type of Harmonisation Action Proposed: New Efficacy Guideline as a series under E11: Clinical Investigation of Medicinal Products in the Pediatric Population

Statement of the Perceived Problem:

In both the US and EU, pediatric legislation has increased the number of approved drugs with specific efficacy and safety data in labeling for pediatric populations. However, in many cases, there is still a long gap (between 8-10 years) between the initial adult approval and the inclusion of pediatric-specific information in product labeling. The use of pediatric extrapolation has advanced substantially as an approach to improve the efficiency and success of pediatric drug development. However, there is variability in the interpretation and application of extrapolation across regulatory authorities. Harmonization of methodologies and strategies to incorporate pediatric extrapolation into overall drug development plans will improve the speed of access to new drugs for pediatric patients.

The current E11(R1) concept paper recommends that more detailed guidance be developed to advance the use of pediatric extrapolation. The current E11(R1) guideline only includes a high level description of pediatric extrapolation that encourages sponsors to initiate a discussion of using this approach in regulatory interactions. Therefore, there is a need to provide more detailed guidance about how pediatric extrapolation can be used in successful pediatric product development, leading to marketing authorization.

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 …..

*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

*Presented at DIA/FDA Statistics Forum 24th April 2017, North Bethesda, MD

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"

*Presented at DIA/FDA Statistics Forum 24th April 2017, North Bethesda, MD

Today we announced our detailed work plan for the steps we're taking to implement different aspects of Cures. I want to highlight one example of these steps, which we're investing in, and will be expanding on, as part of our broader Innovation Initiative. It's the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.

In silico clinical trials use computer models and simulations to develop and evaluate devices and drugs. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs. This enables safe and effective new therapeutics to advance more efficiently through the different stages of clinical trials. FDA's efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertise and infrastructure to advance the development of these state-of-the-art technologies.

FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms. We'll be putting out additional, updated guidance on how aspects of these in silico tools can be advanced and incorporated into different aspects of drug development.

A variety of drug development, regulatory, and therapeutic questions are addressed by CDER through modeling and simulation strategies. CDER's Office of Translational Sciences (OTS) uses these same strategies in the review of Investigational New Drugs Applications (INDs) and New Drug Applications (NDAs). To take just one example of the benefits of these approaches, as we enter an era of drug individualization, modeling and simulation that incorporates aspects of individual physiology and genetics in drug metabolizing enzymes is being used to identify patient subgroups that need dose adjustments. These approaches are incorporated to assess the combined effect of drug interactions, renal impairment, and hepatic insufficiency in patients, with clinical management strategies described in drug labeling where appropriate.

Another example is the use of modeling and simulation to assist in the creation of natural history databases to support model-based drug development. This could make clinical trials more efficient—for example, by enabling FDA to model some aspects of the behavior of the placebo arm in clinical trials. Right now, FDA is collaborating with scientists to develop such natural history models in Parkinson's disease, Huntington's disease, Alzheimer's disease, and muscular dystrophy. An important objective of modeling and simulation is to better evaluate the behavior of new treatments in rare disease populations that are inherently hard to study due to their small size.

To advance these opportunities, we need to continue to invest in high performance computing. These computing capabilities are becoming a key requirement to the ability of our review staff to manipulate the large data sets that are now a common feature of drug applications. FDA is actively working to expand the agency's capabilities in high performance computing, and to explore modeling approaches and enhance their regulatory impact, through an effort enabled by the work of the agency's Scientific Computing Board.

Presentation Outline

- ***Why*** Extrapolation
  - Personal (Clinical Pharmacology/Pharmacometrics) perspective
- ***What*** does it look like (from the above perspective)
  - The "Quantitative Framework"
- ***How*** could it be performed
  - Bulk of the presentation
- ***Why now…..***