Good Practices in Model Informed Drug Discovery & Development (MID3): Practice, Application, Documentation and Reporting

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on behalf of the EFPIA MID3 Workgroup

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Outline

- Progress against Actions from EFPIA/EMA M&S workshop (2011)
- Good Practice Overview
  - Highlights of Part 1 : Practice & Application
  - Highlights of Part 2 : Documentation & Reporting
- Next Steps

EFPIA/EMA M&S Workshop (Dec 2011): Objectives and Outputs

Workshop's 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

EDITORIAL

Regulatory Modeling and Simulation Moves Into the Next Gear in Europe

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e32; doi:10.1038/psp.2013.8; advance online publication 27 February 2013

PERSPECTIVE

The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output From the EFPIA/EMA Modeling and Simulation Workshop

E Manolis[1], S Rohou[2], R Hemmings[1,3], T Salmonson[1,4], M Karlsson[5] and PA Milligan[6]

PERSPECTIVE

Modeling and Simulation at the Interface of Nonclinical and Early Clinical Drug Development BOS 1

SAG Visser[1,2], E Manolis[3], M Danhof[4] and T Kerbusch[5]

PERSPECTIVE

Modeling and Simulation in Clinical Pharmacology and Dose Finding BOS 2

A Staab[1], E Rook[2,3], M Maliepaard[2,3], L Aarons[4] and C Benson[5]

PERSPECTIVE

Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations BOS 3

L Harnisch[1], T Shepard[2,3], G Pons[3,4] and O Della Pasqua[5]

PERSPECTIVE

Modeling and Simulation to Optimize the Design and Analysis of Confirmatory Trials, Characterize Risk–Benefit, and Support Label Claims BOS 4

SF Marshall[1], R Hemmings[2,3], F Josephson[2,4], MO Karlsson[5], M Posch[2,7] and J-L Steimer[6]

EFPIA/EMA M&S Workshop (Dec 2011) : Progress against Actions

Opportunities	Challenges	Action
• Increase efficiency of R&D through data Integration & design optimisation •Robust informed R&D decision making & regulatory assessment •Support extrapolation across populations •Informed Risk-Benefit assessment & labelling •Integration of omic data	Heterogeneity & inconsistency of practice across industry. Need for standardisation of analysis & reporting	Agree on common Good Practices : Standardisation and Reporting
	Variable readiness of regulatory system to evaluate approaches	Integrate and expand competence in EU regulatory framework
	Communication gap between modeller & non-modeller	Workshops & utilisation of current regulatory pathways
	Mis-perception that dose response is only company risk	Debate update to regulatory guidance
	Data sharing	Strengthen data sharing initiatives

EFPIA MID3 Workgroup Membership

Name	Affiliation
Rolf Burghaus	Bayer
Valerie Cosson	F. Hoffmann-La Roche
S. Y. Amy Cheung	AstraZeneca
Marylore Chenel	Servier
Oscar Della Pasqua	GlaxoSmithKline
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Bengt Hamren	AstraZeneca
Lutz Harnisch	Pfizer
Frederic Ivanow	Johnson & Johnson
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Peter Milligan	Pfizer
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Jean Louis Steimer	Novartis
Christoffer Tornoe	Novo Nordisk
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Acknowledgements:

Name	Affiliation
Efthymios Manolis	EMA
Terry Shepard	MHRA

Members of EMA MSWG are involved in the review of the document and are aligned with the covered principles.

EFPIA Model Informed Drug Discovery & Development (MID3) Document

- Introduction & Definitions

Part 1

- Practice & Application
  - Rationale
  - Strategic Planning
  - MID3 Approaches
  - MID3 Applications

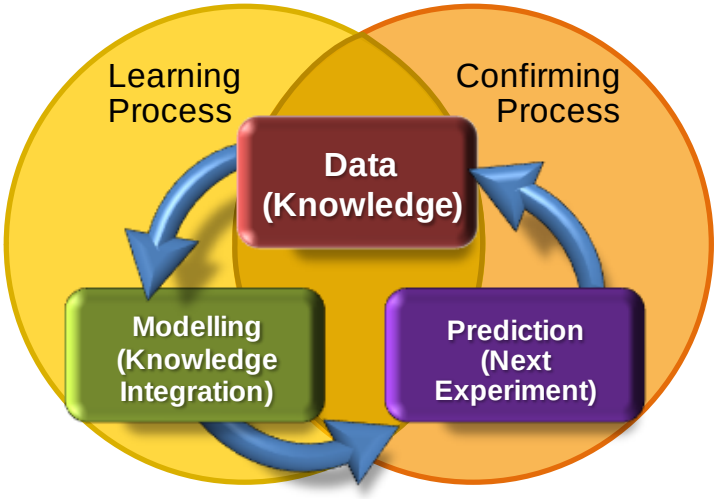
Part 2

- Document & Reporting
  - Current Limitations
  - Good Doc Practice
  - Assumptions
  - Components & Considerations:
    - Analysis Plan
    - Simulations Plan
    - Report

- Glossary & References

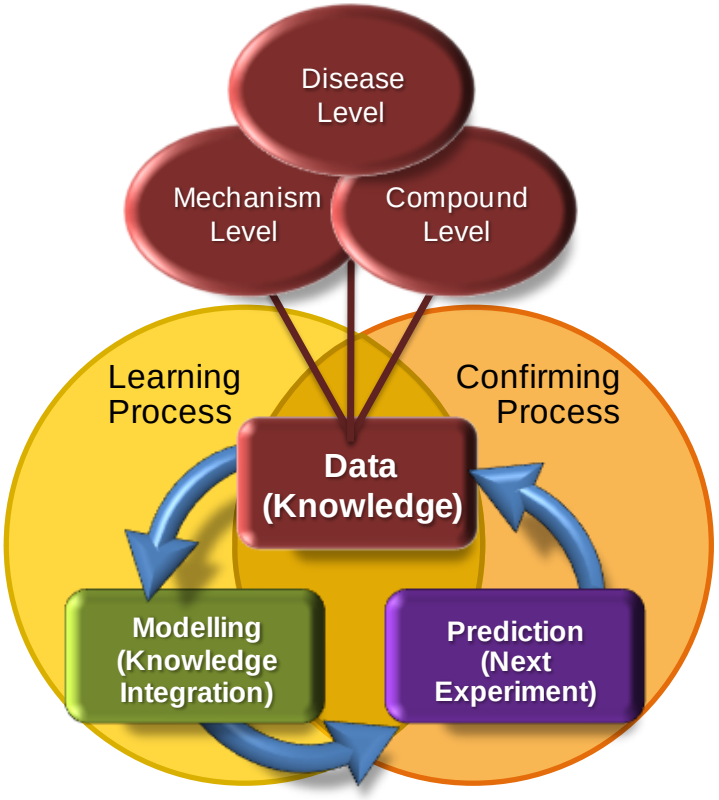
MID3 Concepts: Rationale

Part 1:
Practice & Application
Rationale
Strategic Planning
MID3 Approaches
MID3 Applications



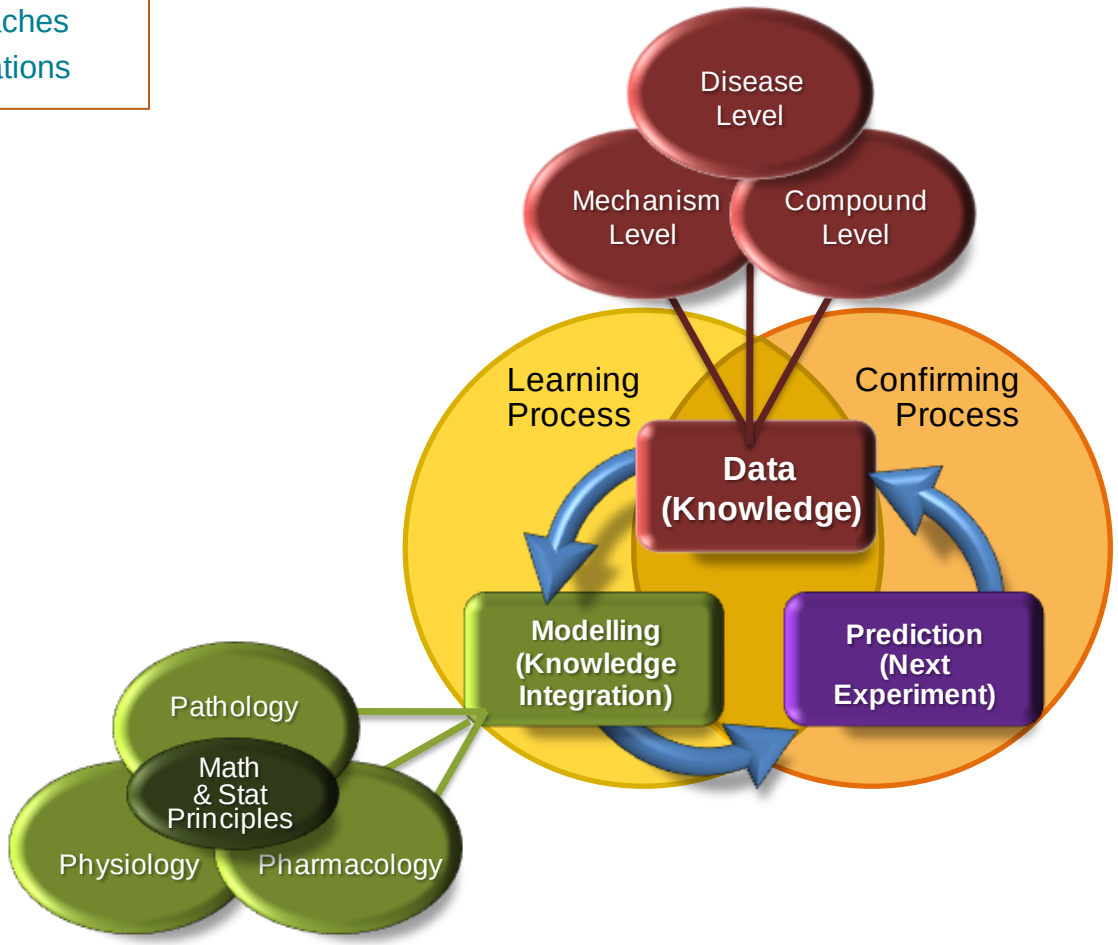
MID3 Concepts: Rationale

Part 1:
Practice & Application
Rationale
Strategic Planning
MID3 Approaches
MID3 Applications



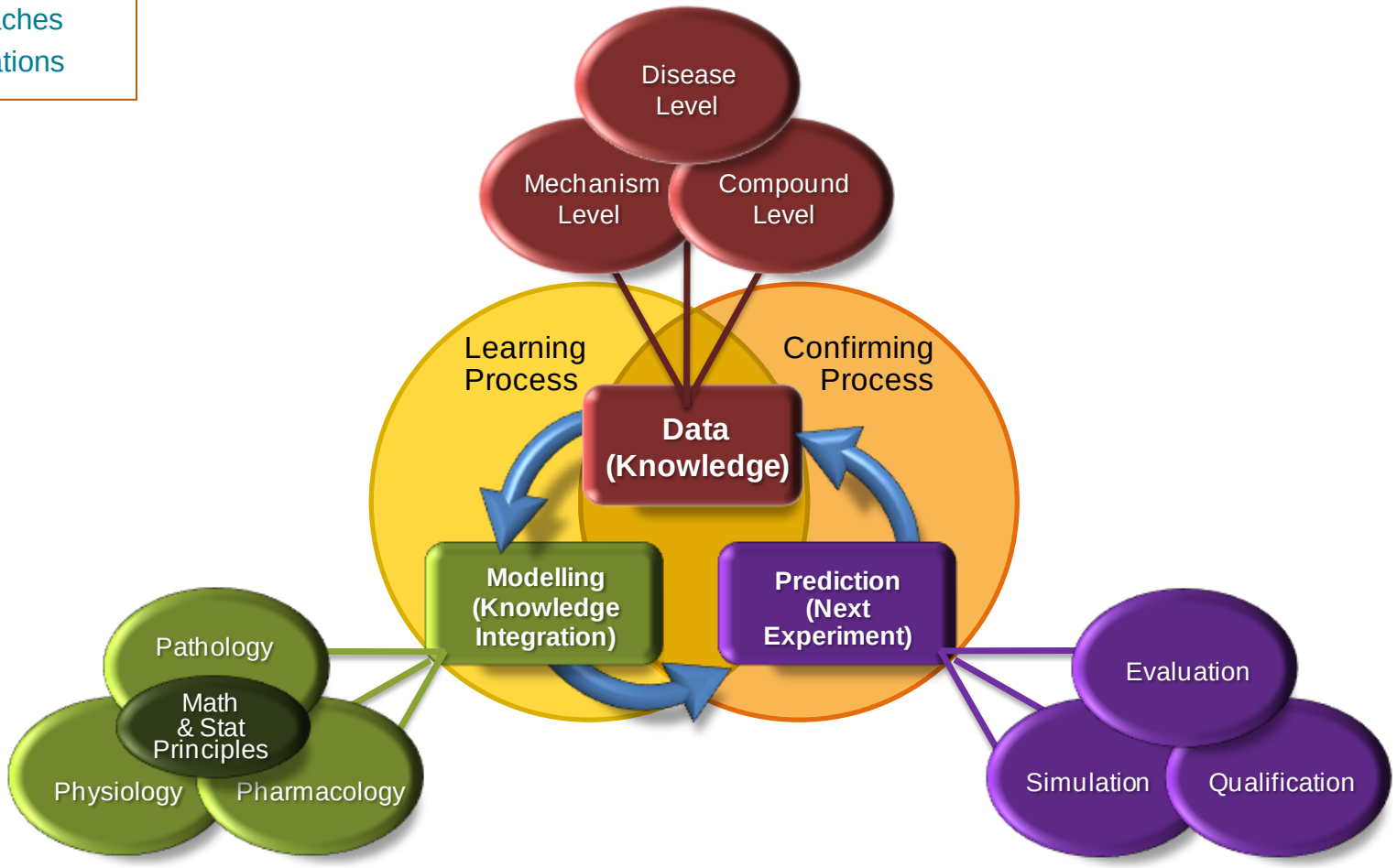
MID3 Concepts: Rationale

Part 1:
Practice & Application
Rationale
Strategic Planning
MID3 Approaches
MID3 Applications



MID3 Concepts: Rationale

Part 1:
Practice & Application
Rationale
Strategic Planning
MID3 Approaches
MID3 Applications



MID3: Strategic Planning

Part 1:
Practice & Application Rationale
Strategic Planning
MID3 Approaches
MID3 Applications

- MID3 plan proposed and endorsed along side R&D plans:
  - Link to data generation
  - Refreshed at key R&D milestones
  - Tracked with other R&D components

Good Practice MID3 Grid

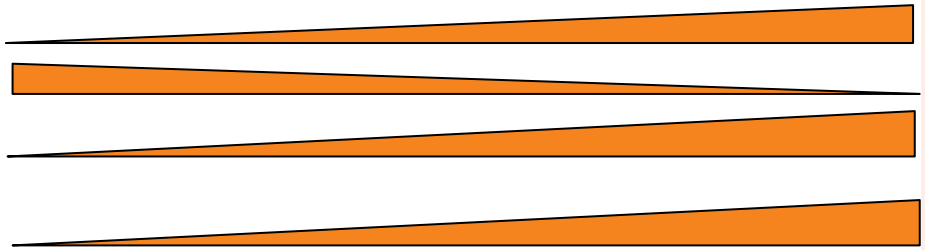
Theme		Activity Level		
		Disease	Mechanism	Compound
	PK	**Generic Questions?** **Proposed Activities**		
	Safety			
	Efficacy			
	Benefit /Risk			
	Commercial Viability			
	Clinical Viability			
	Study Design			

- Analysis of Return on Investment
  - What information will be generated ?
  - How will the activity inform the decision(s)?
  - What would be the impact of not conducting this work?
  - What are the interdependencies in MID3 plan?
  - What are the likely key assumptions & limitations?

MID3: Comparison of Modelling Approaches (Extract)

Part 1:
Practice & Application
Rationale
Strategic Planning
MID3 Approaches
MID3 Applications

- Recognised as Subjective
- Current EFPIA Viewpoint to drive discussion
- Identify gaps & Opportunities

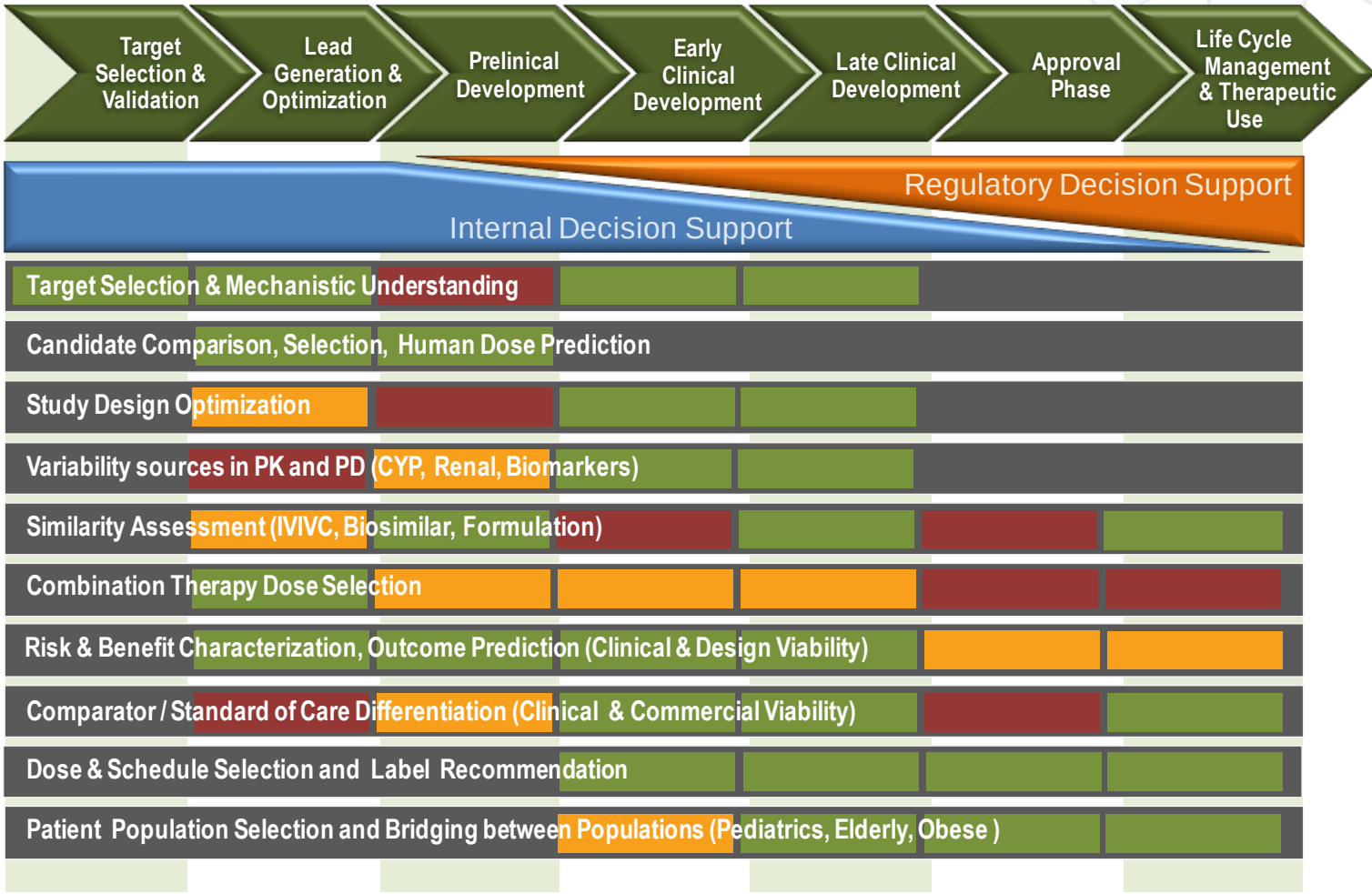
		Modelling Approach				
		Empirical Dose Time Analysis	Empirical PK/PD	Model based Meta-analysis	(Semi) Mechanistic PK/PD (PBPK)	Systems Pharma-cology modeling
Description & Nature of Model	**Assumptions**					
	Stat Rigour					
	Biologically Principles					
	Ability to Extrapolate					
Data Source & Experimental Design	Use Totality of indiv .data	++	+++	+	+++	+
	Use of Lit data	-	+	+++	++	+++
	Bayesian Priors	++	+++	-	++	-

- Also Covers:
- Model Building, Evaluation & Qualification
- Role in Decision Making

MID3: Applications & Request for More Case Studies? Please send to : Sandra.Visser @ merck.com

Part 1:
Practice & Application
Rationale
Strategic Planning
MID3 Approaches
MID3 Applications

- 90 case studies
- Arranged by
  - Application Type
  - R&D stages
- Summarised by
  - Key Themes
  - Activity Levels
  - Modelling(es) Approach
  - R&D Question(s)
  - Internal Impact



MID3 Documentation: Good Practice

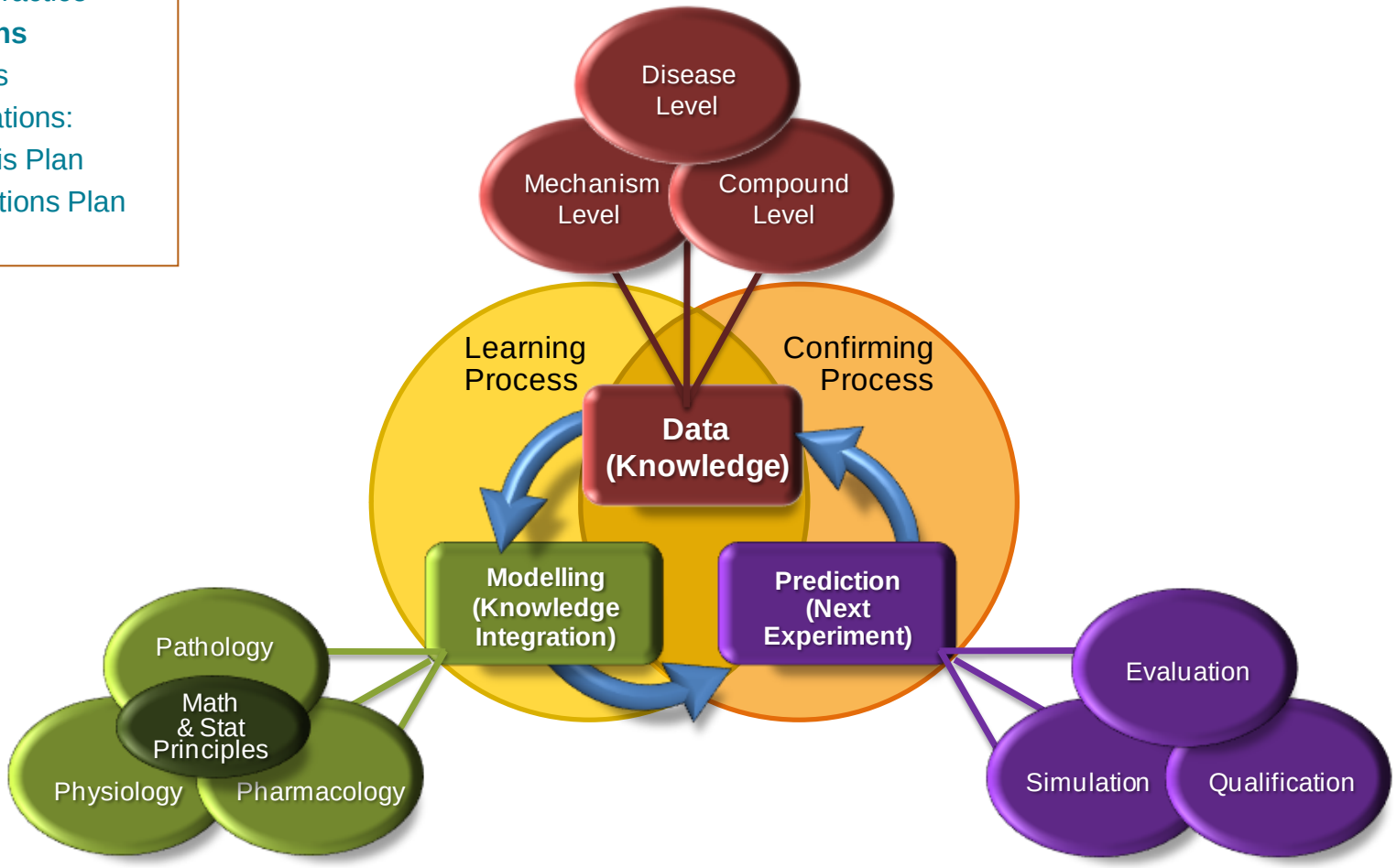
Part 2:
Document & Reporting
Current Limitations
Good Doc Practice
Assumptions
Components
& Considerations:
- Analysis Plan
- Simulations Plan
- Report

Good Practice
Clarity on the key questions & Objectives
Transparency of Assumptions & their Evaluation
Simulations to Integrate the necessary Levels of Uncertainty
Reproducible Research (Utilise QA/QC Risk Based Guideline)
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

- QA/QC Risk Based Guideline:
  - QA : Audit Trail
  - Scientific Review
  - Risk assessment to determine the extent of the QC required

MID3: Assumptions

Part 2:
- Document & Reporting
- Current Limitations
- Good Doc Practice
- **Assumptions**
- Components & Considerations:
  - Analysis Plan
  - Simulations Plan
  - Report



MID3: Assumptions

Part 2:
- Document & Reporting
- Current Limitations
- Good Doc Practice
- **Assumptions**
- Components & Considerations:
  - Analysis Plan
  - Simulations Plan
  - Report

MID3: Assumptions

Part 2:
Document & Reporting
Current Limitations
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Assumptions	Justification	New/ Established	Testable/ Not-Testable	Test/Approach to assess impact	Evaluation
Pharmacological assumptions					
Physiological assumptions					
Disease assumptions					
Data assumptions					
Mathematical and statistical assumptions					

Components of Good Practice Plans : "Fit for Purpose"

Part 2:
Document & Reporting
Current Limitations
Good Doc Practice
Assumptions
Components & Considerations:
- **Analysis Plan**
- **Simulations Plan**
- **Report**

- List of suggested Components
- Guiding principles
- Collation of References
- "Fit for Purpose" Guidance

Analysis Plan

- Introduction
- Objectives
- Data Plan
- Data Exploration
- Methods
  - Model Building
  - Selection& Evaluation
  - Qualification
- Assumptions
- Results
  - Key Displays to support Claims

Simulation Plan

- Introduction
- Objectives
- Additional Data
- Methods
  - Identify models
  - Limitations
  - Qualification
- Assumptions
- Results
  - Key Displays to support Claims

Report

- Synopsis
- Introduction
- Objectives
- Data
- Methods
- Assumptions
- Result
  - Key Displays to support Claims
- Applications /Simulations
- Discussion
- Conclusions
- Appendix

Next Steps

- Develop full text document
- Complete application examples (Help Please!)
- Document finalisation and publication:
  Target PSP 3Q 2014
- Share & engage with ISOP Standards & Best Practice Committee
- Continue dialogue with MSWG colleagues including support to development of future Regulatory Guidelines