U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Clinical Pharmacology

The ICH M15 Guidance: Assessment of Model-Informed Drug Development (MIDD) Evidence

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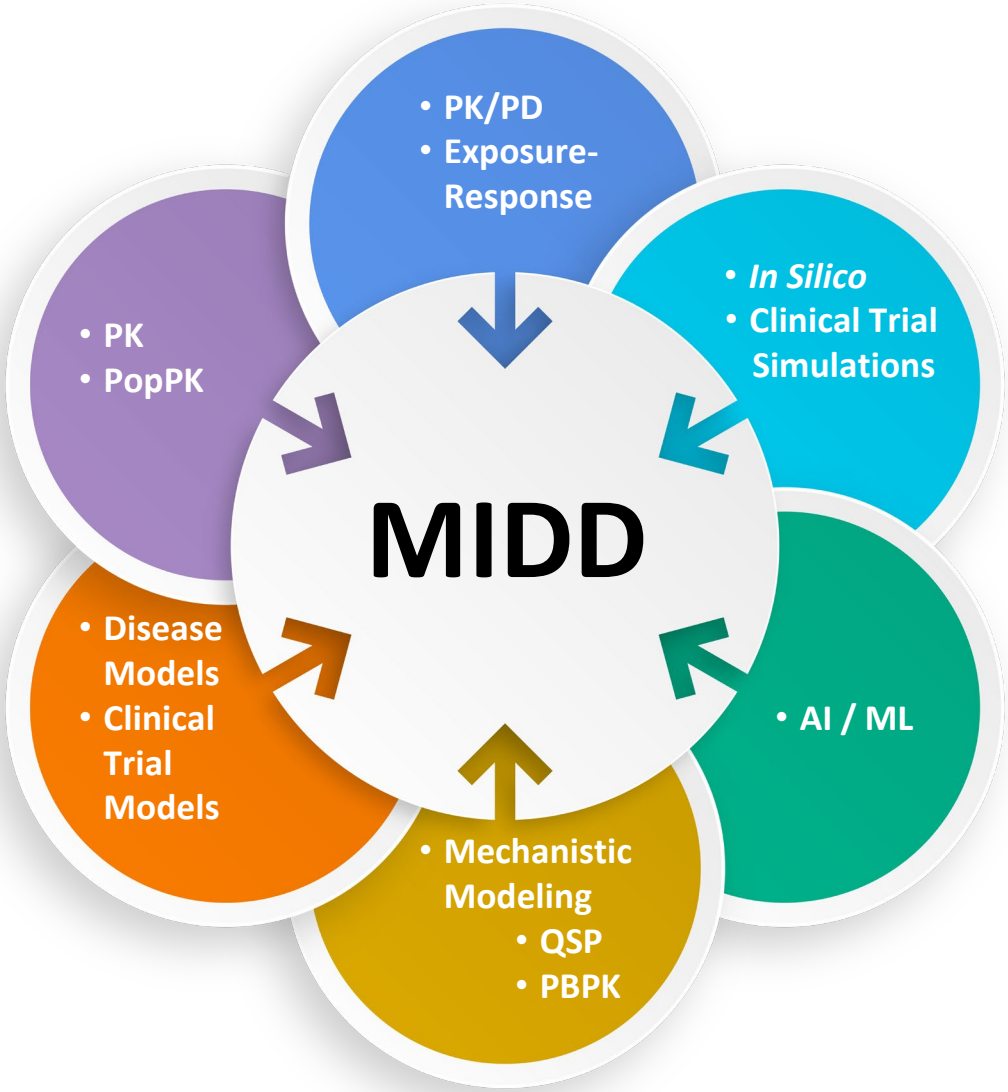
Center for Drug Evaluation & Research

Model-Informed Drug Development (MIDD)

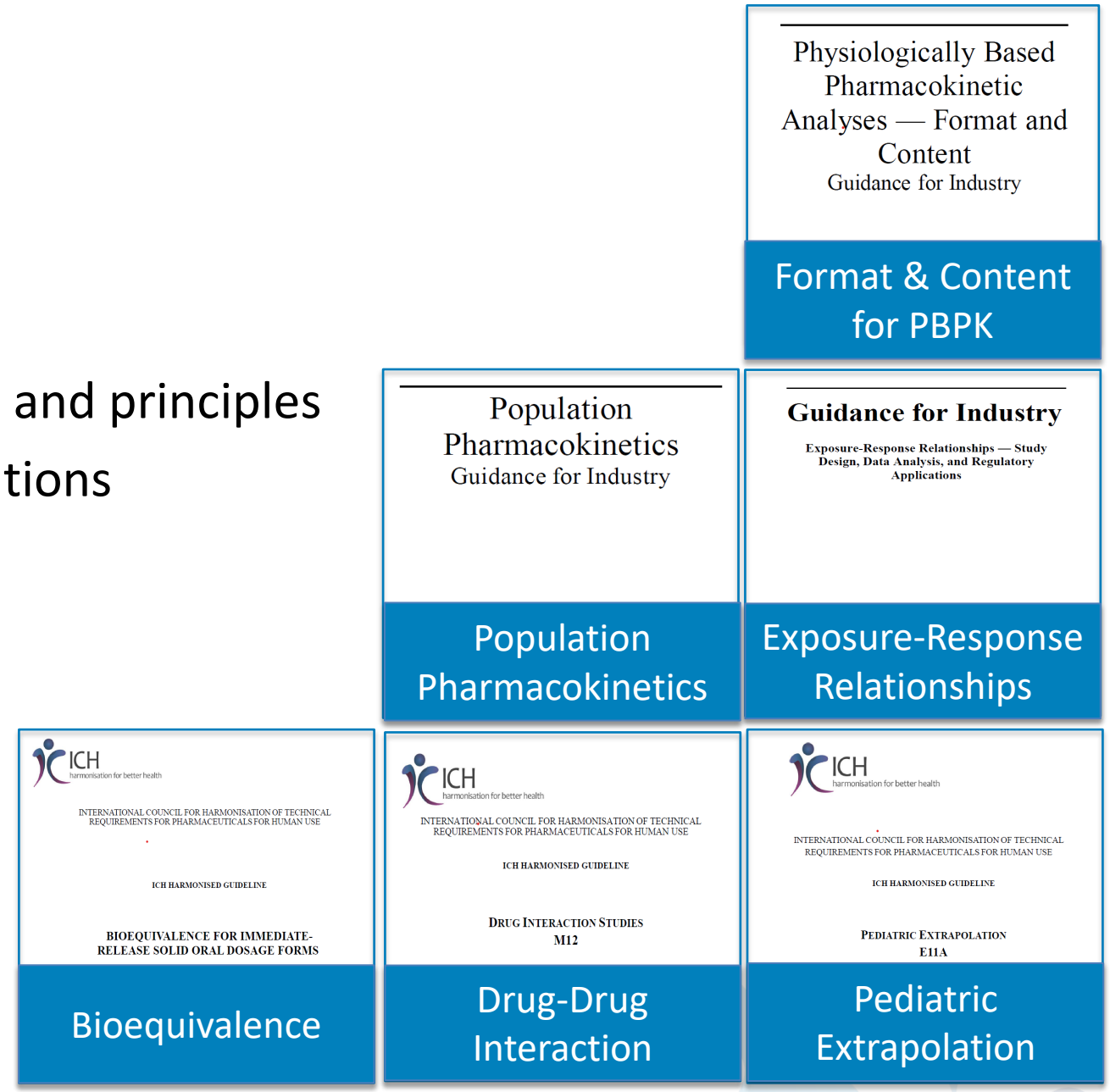


Courtesy by Huang SM 2019 AAPS

"MIDD is defined as the strategic use of computational modeling and simulation (M&S) methods that integrate nonclinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence"

M15 Motivations

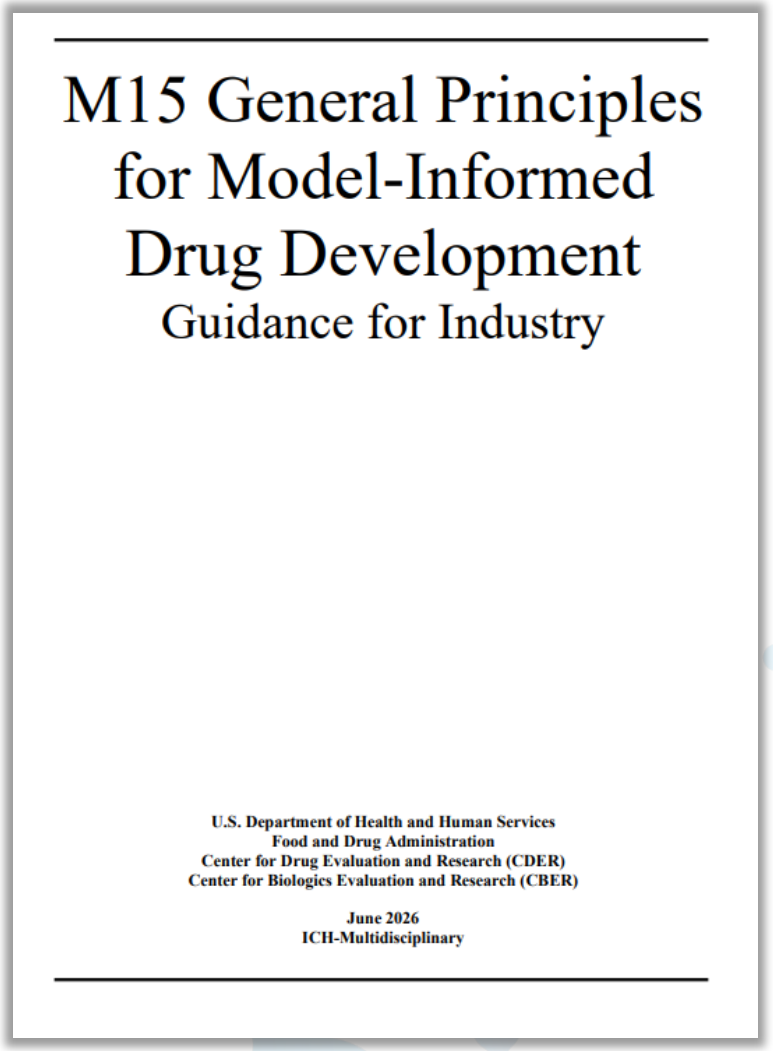
- Some MIDD guidances
- Lack of common:
  - Understanding of concepts and principles
  - Model assessment expectations
  - Documentation standards



Courtesy of Jeffery Florian

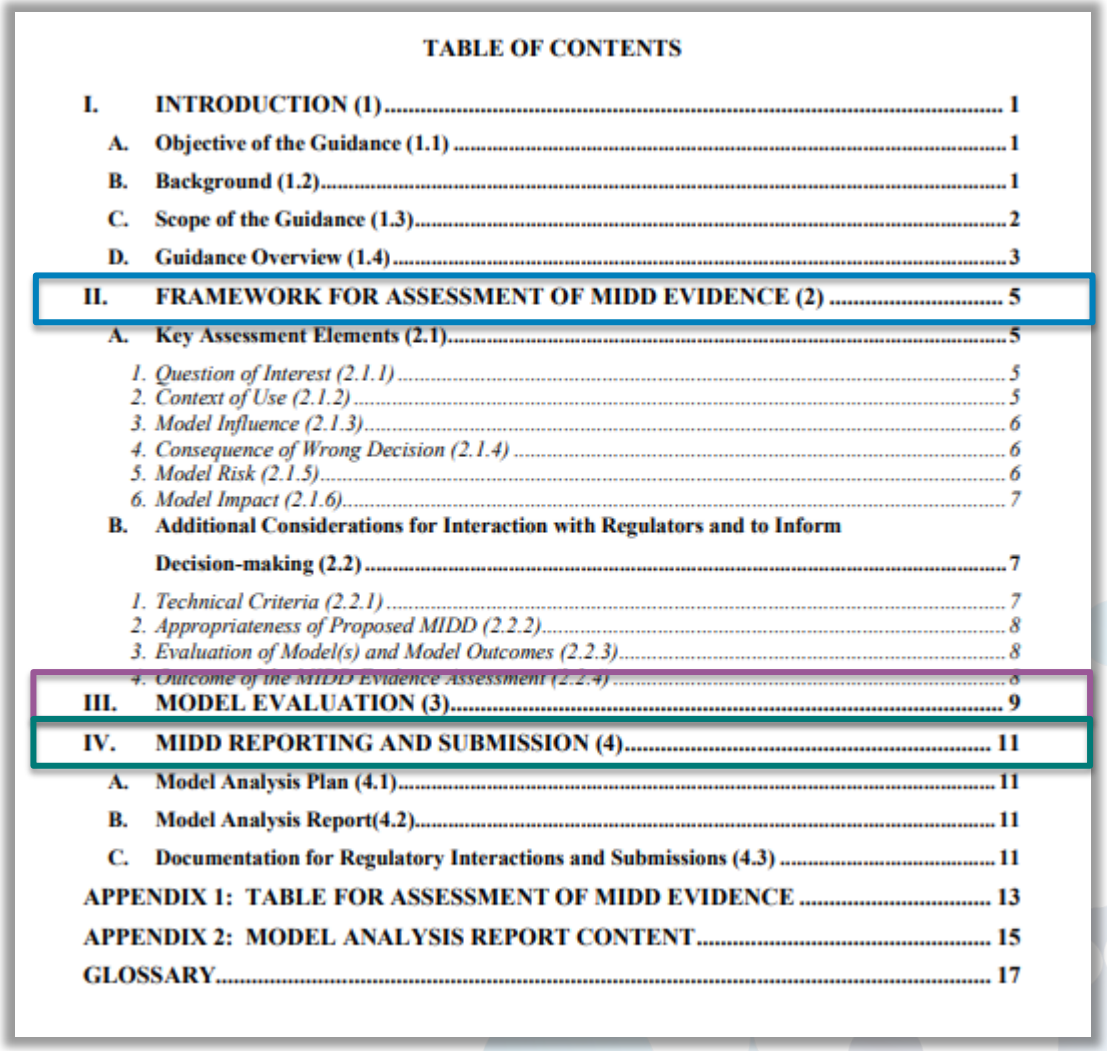
M15 Scope

- To be used with current accepted standards and practices
- Applies to current and emerging M&S methods, approaches, and applications
- Intended to facilitate multidisciplinary understanding



M15 Objectives

- MIDD evidence
  - Planning & documentation
  - Model evaluation
- Establishes a harmonized assessment framework



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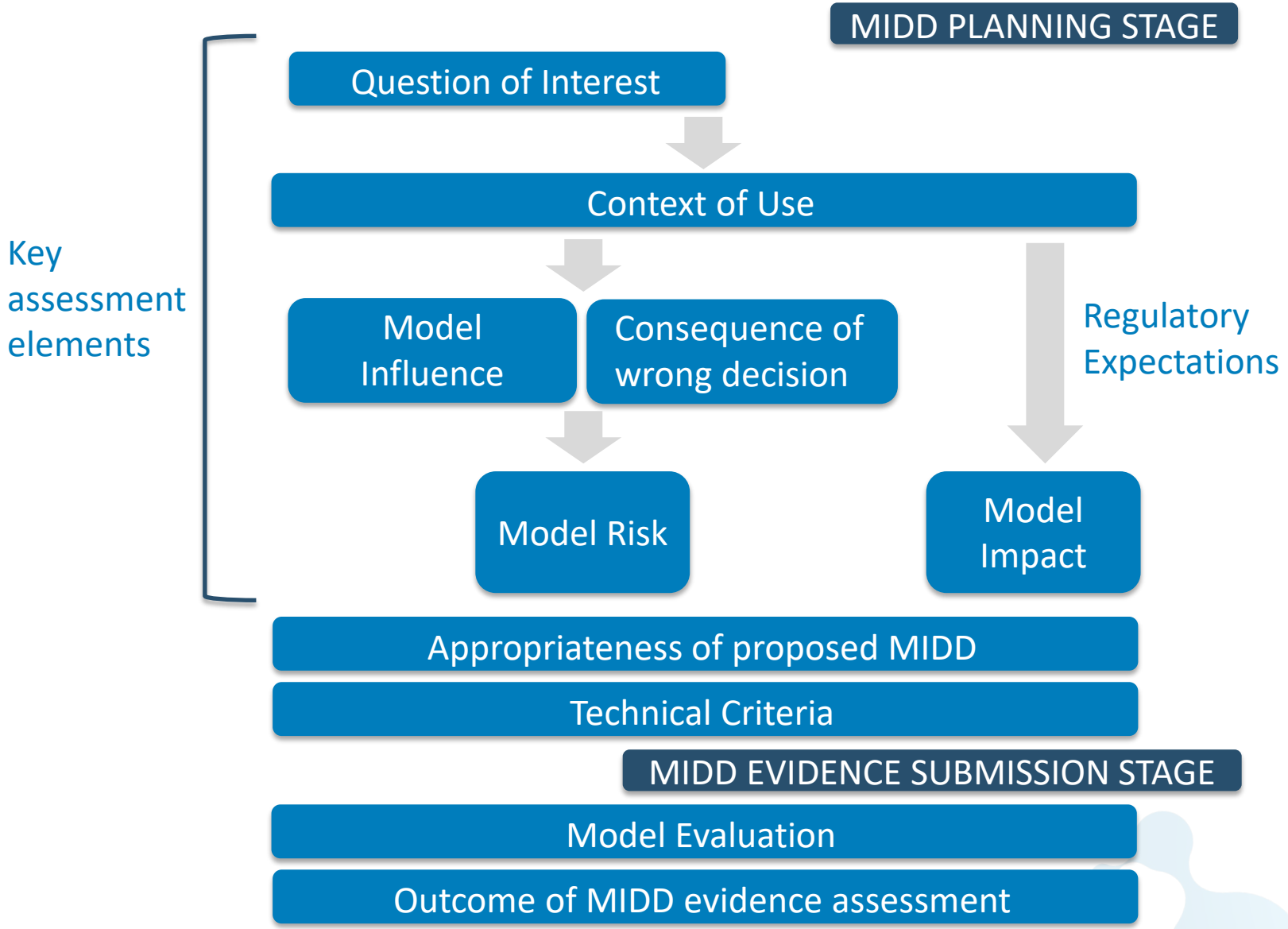
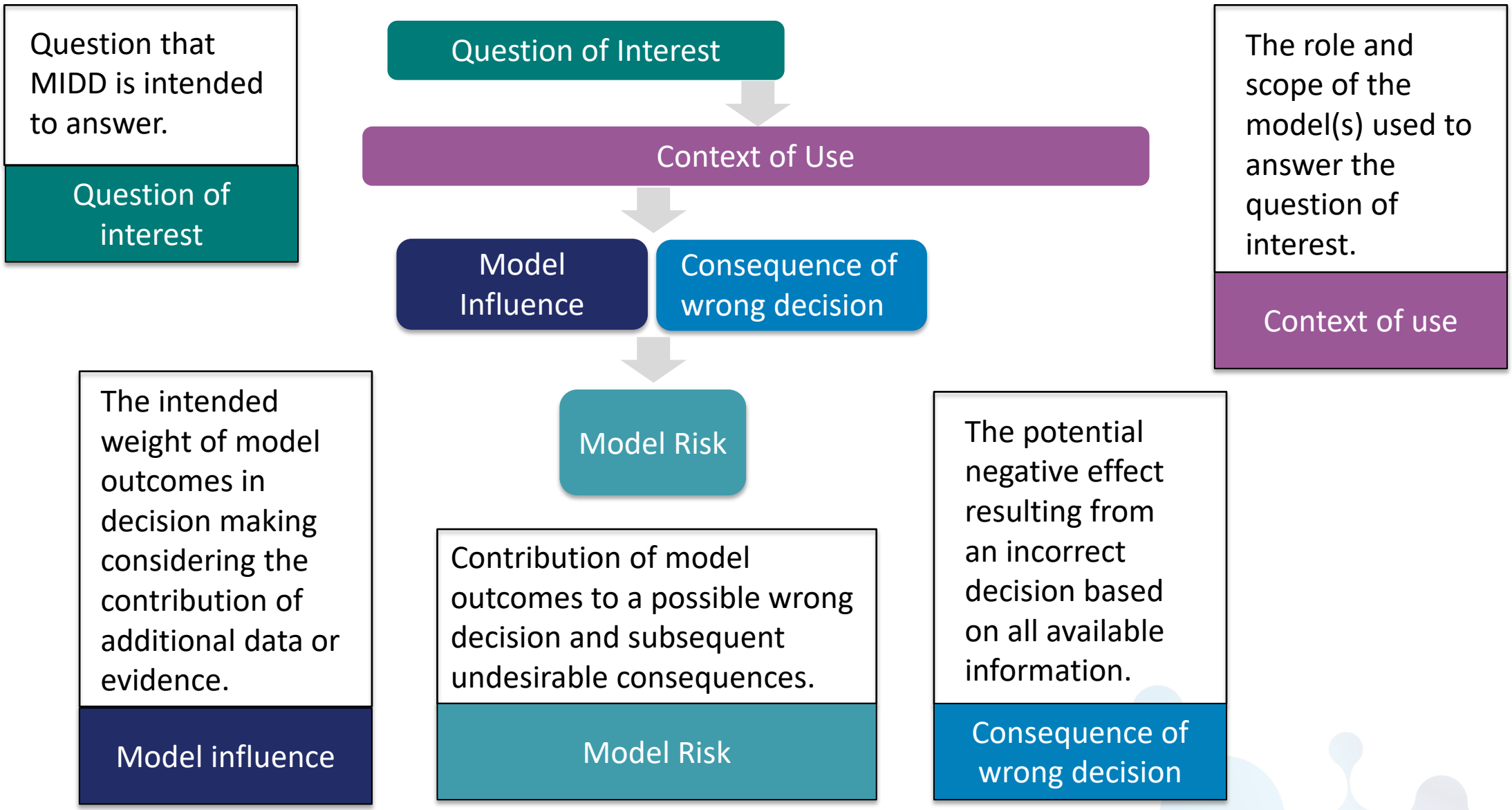
M15 Overview



MIDD Evidence Assessment Framework



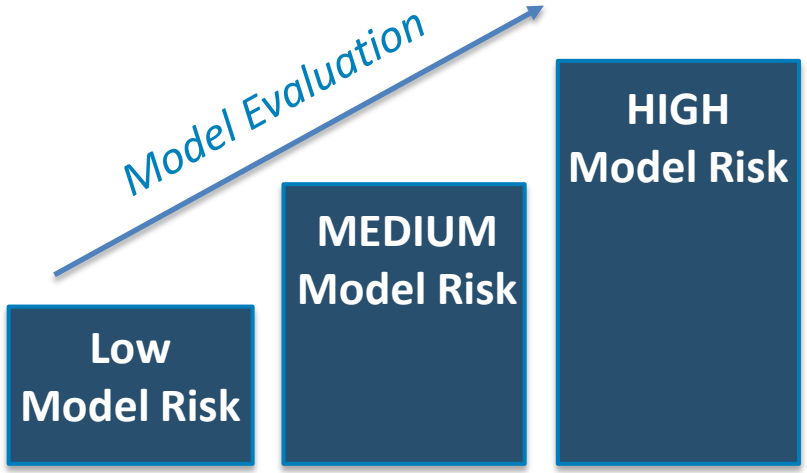
Model Evaluation

Model evaluation should:

- At minimum meet the current accepted standards or established scientific practices
- Be commensurate with model risk

Verification activities: code, equations, assumptions, calculations
Validation & Applicability activities: performance and robustness of the model and relevance and appropriateness of the data.

Model Evaluation

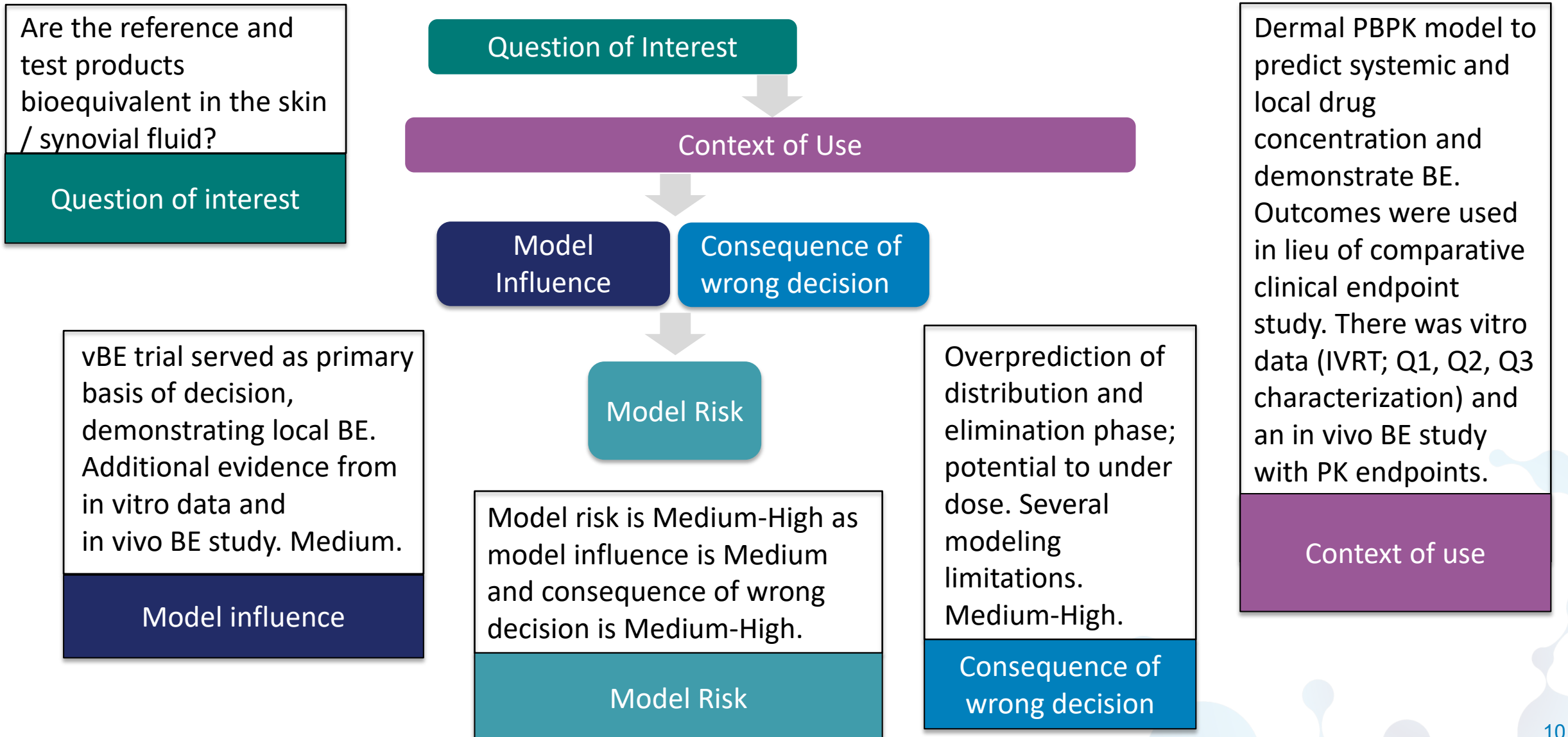


Example: Diclofenac sodium topical gel, 1%

- Approved 2019 for relief of pain and osteoarthritis of the joints for topical treatment
- Other approved therapeutically similar products
- Product specific guidance recommended:
  1) In vivo BE study with PK endpoints in healthy volunteers
  2) In vivo comparative clinical endpoint BE study in men and women with osteoarthritis of the knee
- Applicant proposed alternative model-based approach

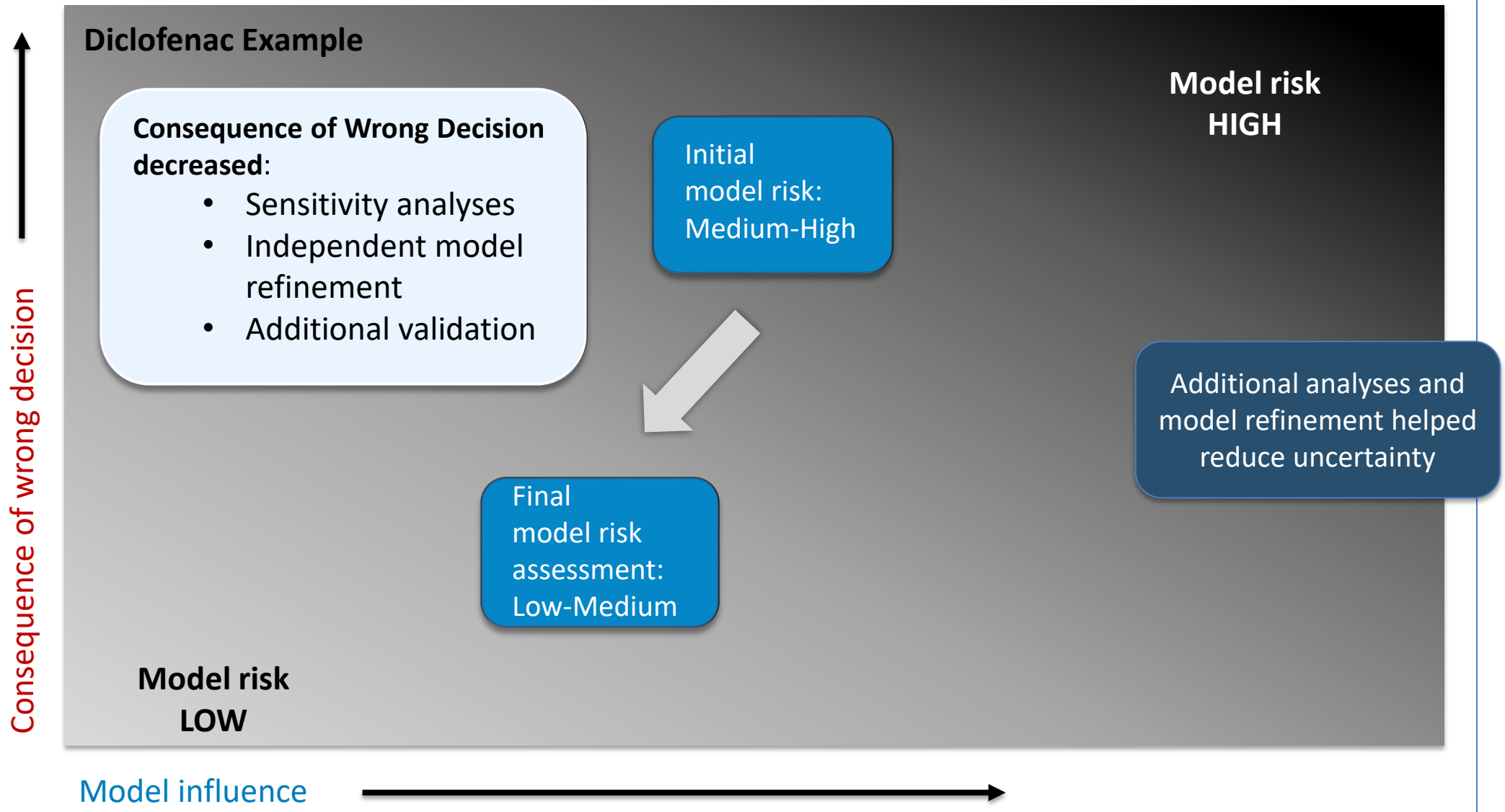
Tsakalozou et al 2020

*Diclofenac Example: Applying the Assessment Framework



*For illustrative purposes only

Assessments Can Change Over Development



Reporting & Interactions

Model assessment table (Appendix 1)

- Communication tool; dynamic
  - Maybe updated as data or information is accumulated, or ratings evolve; new questions of interest emerge → separate tables
  - It asks for input across multidisciplinary teams
  - Can be used for early alignment with regulators; M15 encourages
- Should be brief (< 10 pages)
- Other relevant documents should be cross-referenced (e.g., model analysis plan, model analysis report)

APPENDIX 1: Model assessment table

Item	Definition	Instruction	Entry
Key Assessment Elements			
Question of Interest[1]	The question that MIDD is intended to answer.	State the Question of Interest.	
Context of Use	A description of the model(s) and its specific role and scope to answer the Question of Interest.	Provide a concise, clear, and explicit description of the model, the data used to build the model, the specific role of the model outcomes, and the other data or evidence that will contribute to the answer to the Question of Interest.	
Model Influence	The intended weight of the model outcomes in decision-making considering the contribution of other relevant information.	Describe the Model Influence; rate it as low, medium, or high considering other relevant information (e.g., nonclinical and clinical) to inform decision-making; and justify the rating.	
Consequence of Wrong Decision	The consequences (e.g., with respect to patient safety and/or efficacy) if a wrong decision is made, based on all available information.	Describe the consequence of a wrong decision; rate it as low, medium, or high based on the severity of the consequences a wrong decision may have on patient safety and efficacy; and justify the rating.	
Model Risk[2]	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	Describe the risk; rate it as low, medium, or high based on the Model Influence rate and the Consequence of a Wrong Decision rate; and justify the rating.	
Model Impact	The contribution of the model outcomes in relation to current regulatory expectations or standards in answering the Question of Interest.	Describe the impact; rate it as low, medium, or high considering current regulatory expectations or standards; and justify the rating.	
MIDD Planning Stage[3] The following items/rows are to be completed at the MIDD Planning Stage.			
Appropriateness of Proposed MIDD	The rationale for why the proposed MIDD is suitable to answer the Question of Interest and cover the related key assumptions and required data.	Include a description and justification sufficient to facilitate regulatory interaction on the appropriateness of the proposed MIDD to answer the Question of Interest.	
Technical Criteria	A summary and rationale of the key criteria for Model Evaluation and model outcomes to establish the acceptability of the model (e.g., using an acceptance standard such as bioequivalence acceptance limits).	Include a description of the Technical Criteria for the assessment of Model Evaluation and model outcome. This should include sufficient details on the relevant metric(s).	
MIDD Evidence Submission Stage The following items/rows are to be filled at the MIDD Evidence Submission Stage after data collection and execution of the model.			
Model Evaluation	A brief discussion of the key results and conclusions of the technical evaluation[4] of the model.	Describe the key results and how they compare to and fulfill the Technical Criteria and conclude on the acceptability of the model performance and model outcome, with details being provided in the appropriate regulatory documentation (see Section 4).	
Outcome of the MIDD Evidence Assessment[5]	A concise summary of the multidisciplinary assessment of the MIDD evidence to answer the Question of Interest.	Provide a multidisciplinary integrative assessment and conclusion for the acceptability of the MIDD evidence to contribute to the answer to the Question of Interest, referring to the MIDD assessment framework elements.	

[1] If MIDD is planned to answer different Questions of Interest, it is recommended to use separate tables for each question.
[2] Model Risk should be interpreted in the context of answering a specific Question of Interest and is not to be perceived as a risk intrinsic to MIDD or M&S.
[3] These items should also be provided at the MIDD Evidence Submission Stage.
[4] Using the principles of Model Evaluation described in Section 3, with specific focus on Technical Criteria.
[5] "Assessment" in this context does not refer to any regulatory review activities or processes.

Reporting & Interactions

- **Planning stage**:
  - First half of the **model assessment table** (incl. key assessment elements, appropriateness of MIDD approach, technical criteria for evaluation)
  - **Model analysis plan (MAP):** incl. planned model evaluation activities and technical criteria
- **Submission stage**:
  - Full **model assessment table** (incl. model evaluation & outcome of MIDD assessment)
  - Also references the MAP if used earlier
  - **Model analysis report (MAR)**: incl. any additional info regarding data, methods, and model outcomes (Appendix 2)

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Key assessment elements

Planning

Submission

Take Home Messages

- Start early - M15 encourages early engagement.
- The assessment table can facilitate communication and alignment.
- Clearly define question of interest and context of use.
- Assessments can change throughout development.
- Acceptability is based on more than model performance.
- M15 asks for multidisciplinary involvement; it’s not solely for modelers.

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