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Regulatory experience with regard to submissions that include modelling and simulation

Change since Best Practice proposed by EFPIA and EFPSI in 2016?

Michael O'Kelly

Best practice in modelling and simulation

EMA-EFPIA workshop in 2011

EUROPEAN MEDICINES AGENCY
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EMA-EFPIA Modelling and Simulation Workshop

Good practices and next steps

Robert Hemmings, EMA

M&S good practices

- Different standards for different exercises (L,M,H)
- Standard should be high!
  - Assumptions (not only mathematical)
  - Model building rationale
  - Model testing
  - Inference
  - Sensitivity analyses / Challenge assumptions
  - Reporting
- Detail of regulatory response might be vary according to impact

https://www.youtube.com/watch?v=BSsaUmMuUAE&index=12&list=PL7K5dNgKnawY96v4FlgjTwUFAgUCXrRmw.

2016: Best Practice proposed by EFPIA & by EFSPI M&S SIG

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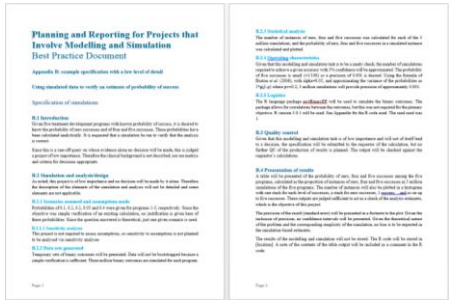
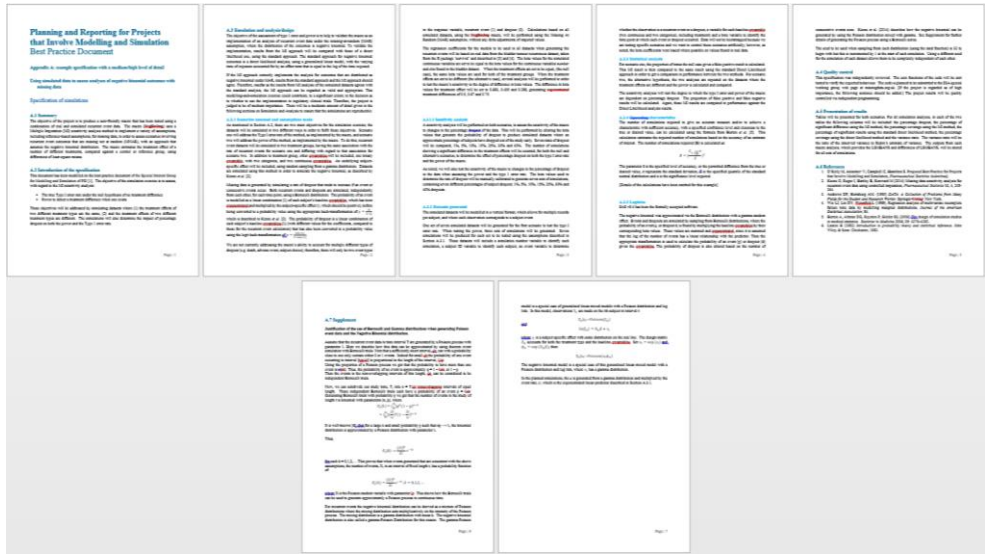
WHITE PAPER

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]

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.





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WILEY

MAIN PAPER

Proposed best practice for projects that involve modelling and simulation

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Modelling and simulation has been used in many ways when developing new treatments. To be useful and credible, it is generally agreed that modelling and simulation should be undertaken according to some kind of best practice. A number of authors have suggested elements required for best practice in modelling and simulation. Elements that have been suggested include the pre-specification of goals, assumptions, methods, and outputs. However, a project that involves modelling and simulation could be simple or complex and could be of relatively low or high importance to the project. It has been argued that the level of detail and the strictness of pre-specification should be allowed to vary, depending on the complexity and importance of the project. This best practice document does not prescribe how to develop a statistical model. Rather, it 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. This document is an initiative of the Special Interest Group for modelling and simulation. The Special Interest Group for modelling and simulation is a body open to members of Statisticians in the Pharmaceutical Industry and the European Federation of Statisticians in the Pharmaceutical Industry. Examples of a very detailed specification and a less detailed specification are included as appendices.

KEYWORDS
best practice, modelling and simulation, Monte Carlo technique, pre-specification, quality control

Has regulatory experience of submissions involving modelling and simulation changed since 2016 Best Practice proposals?

- Has volume of projects that involve modelling and simulation increased?
- Has practice associated with such projects changed?
- Comments on
  - clear definition of assumptions?
  - justification of assumptions?
  - prespecification (of scenarios; of criteria for inference…)?
  - inclusion of useful sensitivity analyses?
  - provision of evidence of robustness to missing data?
- 2011 comment that impact of modelling and simulation could vary (low/medium/high) and detail of regulatory response might vary according to impact.
  - Have submissions shown awareness of differing impact of modelling and simulation, e.g. has the level of impact been specifically addressed in submissions?; reflected in level of detail of prespecification?; reflected in level of evidence to support assumptions?