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FDA workshop: Best Practices for Development and Application of Disease Progression Models

Opportunities and Challenges in Disease Progression Modelling - an EU Perspective

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Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MPA or EMA.

Outline

- Applications
- Interaction with EU regulators
- Development of Disease Progression Models
- Credibility framework

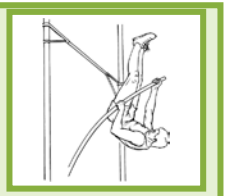
Opportunities for Disease Progression Models - Applications

- Characterization of the time course of drug effects
- Informing the extrapolation concept for various applications (pediatric drug development, rare diseases, etc.)
- Aid in clinical trial design optimization (dose, duration, visits, treatment arms, etc.)
- Clinical trial enrichment
- Biomarker and (surrogate) endpoint qualification
- Other

Regulatory scrutiny of MIDD approaches

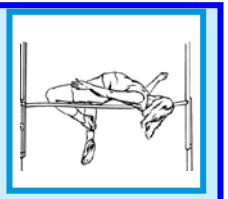
HIGH IMPACT ← M&S to replace

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +++



MEDIUM IMPACT ← M&S to justify

Scientific Advice, Supporting Documentation, Regulatory Scrutiny ++



LOW IMPACT ← M&S to describe

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +

Impact on regulatory decision

Adapted from the framework proposed for M&S in regulatory review, presented at the EFPIA/EMA M&S Workshop 2011 by Terry Shepard (MHRA)

Interacting with regulators in EU

- EMA Innovation Task Force (ITF)
  - Provide a forum for early dialogue with applicants, to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies
- ITF briefing meetings
  - Facilitate informal exchange of information and guidance in the development process, complementing and reinforcing existing procedures such as advanced-therapy-medicinal-product (ATMP) classification and certification, designation of orphan medicinal products and scientific advice
  - Intended to take place much earlier than when one would normally seek scientific advice

Interacting with regulators in EU

- Scientific advice and protocol assistance
  - Clinical aspects (appropriateness of studies in patients or healthy volunteers, selection of endpoints, i.e. how best to measure effects in a study, post-authorisation activities including risk management plans);
  - Methodological issues (statistical tests to use, data analysis, modelling and simulation)

- Prepared by Scientific Advice Working Party, with support from other experts such as Modelling and Simulation Working Party

Interacting with regulators in EU

- Qualification of novel methodologies for medicine development
  - Support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals.
  - Outcomes: **Opinion** on the **acceptability of a specific use of a method** or a **letter of support** when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data

- Examples:
  - Letter of support for “Islet autoantibodies as enrichment biomarkers for type 1 diabetes prevention studies, through a quantitative disease progression model” (europa.eu)
  - Letter of support for Model-based CT enrichment tool for CTs in aMCI (europa.eu)

Development of Disease Progression Models

- Challenging to collect data on natural disease progression
  - Multiple data sources – e.g. clinical trials and register studies
  - Disease definition and clinical endpoints change over time
  - Standard of care change over time

- Collaborative efforts to collect data and develop disease progression models are encouraged

MIDD vs Credibility Assessment

- Model as backbone of knowledge
  - consolidate knowledge
  - inform next step
  - …iterate…
  - open sponsor/regulator dialogue on potential applications

  -> model informed drug development (MIDD)

- Model as a method to answer a question
  - specific applications
  - model assessment

  -> credibility framework

Credibility Matrix

- Investigational product
- Type of model(s)
- Scientific question of interest
- Context of use
- Acceptability criteria
- Regulatory impact
- Risk based analysis of decision consequence
- Credibility activity results
- Model informed decision

Refs: Skottheim Rusten and Musuamba Tshinanu. White paper. Scientific and regulatory evaluation of empirical pharmacometric models: An application of the risk informed credibility assessment framework. Submitted.
Musuamba Tshinanu et al. White paper. Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: building model credibility. CPT. Pharmacometrics & Systems Pharmacology

Example of how a credibility matrix can be used for a disease progression model qualification procedure

Credibility matrix	***Description – entry***
Investigational product	All potential new drugs indicated to prevent onset of disease
Type of model	(Library of) semiparametric Cox Propotioal Hazard models
Scientific question(s) of interest (QOI)	Can biomarkers be used as a means of patient selection in clinical trials investigating therapies that are intended to prevent or delay the clinical diagnosis?
Context of use	The developed models were to demonstrate that the baseline presence significant predictors of the time-varying probability of conversion to a diagnosis. Furthermore, biomarker measurements, sex, and baseline age within this specific population were to further contribute as independent predictors, thereby increasing the accuracy of predicting the time-varying probability of conversion the diagnosis. Biomarkers to be used as enrichment biomarkers in individuals at risk of developing the disease, together with other patient features to optimize the selection of individuals for clinical trials of therapies intended to prevent or delay the clinical diagnosis. The data used for the model development, cross-validation and external validations originated from three datasets; studies X, Y and Z, including xxx patients in total.

Acceptability criteria	- Adequacy of data sources for generalizability of results - Model technical assessment o Software quality control o Model structure and parameterization o Selection of Parametric Distribution o Analysis of Correlation and Association between Covariates o Univariate and Multivariate Analyses o Model Diagnostics o Model Performance and internal Validation o Model External Validation
Regulatory impact	Medium. Models will be used to optimize the design of Phase 2 and 3 studies.
Risk based analysis of decision consequence	Medium: Inadequate or failure in model failure can lead to trial failure and delay in development programs and per se in patient access to drugs.
Credibility activities results	All the activities described under "acceptability criteria were implemented with acceptable results.
Model informed decision	Can the model be qualified for use in clinical trial design?

Concluding remarks

- Opportunities
  - Enhanced understanding of disease progression
  - Improved clinical trial design
  - Aid in identification of study population

- Challenges
  - Gather reliable disease progression data
  - Develop models that are credible for regulatory purposes

- ***Encourage early interactions with regulatory bodies to discuss the development and use of disease progression models***

Acknowledgements

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