Regulatory model-informed drug development in EU – News flash and examples

PAGE 13 June 2019

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Disclaimer

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

Outline

- EMA Modelling and Simulation Working Party
- Recent documents
- In the pipeline
- Examples → Flora

Modelling and Simulation Working Party (MSWP)

April 2018 – Upgraded to working party

27 Members and observers

Chair: Kristin Karlsson, SE
Vice Chair: Flora Musuamba Tshinanu, BE
Julie Bertrand, FR*
Catherine Byrne, IE
Susan Cole, UK
Pieter Colin, BE*
Aristeidis Dokoumetzidis, GR*
Isabel Garcia Gallego, ES
Anne-Mette Hoberg, DK
Essam Kerwash, UK
David Khan, SE
Jeroen Koomen, NL
Hafedh Marouani, FR
Justin Pittaway-Hay, UK
Frederike Lentz, DE
Victor Mangas Sanjuan, ES*
Dana Gabriela Marin, RO
Marina Senek, SE
Francesca Serone, IT
Ine Skottheim Rusten, NO
Juha Vakkilainen, FI
Michiel van den Heuvel, NL
Anke-Katrin Volz, DE
Pyry Välitalo, FI
Gaby Wangorsch, DE
Christian Woloch, FR
Wei Zhao, FR*

EMA
Efthymios Manolis

* Academically affiliated experts

What is the role of MSWP?

- Provide support for
  - Scientific Advice Working Party
  - Paediatric Committee (Paediatric Investigation Plans)
  - Other (CHMP, PRAC)
- Act as a network for pharmacometric assessors
  - Support between national agencies
  - Harmonization of pharmacometric assessments
- Strategic work within EMA framework

EMA Regulatory Science to 2025

This strategic reflection document sets out working proposals on the key areas with which EMA intends to engage, in order to ensure that it has the regulatory tools to continue supporting the network and fulfilling its ongoing mission in light of upcoming scientific challenges.

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Public consultation open until 30 June 2019
https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-2025

• herbals • homeopathics • information • inspection laboratory analysis • market surveillance • medicinal products • medical devices • narcotics • public health •

EMA Regulatory Science to 2025

Goal 3.2.6:

Optimise capabilities in modelling, simulation and extrapolation	▸ Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects ▸ Promote development and international harmonisation of methods and standards via a multi-stakeholder platform ▸ Increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange.

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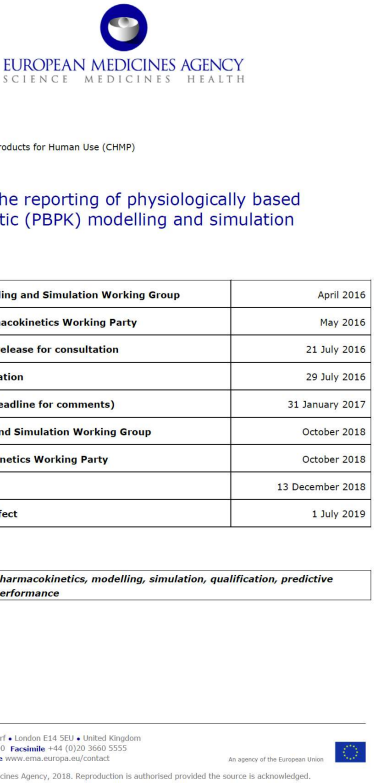
PBPK guideline
Published December 2018

Aim:

To describe the expected content of PBPK modelling and simulation reports included in regulatory submissions, such as applications for authorisation of medicinal products, paediatric investigation plans and clinical trial applications. This includes the documentation needed to support the qualification of PBPK platform for the intended use and the evaluation of the drug model. The guideline applies to commercially available platforms and to in-house built platforms.



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13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

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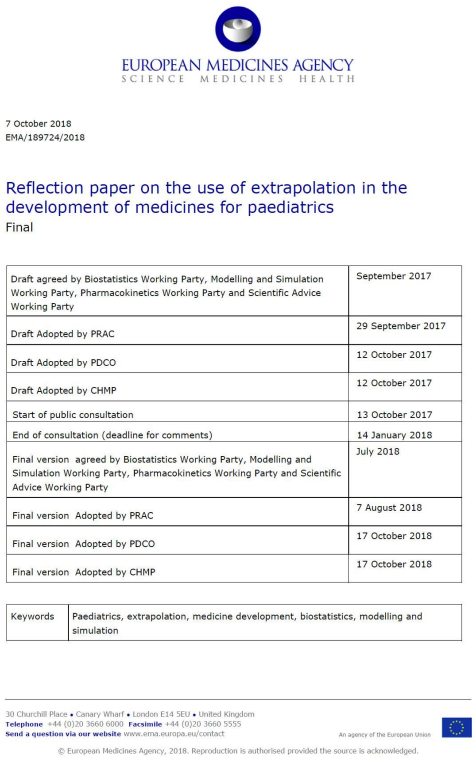
Extrapolation Reflection Paper
Published October 2018

Aim:

The main focus of this document is to provide a framework for extrapolation as an approach to generate evidence on one or more specific research questions to support regulatory assessment of marketing authorisation application in a target population. Specifically, the document promotes the use of quantitative methods to help assess the relevance of existing information in one or more source populations to one or more target population(s) in respect of the disease, the drug pharmacology and clinical response to treatment.



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7 October 2018
EMA/189724/2018

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

Draft agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and 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
Final version agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	July 2018
Final version Adopted by PRAC	7 August 2018
Final version Adopted by PDCO	17 October 2018
Final version Adopted by CHMP	17 October 2018

Keywords	Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

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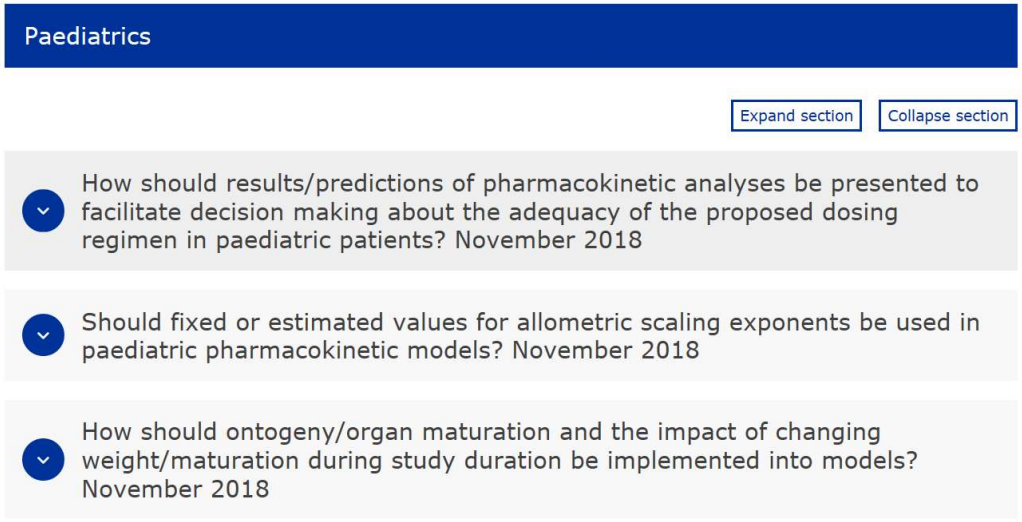
Modelling and simulation: questions and answers
Published November 2018 – EMA Webpage



https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers

In the pipeline

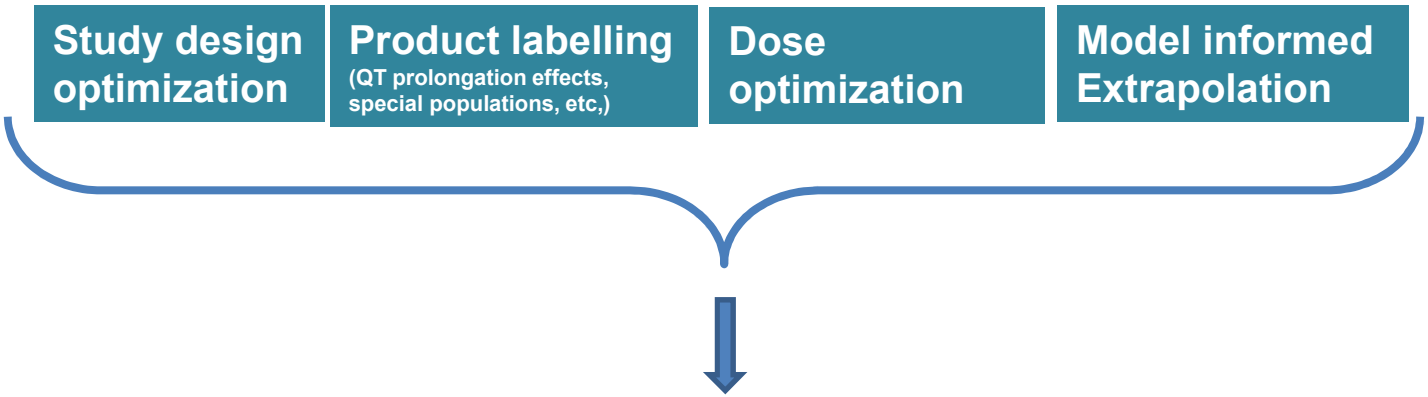
- ICH E11A Paediatric Extrapolation
- ICH E14/S7B Q&A: Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential
- EMA Paediatric Clinical Pharmacology Guideline

Model evaluation:
Examples from regulatory applications

federal agency for medicines and health products

Added-value of modelling and simulation in drug development and evaluation

The favourable aspects of modelling and simulation can be split up into four avenues:



Optimal drug development program/drug evaluation/drug use

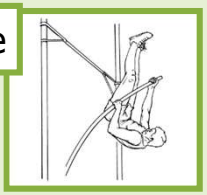
Decision criteria

Framework for M&S in Regulatory Review
According to impact on regulatory decision

High impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +++

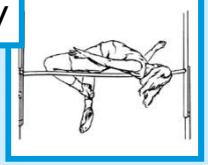
Replace



Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny ++

Justify



Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +

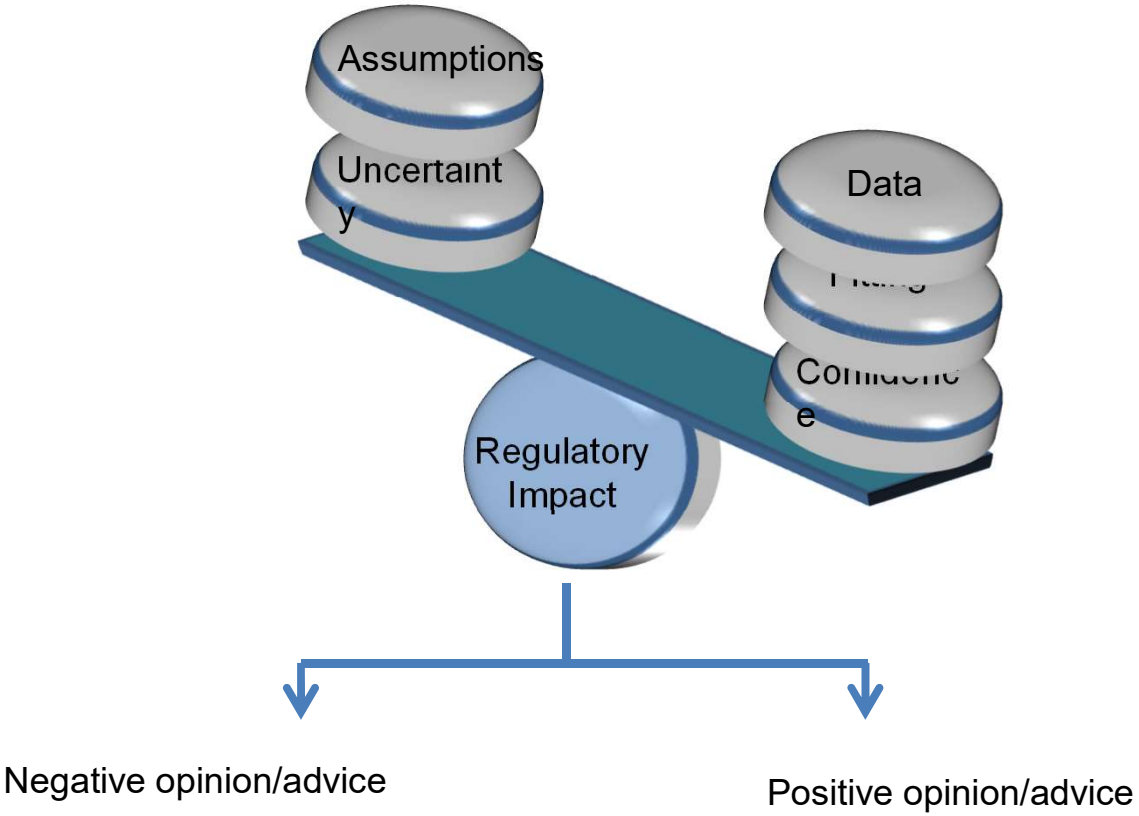
Describe

Impact on regulatory decision

From EMA-EFPIA Modelling and Simulation Workshop, December 2011

Decision criteria

Minimum requirements?



Examples

Case study 1: Hormone replacement therapy

Model informed dose optimization in adult and children

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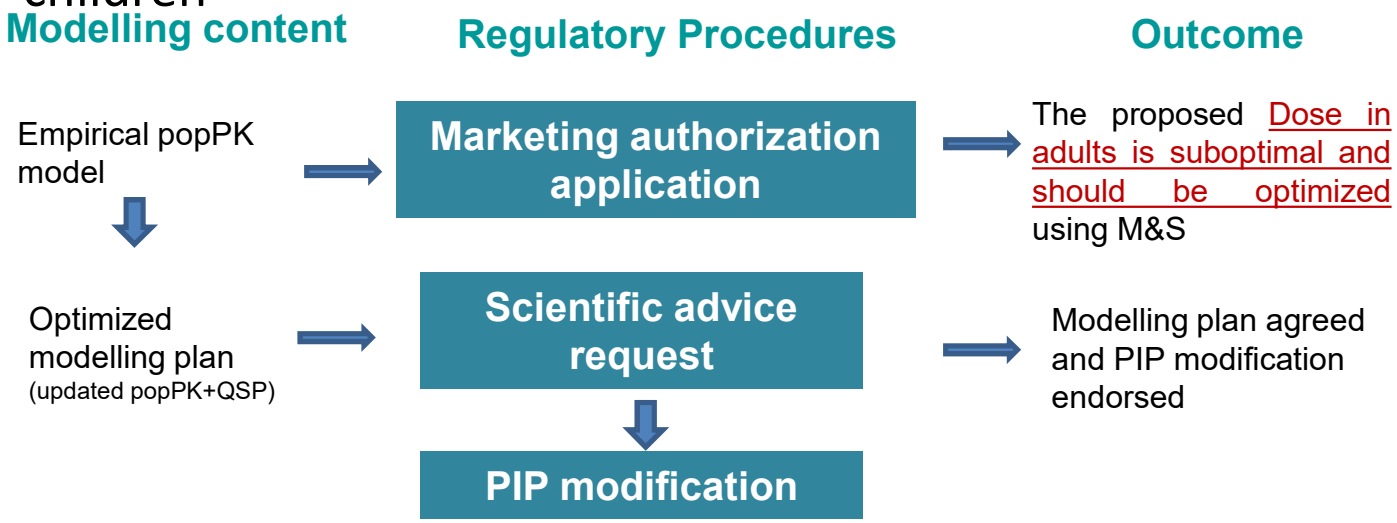

Examples

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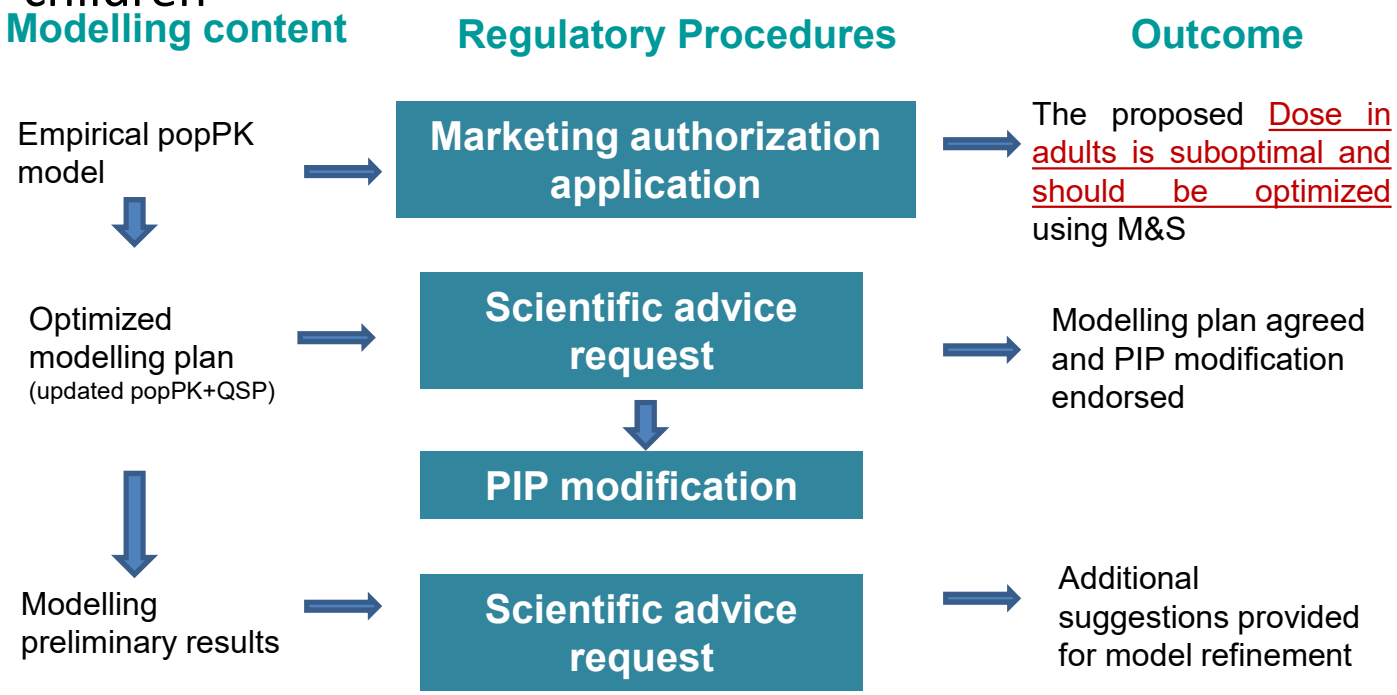

Examples

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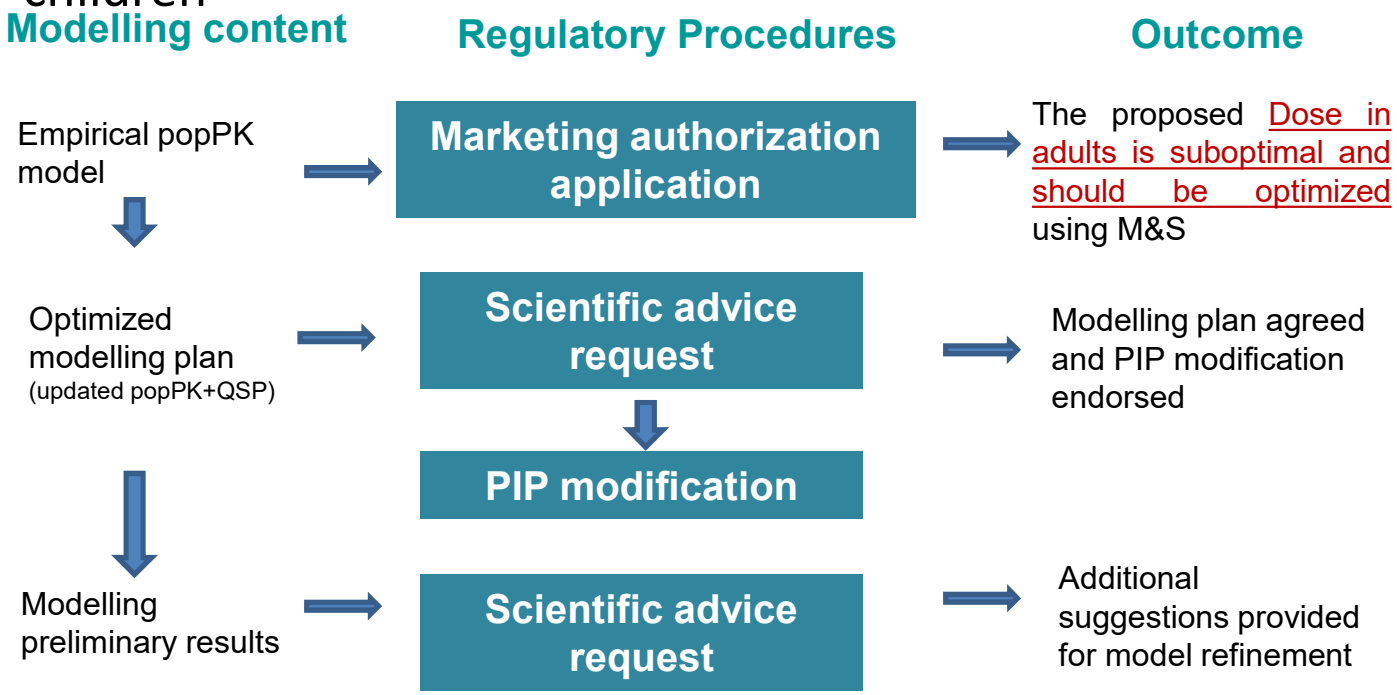

Case study 2:
SA for a new mAb drug development

A Phase 2 dose range finding study is planned to assess 3 doses of the drug in comparison to placebo and to the comparator.

Adult data are available from 2 studies in HV as well as from 2 studies in patients
No paediatric PK data are available.

A pop-PK-PD-response model is used to define doses for the adult phase II, adult phase III (after updating the model with the phase II data) as well as for defining doses for adolescents 12-17 years which will only be studied in phase III.

Extrapolation: a separate PKPD study is not planned in adolescents, and the applicant intends to define the dose for the adolescent Phase III studies based on extrapolation, by means of allometric scaling of the adults phase II data.

The regulatory impact is perceived as moderate to high.

Examples

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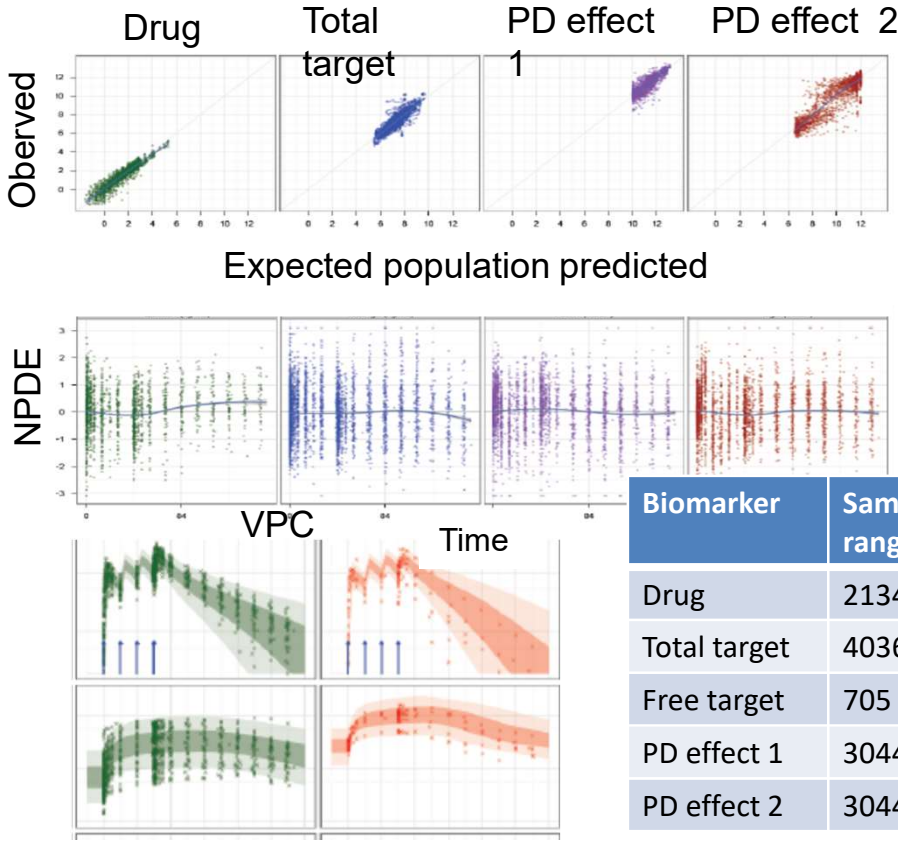
SA for a new mAb drug development



Biomarker	Samples in range	Samples BLOQ	Samples ALOQ
Drug	2134	410	
Total target	4036		
Free target	705	1743	1595
PD effect 1	3044		
PD effect 2	3044		

Conclusion

Regulatory model evaluation is currently done based on diffent criteria including:

- ✓ Regulatory impact
- ✓ Quality and information included in the data
- ✓ Fitting performances
- ✓ Model assumptions
- ✓ Confidence/Uncertainty

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