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ASCPT 2019 ANNUAL MEETING

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European Experience of Biopharmaceutical Applications of PBPK Models

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Disclaimer

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

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Overview

- PBPK Models in EU Regulatory submissions
- Biopharmaceutical application
- CHMP guidance and model qualification
- CHMP guidance on locally acting products
- Conclusions

PBPK in EU Regulatory submissions

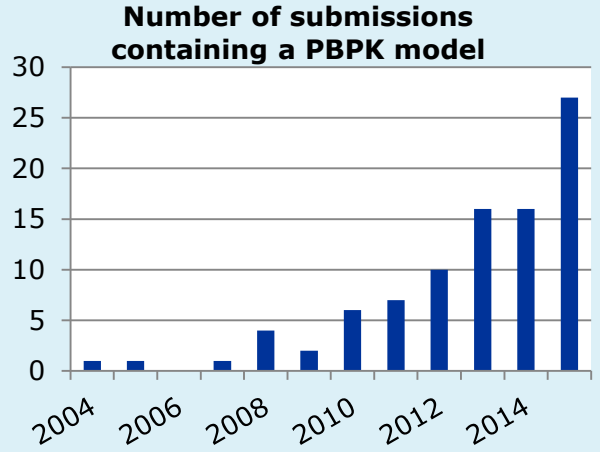
Still increasing in EU Regulatory submissions

DDIs predominant, other clearance pathways e.g. UGTs and Transporters

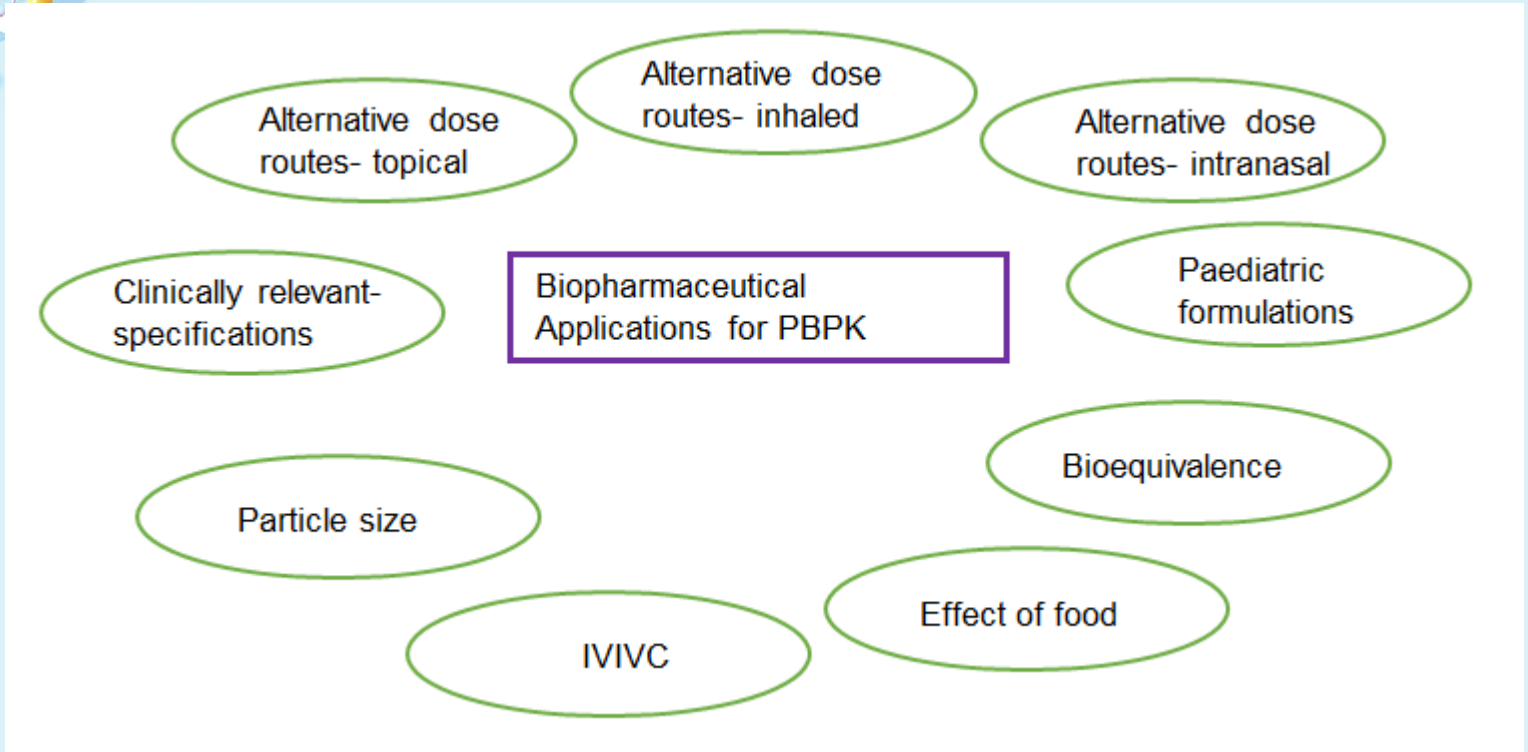
Often discussed in scientific advice requests

More diverse applications:

- Special populations- paediatrics, pregnancy
- Diseases states- Oncology, Gastroenterology
- More focus on PD end point
- Biopharmaceutical Applications
- Limited experience of locally acting products



Biopharmaceutical applications



PBPK models for non-oral dose routes- systemic exposure

- Subcutaneous, Intranasal, Topical, Inhaled routes
- Prediction of systemic exposure- either site of action, or for safety
- Have not seen adequate qualification data sets
- Not accepted in place of a clinical study to predict systemic exposure
- Have accepted to inform DDIs by the alternate dose route
- Additional uncertainty in predictions to children

Beclomethasone inhalers

- Different potencies of CFC-free beclomethasone inhalers
- Qvar and Clenil Modulite are pressurised metered-dose inhalers that contain beclomethasone diproprionate. Qvar has extrafine particles, is more potent than traditional CFC-containing inhalers, twice as potent as Clenil Modulite.
- Clenil Modulite may be used in children
- Extrafine particles in children? Potential risk on growth and adrenal function
- PBPK considered to understand increased exposure
- Unlike adults, the evidence regarding sites and extent of deposition for aerosols in children as a function of physicochemical properties is inconclusive in the scientific literature.

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

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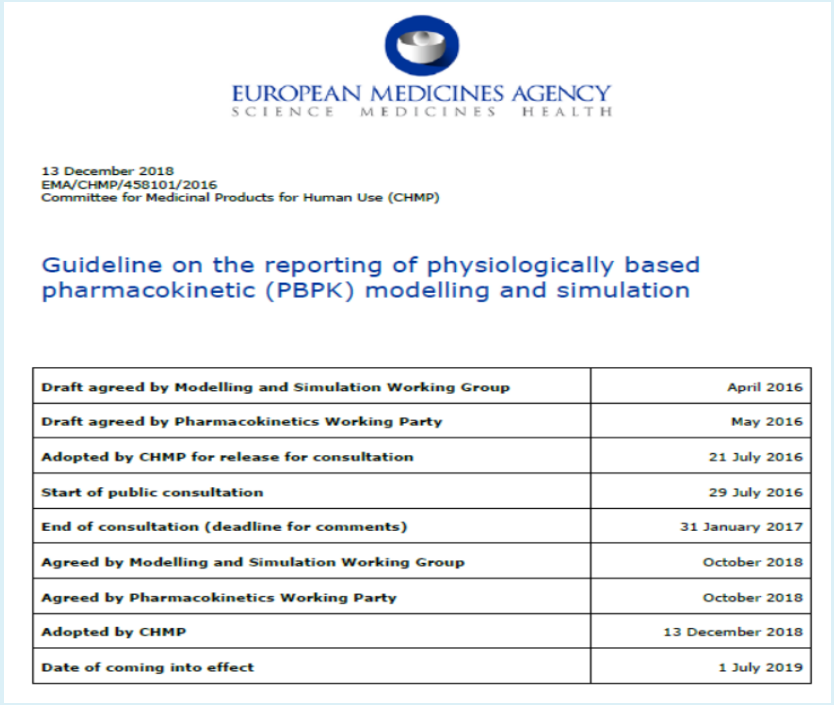
Final guideline for adoption CHMP December 2018

- Concept paper published 27 June 2014
- Public consultation on draft ended 31 January 2017
- Workshop at EMA 21 November 2016



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Appendix 1: Qualification of the PBPK platform

Appendix 2: Evaluation of the predictive performance of the drug model.

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- **Predictive performance of drug model:** The process of establishing confidence in the drug model. The reliability is assessed on the basis of how well important characteristics of the drug model has been tested against *in vivo* pharmacokinetic data and whether adequate sensitivity and uncertainty analyses have been conducted to support the models ability to provide reliable predictions.

- **Qualification:** The process of establishing confidence in a PBPK platform to simulate a certain scenario, in a specific context, on the basis of scientific principles and ability to predict a large dataset of independent data thereby showing the platforms ability to predict a certain purpose. In the context of PBPK models, qualification is purpose and platform version specific.

Qualification for the intended use

- Is there enough scientific support for a certain use of the model?

DDI •Enzyme inhibition •Induction •Transporter	Prediction of PK in Special populations	Formulation changes
Extrapolation of PK data in young children	Food effects	IVIVC

Qualification is important for high regulatory impact decisions

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High regulatory impact decisions

- All changes to SmPC (i.e. label)
- Use of a PBPK model in place of clinical data (DDI, BE study)
- Non studied scenarios
- **Extrapolation** outside the studied area

Medium regulatory impact decisions

- Such as paediatric dose setting that will be confirmed by a clinical study

Not required for Low regulatory impact decisions

- To inform dose selection for FIH

How to ‘Qualify’?

- Qualification may be obtained via:
  - a **regulatory submission** (specific to this, subsequent needs re-evaluation);
  - a **CHMP qualification procedure** https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development (can be cited in future applications);
  - **Published papers** if the included validation dataset is sufficiently current and described in sufficient detail to allow a thorough understanding of the data by regulators.

Draft guideline on quality and equivalence of topical products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
CHMP/QWP/708282/2018
Committee for Medicinal Products for Human Use (CHMP)

Draft guideline on quality and equivalence of topical products

Draft Agreed by QWP	7 June 2018
Adoption by CHMP for release for consultation	18 October 2018
Start of public consultation	14 December 2018
End of consultation (deadline for comments)	30 June 2019
Agreed by QWP	
Adopted by CHMP	
Date for coming into effect	

Topical guideline- Equivalence with respect to efficacy

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5.3.1 Methods

The following methods are considered suitable for equivalence testing, *in lieu* of a clinical therapeutic study:

Permeation Kinetics Studies

- *In vitro* skin permeation
- Stratum Corneum Sampling (Tape Stripping)
- Pharmacokinetic bioequivalence

These tests provide a means of measuring equivalence in active substance permeation kinetics of drug products applied to intact skin.

Human bioequivalence studies are appropriate when the active substance has quantifiable systemic bioavailability. *In vitro* skin permeation studies are suitable when the active substance diffuses through the skin to permit quantification in the receptor cell. Stratum Corneum Sampling (Tape Stripping) is suitable when there is sufficient quantifiable drug diffusion across the stratum corneum.

Other techniques, such as Microdialysis and Confocal Raman spectroscopy are not sufficiently established to provide pivotal equivalence data but may be supportive.

Pharmacodynamic Studies

- Vasoconstriction Assay for corticosteroids.
- Antiseptic and anti-infective studies.

These studies provide a means of measuring equivalence in active substance pharmacodynamic activity of drug products applied to intact skin.

Topical guideline- Biowaivers

5.5.1 Biowaivers

A waiver of the need to provide permeation kinetic or pharmacodynamic equivalence data can in principle be acceptable for:

- Simple formulations with a single-phase base in which the active substance is in solution or suspension e.g. cutaneous solutions, single phase gels and ointments; cutaneous suspensions.
- If the objectives and purpose of the drug product is only administration of the active substance to the surface of the skin (see section 4.2.1), then extended pharmaceutical equivalence, including *in vitro* drug release for gels, ointments and suspensions, and equivalence in administration should normally be sufficient

Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
CPMP/EWP/239/95 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract[†]

Draft agreed by Gastroenterology Working Party and Quality Working Party	October 2016
Draft agreed by Pharmacokinetics Working Party	February 2017
Adopted by CHMP for release for consultation	23 March 2017
Start of public consultation	1 April 2017
End of consultation (deadline for comments)	30 September 2017
Agreed by PKWP	June 2018
Adopted by CHMP	18 October 2018
Date of coming into effect	1 May 2019

Equivalence requirements for:

- Products acting locally in the mouth and/or throat
- Products acting locally in the oesophagus or the stomach.
- Products acting locally in the intestine.
- Products acting locally in the rectum.
- Requirements for additional strength

General requirements for demonstration of equivalence

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- In principle, clinical trials with clinical endpoints are considered necessary to demonstrate therapeutic equivalence, **but alternative approaches may be used provided they have a sound justification and appropriate qualification**, taking into consideration all parameters with relevant impact on in vivo transit, release and dissolution**. In vitro test(s)/model(s) should reflect the particular (unique) characteristics of the pharmaceutical form** for which equivalence is being claimed. A comprehensive and sound justification for the chosen in vitro test(s)/model(s) should be provided. The results of the test method should be robust, reproducible, sensitive and specific for the purpose for which it is intended.
- In order to claim that an alternative model to clinical and PD endpoints is reflecting in vivo drug release and availability at the sites of action, **the applicant should justify the relevance for the therapeutic effect and the higher or similar sensitivity to detect differences between formulations**, in comparison with clinical and/or PD data, based on their own experimental data or literature data

Ferric citrate coordination complex 1g film-coated tablets - product specific guidance

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- ***Option 1 Biowaiver based on BCS classification***

Ferric citrate coordination complex is a highly soluble substance with very low (<1%) systemic absorption and can be considered as a BCS class III substance. As such, a biowaiver can be established according to BCS classification in line with the requirements of Appendix III of the 'Guideline on the investigation of bioequivalence CPMP/EWP /QWP/1401/98 Rev.1/Corr**)'. However, in BCS III drugs that are without or with very low systemic bioavailability, such as ferric citrate coordination complex, very rapid dissolution is not essential and similar rapid dissolution is also acceptable.

- ***Option 2 In vitro studies***

In case a biowaiver based on BCS classification, as mentioned above, is not possible, in vitro phosphate binding studies comparing the test and reference products are considered acceptable surrogates for the assessment of efficacy, as ferric citrate coordination complex acts locally in the GI tract

Conclusions

- Increasing use of PBPK models in Regulatory submissions
- More diverse applications- inc. Biopharmaceutics area
- Limited experience currently for Locally acting products
- Qualification of models is important
- New guidance on locally acting products increases emphasis on *in vitro* methods.

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