EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Use of PBPK on regulatory submissions to EMA

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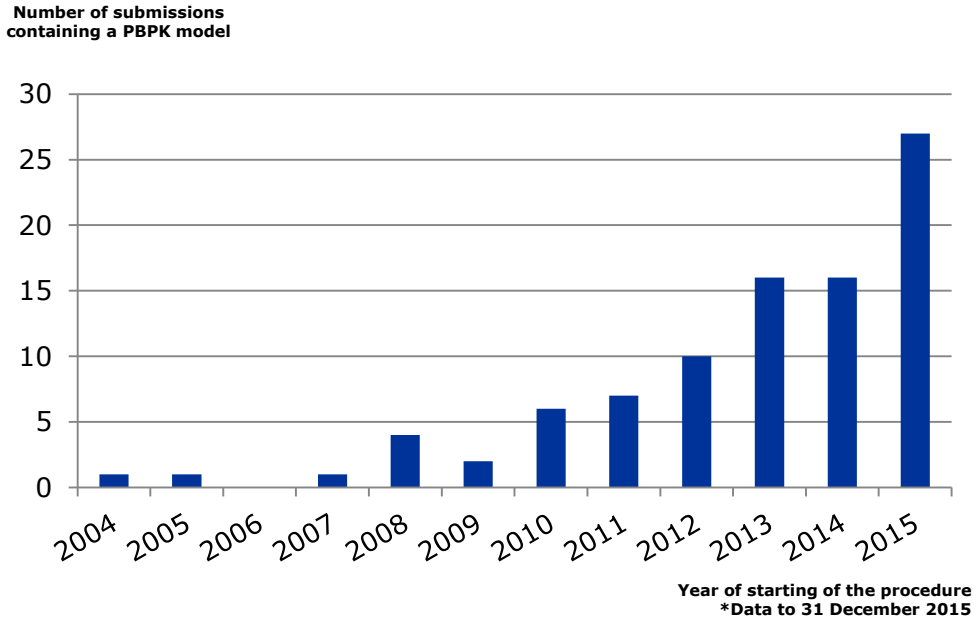
A growing number of submissions incorporate PBPK



Presence of PBPK model in public documents

- From 2004 to 2015, **110 procedures** for which a PBPK model has been either suggested or submitted, corresponding to **96 products**, have been identified
- At least **12 of the SmPCs** of these products include statements based on PBPK (alone or in combination with other in vivo/in vitro findings)
- **12** of the procedures include a request of a PBPK model within the **RMP**
- Only **38 public documents** (EPAR, variation reports) include an explicit mention to PBPK

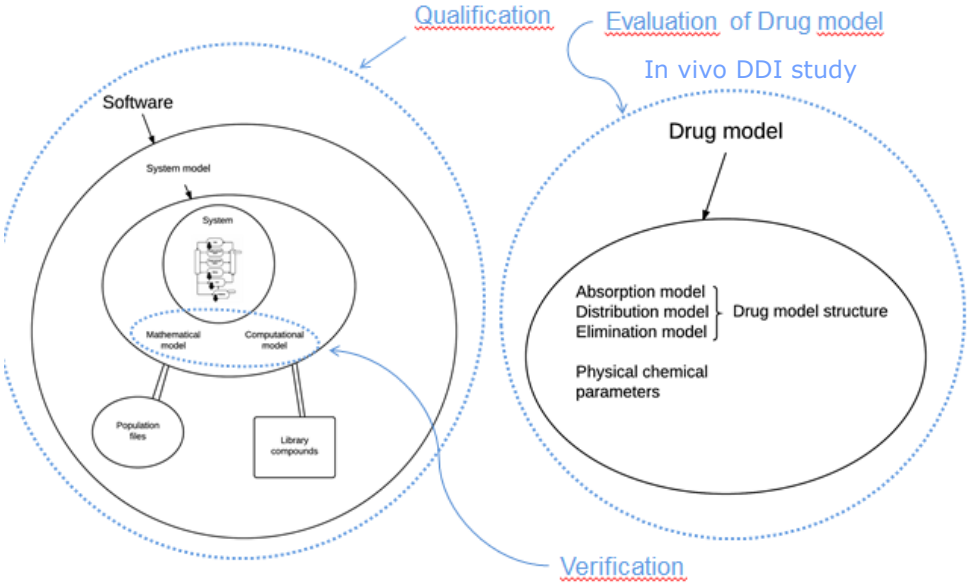
Purpose of PBPK

- In about **75%** of procedures where a PBPK model is suggested/ submitted, at least one of the purposes relates to **DDI** (as victim or as perpetrator), specially to **CYP3A4** mediated interactions

- Other purposes include
  - Better understanding of PK, role of enzymes/transporters…
  - Dose recommendations
  - Food effect
  - Effect of polymorphisms / ethnic differences
  - PK in special population (renal/hepatic impairment)

Guideline on the Qualification and reporting of PBPK Modelling and Simulation – Draft 2016

- High regulatory impact analyses – dose recommendations
- Low - Moderate regulatory impact



Acknowledgements

Elisa Luzon, Kevin Blake, Eva Gil Berglund, Susan Cole

Panel questions

If dosing recommendations in the label were derived from PBPK simulation, should the label include simulation results? If so, how much details should be included?

Currently, a substrate's PBPK model needs to be verified with clinical DDI data (e.g., with a strong CYP inhibitor) before it can be used to support dosing recommendations in the label. Under what conditions can simulations using "non-verified" model be included in the label?

Should findings that are derived from modeling or simulation (e.g., pop-PK, PBPK, etc.) be communicated differently in labeling compared to similar information derived from a clinical study?

Example labelling: Cerdelga - eliglustat

Metabolism: CYP2D6 and CYP3A4

-**DDI study with paroxetine in intermediate and extensive metabolisers**

After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with paroxetine resulted in a 8.9-fold increase in eliglustat AUC0-12, respectively. A dose of eliglustat 84 mg once daily should be considered when a strong CYP2D6 inhibitor is used concomitantly in IMs and EMs.

At 84 mg twice daily dosing with eliglustat in non-PMs, *it is predicted that concomitant use of moderate CYP2D6 inhibitors would increase eliglustat exposure approximately up to 4-fold.* Caution should be used with moderate CYP2D6 inhibitors in IMs and EMs.

Example labelling: Cerdelga - eliglustat

- **DDI study with ketoconazole in intermediate and extensive metabolisers**

After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with ketoconazole resulted in a 4.3-fold increase in eliglustat AUC0-12, respectively. Caution should be used with strong CYP3A inhibitors.

At 84 mg twice daily dosing with eliglustat in non-PMs, *it is predicted that concomitant use of moderate CYP3A inhibitors would increase eliglustat exposure approximately up to 3-fold*. Caution should be used with moderate CYP3A inhibitors.

In poor metabolisers (PMs): At 84 mg once daily dosing with eliglustat in PMs, *it is predicted that concomitant use of strong CYP3A inhibitors would increase the Cmax and AUC0-24 of eliglustat 4.3- and 6.2-fold*. The use of strongCYP3A inhibitors is contraindicated in PMs.

Example labelling: Odomzo - sonidegib

CYP3A4 inducers

In healthy subjects, co-administration of a single dose of 800 mg sonidegib with rifampicin (600 mg daily for 14 days), a strong CYP3A inducer, resulted in 72% decrease in sonidegib AUC compared with when sonidegib was given alone. If a strong CYP3A4 inducer must be used concomitantly, *the daily dose of sonidegib should increased to 400-800 mg.* This dose of sonidegib is predicted to adjust the AUC to the range observed without inducers based on pharmacokinetic data when *the concomitant treatment with the inducer is no longer than 14 days. Longer concomitant treatment with inducer is not recommended because sonidegib exposure will be decreased and this may compromise efficacy.*

Example labelling: Odomzo - sonidegib

CYP3A4 Inhibitors

In healthy subjects, co-administration of a single 800 mg dose of sonidegib with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A inhibitor, resulted in a 2.25-fold increase in sonidegib AUC compared with sonidegib alone. Longer duration of concomitant use of CYP3A4 strong inhibitors will lead to a larger fold change in sonidegib exposure based on simulation. If concomitant use of a strong CYP3A inhibitor is required, *the sonidegib dose should be reduced to 200 mg every other day*.