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Exploring Recent Trends in PBPK Applications in New Drug Approvals in Japan

Regulations and Reviews by PMDA

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Life forward

Contents

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Guideline for Analysis Reports

- Issued in 2020 https://www.pmda.go.jp/files/000267935.pdf
- The objectives:
  - ✓ To ensure the consistency of data submitted to the regulatory authority
  - ✓ To facilitate timely decision-making in clinical trial consultations and regulatory reviews, etc.
  - ✓ To standardize the content of PBPK model analysis reports for the appropriate provision of information
- This guideline summarizes points to consider in reporting the results of PBPK model analysis.

- This guideline also states that the usability of the simulation results by a PBPK model analysis is determined specifically for each drug, considering the objective and reliability of the analysis

Content of an analysis report shown in the Guideline

Sections	Contents
Summary	• The objective, methods, results, discussion and important conclusion
Objective	• Intended purpose
Background Information	• Clinical development strategies related to PBPK model analysis (i.e., the reasons why PBPK model analysis is planned) • ADME properties including mass balance (using figures as necessary)
Method of analysis	• Model analysis workflow including model building, refinement, qualification and application (using figures as necessary) • Platform • Physiological parameters, Drug parameters with references • Simulation condition • Model qualification, Parameters optimization and Sensitivity analysis
Results	• Model qualification • Final simulation
Discussion	• Impacts on clinical development strategy and regulatory decision make

Key points in preparing PBPK model reports

1. Platform
   - Both commercially available and proprietarily built platforms are acceptable.
2. Model qualification
   - Model verification: the correctness of the underlying mathematical code and computation
   - Model validation: predictive performance by comparison of the predicted data and observed data
3. Optimization
   - Data used for optimization, optimization process, validity of the estimated numerical value (e.g., biological plausibility, precision of estimation) should be clearly explained.
4. Sensitivity analysis
   - Parameters that are likely to influence the outcome or highly uncertain parameters
   - Justification for the range of the parameter values
   - Outcome of the “worst-case scenario”

Technical Conformance Guides on Electronic data submission

- Issued in 2015, revised several times thereafter, and the latest version was revised in 2024

- Detailed matters and precautions regarding the submission of electronic data are provided in this Guide
  - ➢ CDISC-conformant electronic study data (SDTM and ADaM) and relevant documents
  - ➢ Population PK analysis
  - ➢ PBPK model
    - ✓ There have been no change since the first edition in 2015 regarding the electronic data submission of the PBPK model

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Submission of electronic data of PBPK model

1. Files that contain information on the model structure used for the analysis, the set values of drug and physiological parameters, analysis results, and sensitivity analyses
   - ➢ E.g., Project file in PKsim, SimCYP, or Gastroplus meets this requirement.
   - ➢ Should be stored in the folder of “m5/datasets/iss/cp/…”
     - ✓ The path length counting from the “m5” folder, including the file name, must be 160 characters or shorter
     - ✓ Folder names should be 32 characters and File names should be 64 characters or fewer for files including the extension

2. Procedure manual
   - ➢ Description of the simulation used to create the main figures and tables mentioned in the report.

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Overview of the drug product label including the PBPK model

Name	TA	Year	Intended Use
Eliglustat	Genetics	2015	CYP2D6 Victim DDI
Macitentan	Cardiology	2015	CYP3A Victim DDI
Ibrutinib	Oncology	2016	CYP3A Victim DDI
Busulfan	Oncology	2018	Pediatric
Letermovir	Infection disease	2018	CYP3A Inhibition DDI
Olaparib	Oncology	2018	CYP3A Victim DDI
Lorlatinib	Oncology	2018	CYP3A Victim DDI
Venetoclax	Oncology	2019	CYP3A Victim DDI
Apalutamide	Oncology	2019	CYP3A Victim DDI
Tirabrutinib	Oncology	2020	CYP3A Victim DDI
Siponimod	Neurology	2020	CYP2C9 Victim DDI
Capmatinib	Oncology	2020	CYP3A Victim DDI
Pemigatinib	Oncology	2021	CYP3A Victim DDI
Anamorelin	Oncology	2021	CYP3A Victim DDI in organ impairments
Burigatinib	Oncology	2021	CYP3A Victim DDI
Polatuzumab	Oncology	2021	CYP3A Victim DDI
Selparcartinib	Oncology	2021	CYP3A Victim DDI
Larotrectinib	Oncology	2021	CYP3A Victim DDI
Acalabrutinib	Oncology	2021	CYP3A Victim DDI
Pimitespib	Oncology	2022	CYP3A Victim DDI, Transporter Inhibition DDI
Valbenazine	Neurology	2022	CYP3A and CYP2D6 Victim DDI
Valemetostat	Oncology	2022	CYP3A Victim DDI, Transporter Victim DDI
Finerenone	Cardiology	2022	CYP3A Victim DDI
Selumetinib	Oncology	2022	CYP3A Victim DDI
Brexpiprazole	Mental disorders	2023	CYP3A and CYP2D6 Victim DDI
Futibatinib	Oncology	2023	CYP3A Victim DDI, Transporter Inhibition DDI
Vonoprazan	Gastroenterology	2024	CYP3A Victim DDI
Aspirin and Vonoprazan	Cardiology	2024	CYP3A Victim DDI
Amoxicillin and Vonoprazan	Gastroenterology	2024	CYP3A Victim DDI
Pirtobrutinib	Oncology	2024	CYP3A Victim DDI
Capivasertib	Oncology	2024	CYP3A Victim DDI, Transporter Inhibition DDI
Belumosudil	Oncology	2024	CYP3A Victim DDI, CYP3A Inhibition DDI, CYP1A2 Inhibition DDI
Brivaracetam	Neurology	2024	CYP2C19 Inhibition DDI

- This survey is conducted by the presenter themselves and it is not guaranteed to be a comprehensive list covering all products

- 33 drug product labels from 2015 to present
- Mainly in Oncology
- CYP3A victim DDI for predicting DDI magnitude with moderate or weak CYP3A inhibitors or inducers.

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PMDA Review Case 1
Prediction of P-gp or BCRP inhibition by Futibatinib

Background and Regulatory Purpose:

- A kinase inhibitor of fibroblast growth factor receptor (FGFR) for the treatment of intrahepatic cholangiocarcinoma
- IC50 of P-pg and BCRP were 0.296 and 0.348 uM, respectively. According to the cut-off values in the drug interaction guidelines, it cannot be excluded that P-gp- or BCRP inhibition may occur in clinical setting.
- To provide quantitative information on the increase in blood concentration of the substrates of P-gp (digoxin) and BCRP (rosuvastatin), and to state that the risk of drug interactions is low.

Model building and quantification

- Simcyp
- Digoxin and Rosuvastatin model were qualified based on the published literatures.
- Futibatinb model was build and qualified using a food effect study, hADME study and TQT study.

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PMDA Review Case 1
Prediction of P-gp or BCRP inhibition by Futibatinib

- PBPK Simulation

P-gp

Futibatinib dose	Digoxin dose	Input K_i value for P-gp	Predicted C_{max} ratio (90% CI)	Predicted $AUC_{0\text{-}96}$ ratio (90% CI)
20 mg QD for 10 days (fasted)	0.5 mg SD on Day 7 at the same time as futibatinib	0.296 µmol/L (in vitro K_i)	1.07 (1.07-1.07)	1.02 (1.02-1.02)
	0.5 mg SD on Day 7 at the same time as futibatinib	0.0296 µmol/L (0.1-fold K_i)	1.39 (1.36-1.41)	1.11 (1.10-1.12)
	0.5 mg SD on Day 7 at the same time as futibatinib	0.00296 µmol/L (0.01-fold K_i)	1.84 (1.78-1.90)	1.28 (1.25-1.32)
	0.5 mg SD 2 hrs after futibatinib on Day 7	0.00296 µmol/L (0.01-fold K_i)	1.42 (1.39-1.45)	1.17 (1.15-1.19)
	0.5 mg SD 4 hrs after futibatinib on Day 7	0.00296 µmol/L (0.01-fold K_i)	1.21 (1.19-1.22)	1.11 (1.09-1.12)
	0.5 mg SD 6 hrs after futibatinib on Day 7	0.00296 µmol/L (0.01-fold K_i)	1.15 (1.13-1.16)	1.09 (1.08-1.10)

BCRP

Futibatinib dose	Rosuvastatin dose	Input K_i value for BCRP	Predicted C_{max} ratio (90% CI)	Predicted $AUC_{0\text{-}96}$ ratio (90% CI)
20 mg QD for 10 days (fasted)	10 mg SD on Day 7 at the same time as futibatinib	0.348 µmol/L (in vitro K_i)	1.04 (1.04-1.04)	1.02 (1.02-1.02)
	10 mg SD on Day 7 at the same time as futibatinib	0.0348 µmol/L (0.1-fold K_i)	1.50 (1.45-1.54)	1.15 (1.14-1.16)
	10 mg SD on Day 7 at the same time as futibatinib	0.00348 µmol/L (0.01-fold K_i)	3.61 (3.41-3.83)	1.79 (1.73-1.86)
	10 mg SD 2 hrs after futibatinib on Day 7	0.00348 µmol/L (0.01-fold K_i)	2.01 (1.93-2.09)	1.45 (1.41-1.49)
	10 mg SD 4 hrs after futibatinib on Day 7	0.00348 µmol/L (0.01-fold K_i)	1.49 (1.45-1.54)	1.31 (1.28-1.34)
	10 mg SD 6 hrs after futibatinib on Day 7	0.00348 µmol/L (0.01-fold K_i)	1.33 (1.29-1.36)	1.27 (1.24-1.30)

- Scenario 1: Ki in PBPK = in vitro Ki
  - ➢ No DDI risk
- Scenario 2: Ki in PBPK = 1/100 in vitro Ki (worst case)
  - ➢ Cmax of digoxin and rosuvastatin increases by about 2 times and 3.6 times, respectively.
- Scenario 3: Ki in PBPK = 1/100 in vitro Ki and shifting the administration timing
  - ➢ Administering Futibatinib more than 2 hours earlier reduced the DDI magnitude (e.g. The increase was up to a 2-fold of Rosuvastatin's Cmax, at most.)

<u>Applicant's position</u>

The risk of drug-drug interactions of P-gp and BCRP due to Futibatinib is not high.

PMDA Review Case 1
Prediction of P-gp or BCRP inhibition by Futibatinib

- PBPK Simulation

P-gp

Futibatinib dose	Digoxin dose	Input K_i value for P-gp	Predicted C_{max} ratio (90% CI)	Predicted AUC_{0-96} ratio (90% CI)
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	0.5 mg SD 6 hrs after futibatinib on Day 7	0.00296 µmol/L (0.01-fold K_i)	1.15 (1.13-1.16)	1.09 (1.08-1.10)

BCRP

Futibatinib dose	Rosuvastatin dose	Input K_i value for BCRP	Predicted C_{max} ratio (90% CI)	Predicted AUC_{0-96} ratio (90% CI)
20 mg QD for 10 days (fasted)	10 mg SD on Day 7 at the same time as futibatinib	0.348 µmol/L (in vitro K_i)	1.04 (1.04-1.04)	1.02 (1.02-1.02)
	10 mg SD on Day 7 at the same time as futibatinib	0.0348 µmol/L (0.1-fold K_i)	1.50 (1.45-1.54)	1.15 (1.14-1.16)
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<u>PMDA's review</u>

- ✓ Because the extrapolation of in vitro Ki values of transporters to PBPK Ki values in humans is unclear, the applicant's approach of a sensitivity analysis with a smaller Ki and simulating the worst case is appropriate.
- ✓ Since the worst-case scenario indicates the possibility of drug-drug interactions of P-gp and BCRP, it is appropriate to provide information on the risk of these interactions.

<u>Outcome</u>

- ✓ "The PBPK model demonstrates the DDI possibility of P-gp and BCRP inhibition" is described in the drug product label
- ✓ The applicant decided to conduct a clinical drug interaction study to evaluate DDI magnitude.

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PMDA Review Case 2
Prediction of Anamorelin PK by CYP3A moderate inhibitors in patients

Background and Regulatory Purpose:

- A ghrelin receptor agonist to improve cancer-related anorexia/cachexia syndrome (CACS)
- The maximum exposure of Anamorelin in all clinical trials was Cmax: 3,670 ng/mL and AUCτ: 14,100 ng·h/mL. An extension of the QRS duration was observed at the Cmax of 3,360 ng/mL in a TQT study.
- To compare the predicted exposure levels in patients with liver impairment who are taking moderate CYP3A inhibitors with the maximum clinical exposure levels, and to discuss the safety in those patients.

Model building and quantification

- Simcyp
- Model building and quantification process is unknown from the published information.

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PMDA Review Case 2
Prediction of Anamorelin PK by CYP3A moderate inhibitors in patients

曝露量を上昇させる可能性のある被験者背景		C_{max}		AUC_{τ}	
肝機能障害の程度	中程度のCYP3A4阻害剤 a)	上昇倍率 b)	定常状態時の予測値 c) (ng/mL)	上昇倍率 b)	定常状態時の予測値 c) (ng·h/mL)
正常	併用なし	–	2,300 d)	–	6,820 d)
軽度	併用なし	1.0	2,300	1.3	8,870
	併用あり	1.4	3,220	2.0	13,600
中等度	併用なし	1.6	3,680	2.3	15,700
	併用あり	2.0	4,600	3.2	21,800
重度	併用なし	1.8	4,140	3.0	20,500
	併用あり	2.1	4,830	3.9	26,600

1. PBPK model was used to calculate the factor of increase of Anamorelin with a moderate CYP3A inhibitor according to the degree of liver impairment.
2. The maximum exposure of target patients with normal liver function, as determined from a population analysis.
3. The exposure levels for each group were calculated by multiplying the factor of increase obtained in step 1 with the exposure amount obtained in step 2.

<u>Outcome</u>

The applicant and PMDA have agreed that administering to patients with moderate and severe liver impairment is contraindicated. This is due to the predicted exposure exceeding the maximum exposure experienced in clinical trials, as well as the exposure extending the QRS duration.

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Summary

- Guidelines have been issued for the analysis reports of PBPK models and for the electronic data submission of PBPK models, and the environment for submitting PBPK models is in place in Japan.

- PBPK models have been mentioned in a number of drug package labels, and many are used to predict drug-drug interactions with CYP3A in oncology drugs.

- PBPK models have also been used in relatively new areas such as predicting drug-drug interactions with transporters and drug-drug interactions in patients with organ impairment. It should be noted that these have been discussed based on conservative predictions (such as smaller Ki values in transporter and estimates of maximum exposure in target population based on population pharmacokinetic analysis).

Disclaimer