独立行政法人 医薬品医療機器総合機構
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Regulatory Discussion/ Case Study 6

Focus: Model Validation and Application

Shinichi Kijima
Associate Senior Scientist for Clinical Pharmacology and Pharmacokinetics
Office of New Drug IV/Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency (PMDA)

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Outline

- Summary of Case Study 6: Drug X
- Overview of PBBM Model: Development, Validation and Application
- Regulatory concerns from Case Study 6
- Conclusion

Summary of Case Study 6 (Drug X)

Model Objective/Regulatory Question -

Does the agency agree that the X% of polymorphic impurity is allowed in the drug product in light of clinically relevant specifications?

Background

BCS II compound
Neutral species in physiological pH range
Immediate Release Oral dosage Form

Issue description

Model was developed to justify that presence of X% of polymorphic impurity in the drug product will not have any impact on the systemic exposure/clinical performance of the drug.

PBBM Model Development, Validation and Application

Develop a PBBM using compound and formulation specific input parameters

↓

Validate the PBBM by comparing predicted versus observed PK data for different formulations

↓

Assess the clinical impact of polymorphic inpurity

Model Development

Develop a PBBM using compound and formulation specific input parameters

Compound Specific parameters

- MW, logP, Peff, Solubility in aqueous and biorelevant media, Distribution and Clearance parameters were derived by population PK model

Formulation Specific parameters

- Dissolution profile was integrated as z factor derived from physiologically relevant dissolution testing (PBDT)
- Novel workflow developed to assess impact of polymorphic impurity on the PK

Model Validation

Validate the PBBM by comparing predicted versus observed PK data for different formulations

Model was validated against the clinical data and non-clinical data available for other critical quality attributes

- Including non-BE relative bioavailability study data
- non-clinical data: data from dog

PBBM Model can predict the *in vivo* relevance of changes in formulation and process parameters

Model Validation with Human PK

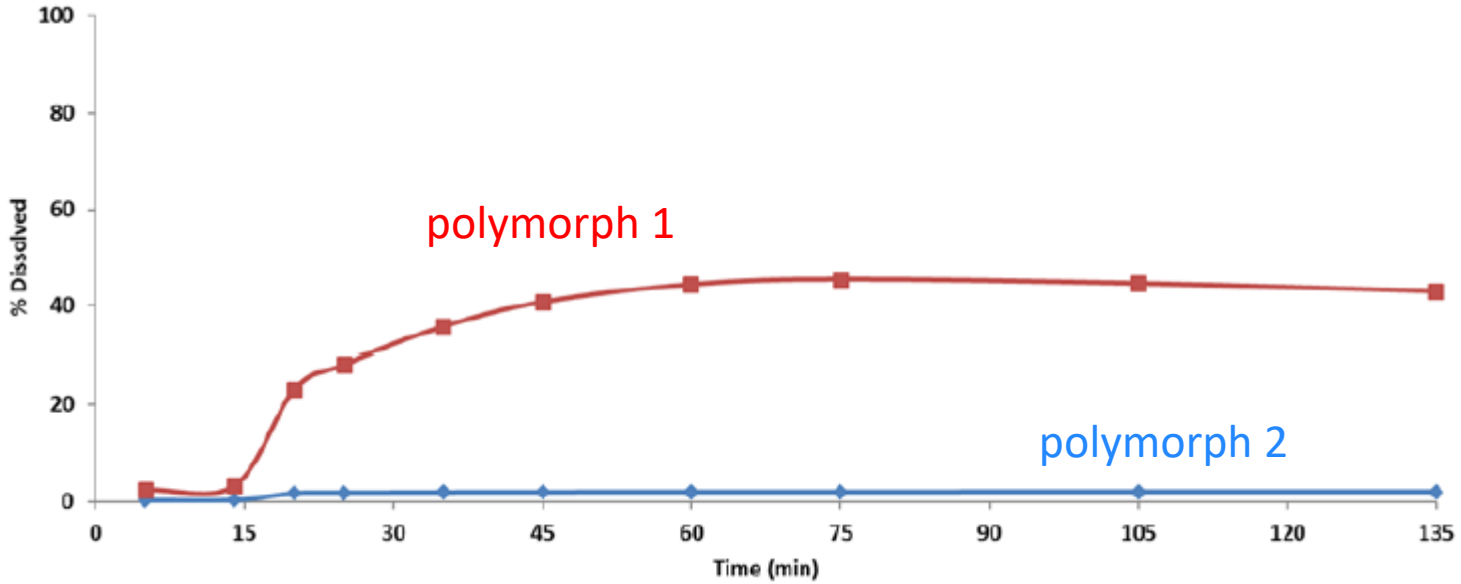
Study	Formulation	Dose	Cmax					AUC				
			In vivo			In silico	Ratio	In vivo			In silico	Ratio
			min	mean	max	mean		mean	Std dev	mean	std dev	
			1.98	2.73	3.34	2.58	0.95	74.20	107.30	148.00	110.67	1.03
			1.29	1.75	2.43	2.13	1.22	75.20	103.00	145.00	105.31	1.02
			0.95	1.94	3.32	2.04	1.05	69.20	99.89	171.00	101.32	1.01
			1.28	1.88	3.35	2.03	1.08	71.70	102.38	149.00	109.57	1.07
			1.39	2.01	3.02	2.17	1.08	69.20	92.86	152.00	99.57	1.07
			1.52	1.97	2.90	2.41	1.22	80.00	102.99	137.00	113.33	1.10
			1.51	2.30	3.39	2.42	1.05	67.10	105.40	145.00	104.84	0.99
			1.47	2.04	2.54	2.19	1.07	67.50	88.22	106.00	95.08	1.08
			1.98	2.70	3.67	2.27	0.84	76.03	98.64	124.52	97.49	0.99
			1.89	2.58	3.43	2.46	0.95	84.47	109.60	142.90	106.23	0.97
			1.97	2.42	3.20	2.41	1.00	92.38	120.48	198.78	108.89	0.90
			1.29	2.05	2.71	2.00	0.98	79.50	107.77	145.04	102.06	0.95
			1.31	2.36	3.87	2.37	1.00	77.59	118.05	196.07	104.76	0.89
			0.428	0.59	0.744	0.574	0.97	21.60	26.55	37.20	24.93	0.94
			0.322	0.57	0.589	0.602	1.05	24.20	29.47	39.60	26.54	0.90
			0.475	0.62	0.810	0.586	0.95	19.50	27.25	35.20	25.55	0.94
			0.43	0.62	0.863	0.599	0.97	18.90	27.86	48.10	26.21	0.94
			0.516	0.67	0.802	0.645	0.97	23.40	29.56	44.70	28.38	0.96
			0.361	0.63	0.994	0.599	0.95	14.12	26.60	40.16	26.21	0.99
			0.419	0.63	1.07	0.605	0.96	19.29	26.44	37.74	26.21	0.99
			0.392	0.61	0.87	0.613	1.00	14.44	26.16	36.30	26.55	1.01

non-BE relative BA study data

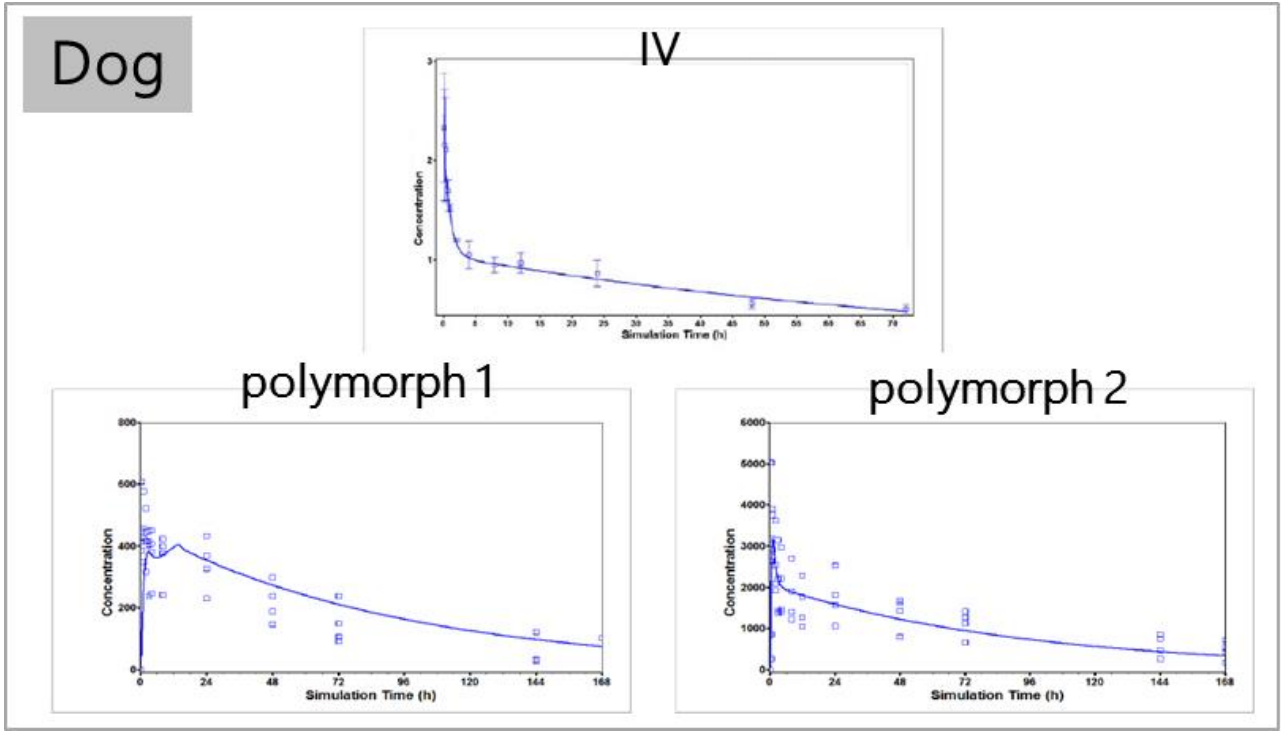
In vivo			
	Geometric mean (n = 15)		Geometric mean ratio (90% CI)
	A (ref)	B (test)	
C_{max}	2.71	1.88	69.23 (60.60 – 79.09)
AUC	105.89	96.97	91.58 (81.16 – 103.33)
In silico			
	Geometric mean (n = 15)		Geometric mean ratio (90% CI)
	A (ref)	B (test)	
C_{max}	2.50	1.97	78.71 (72.50 – 85.46)
AUC	104.50	95.44	91.33 (84.27 – 98.99)

✓ Predictive power for both Cmax and AUC is consistent across all formulations and dose strengths.

PBDT profiles (fasted state)



Model Validation with Dog PK



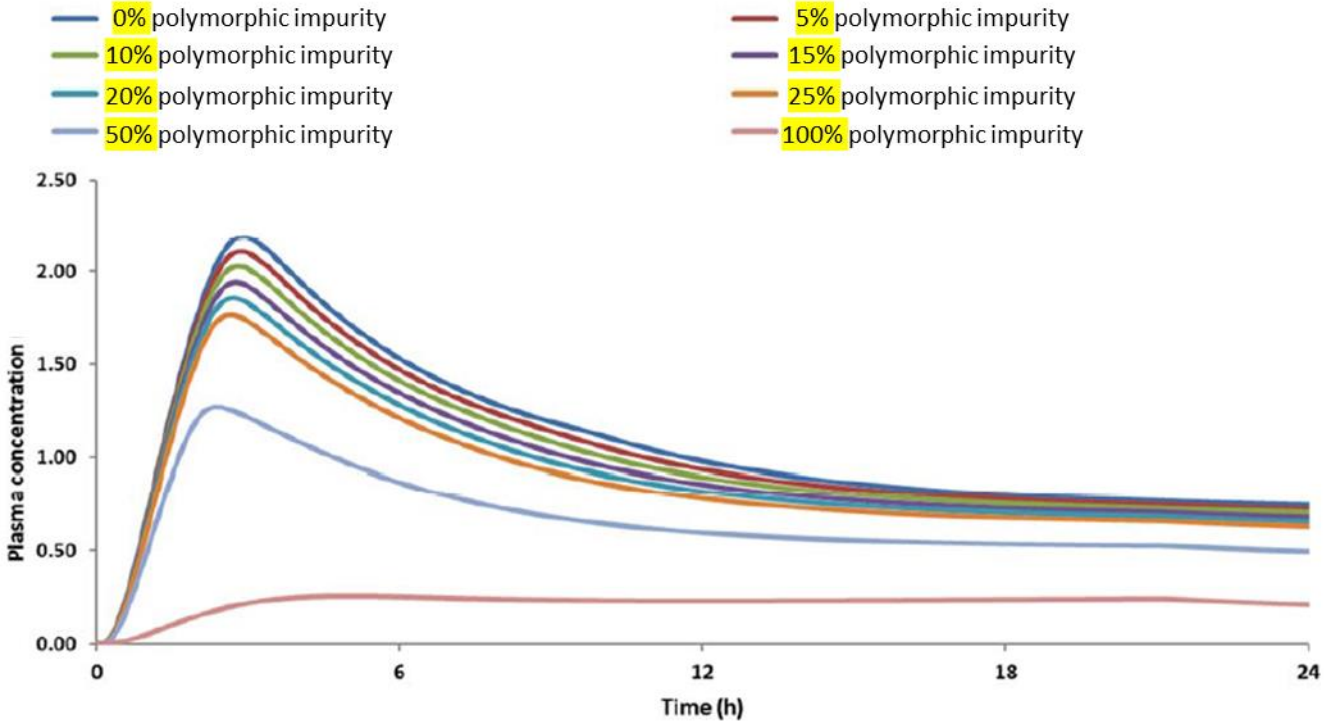
Model Application

Assess the clinical impact of polymorphic inpurity

Validated PBBM Model was applied to assess the impact of polymorphic impurity in the drug product on *in vivo* exposure.

- PK Predictions for Different % of polymorphic impurity
  - Vary % of polymorphic impurity between 0% and 100%
- Conduct Virtual BE trial
  - 10 trails
  - crossover design (N=20)
  - Reference:0%, Test X%

PK Predictions for Different % of polymorphic impurity



Result of VBE trials

Virtual bioequivalence trials																
Virtual Trial Number	A				B				C				D			
	C_{max}		AUC		C_{max}		AUC		C_{max}		AUC		C_{max}		AUC	
	90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI		90% CI	
	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL
1	94.18	102.75	92.98	95.87	88.19	96.22	90.40	93.21	82.21	89.69	87.67	90.40	76.85	83.85	84.60	87.23
2	88.01	95.64	92.69	96.11	81.54	88.60	90.69	94.04	83.25	90.46	87.31	90.53	79.07	85.92	84.28	87.39
3	89.34	97.77	93.15	96.53	85.23	93.26	91.04	94.35	81.25	88.91	87.17	90.33	79.44	86.93	84.66	87.73
4	87.73	95.38	92.36	95.45	84.30	91.65	90.60	93.63	81.87	89.01	86.85	89.75	78.47	85.31	84.28	87.10
5	86.62	94.87	93.63	97.10	80.79	88.49	90.73	94.09	81.75	89.55	87.49	90.73	78.46	85.94	83.52	86.61
6	88.21	95.80	92.78	95.55	86.12	93.54	91.62	94.36	81.70	88.74	87.72	90.34	79.78	86.64	84.97	87.50
7	90.38	97.59	93.66	96.99	86.32	93.21	89.39	92.57	80.08	86.46	87.93	91.06	76.16	82.24	83.86	86.84
8	86.65	94.31	92.69	95.67	83.01	90.36	91.29	94.23	84.16	91.61	88.09	90.92	79.34	86.36	84.66	87.38
9	88.68	96.05	93.89	96.92	81.52	88.30	90.62	93.54	81.30	88.05	87.38	90.20	77.78	84.24	84.55	87.28
10	87.56	95.99	93.33	96.42	83.67	91.73	89.91	92.88	82.35	90.28	86.44	89.29	76.16	83.50	84.29	87.08

Regulatory concerns : Focused on Model Validation and Application

- What is the role of animal PK data in PBBM?
  - Need to "Fit for Purpose"
  - Consideration under conservative conditions
  - The data from the dog model is complementary to the human PBBM for confirming model assumption
- Acceptance Criteria for Virtual BE study
  - How to assess variability
  - How to address to variability uncertainty
  - What if some VBE studies were outside the acceptable limits?

Conclusion

Model Objective/Regulatory Question -
Does the agency agree that the X% of polymorphic impurity is allowed in the drug product in light of clinically relevant specifications?

- The PBBM model showed generally good predictive performance and is therefore acceptable for the purposes presented.
- Whether "X%" is acceptable depends on the evaluation for VBE study. For example, more conservative value of “X” may need to be chosen if the variability setting is assessed as uncertain.

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Thank you