

Regulatory Discussion/ Case Study 6

Focus: Model Validation and Application

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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 impurity

| Model Development

Develop a PBBM using compound and formulation specific input parameters



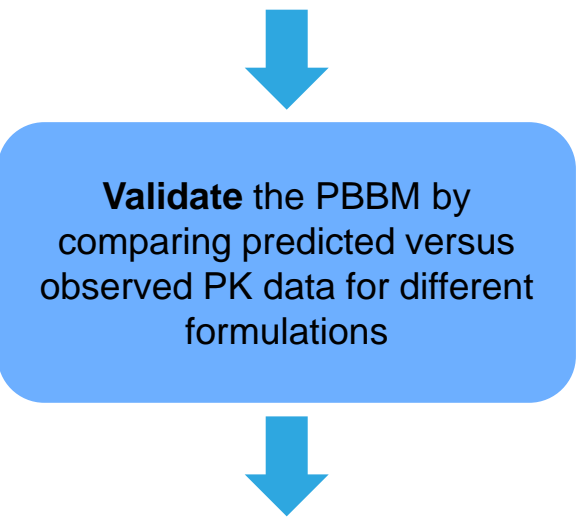
Compound Specific parameters

- 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

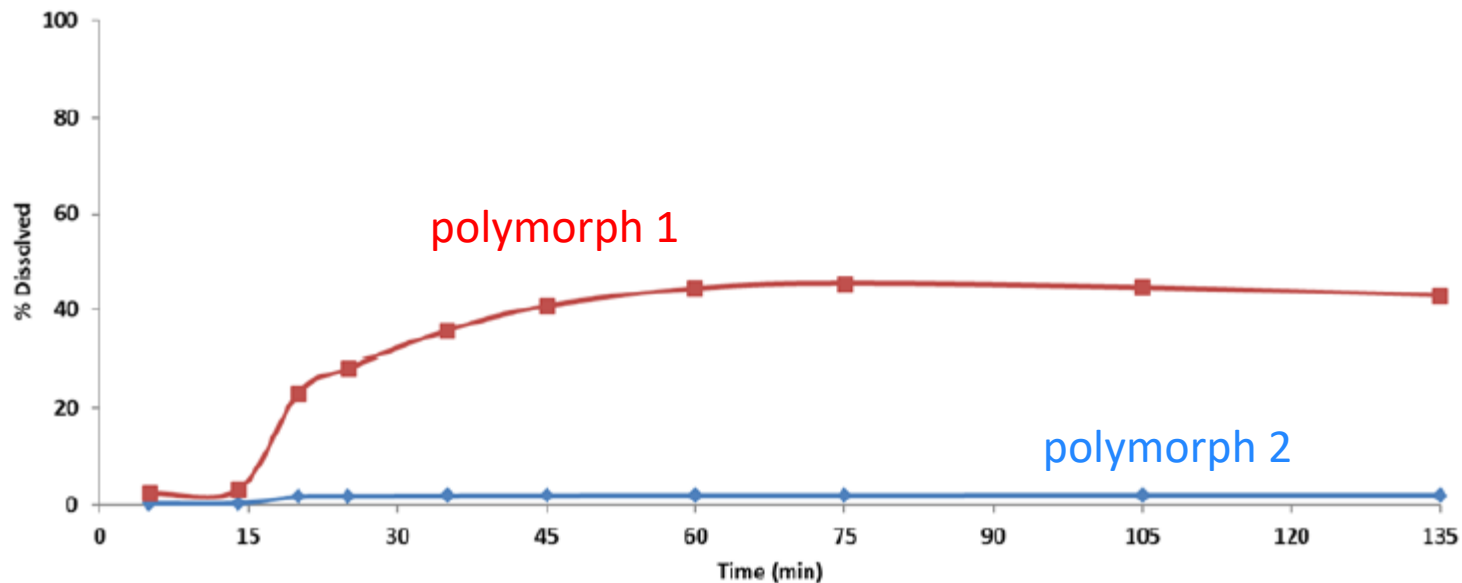
Study	Formulation	Dose	C_{max}					AUC				
			<i>in vivo</i>		<i>in silico</i>		ratio	<i>in vivo</i>		<i>in silico</i>		ratio
			mean	stdev	mean	stdev		mean	stdev	mean	stdev	
			1.98	2.73	3.34	2.58	0.95	74.20	107.30	148.00	110.67	1.03
			1.29	1.75	2.43	2.13	1.22	75.20	103.00	145.00	105.31	1.02
			0.95	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	84.87	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	26.6	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

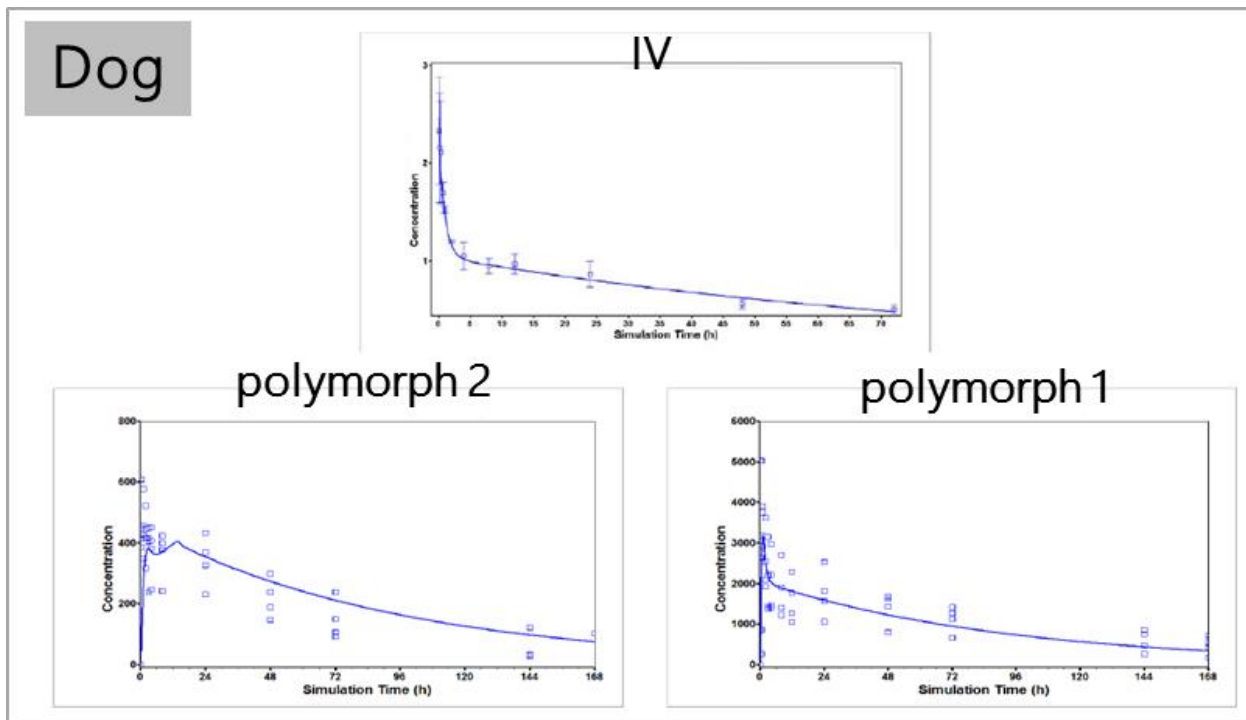
<i>In vivo</i>			
	Geometric mean (n = 15)		Geometric mean ratio (90% CI)
	A (ref)	B (test)	
C_{max}	2.71	1.88	69.23 (60.60 – 79.09)
AUC	105.89	96.97	91.58 (81.16 – 103.33)
<i>In silico</i>			
	Geometric mean (n = 15)		Geometric mean ratio (90% CI)
	A (ref)	B (test)	
C_{max}	2.50	1.97	78.71 (72.50 –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

✓ Predictive power for both C_{max} and AUC is consistent across all formulations and dose strengths.

PBDT profiles (fasted state)



Model Validation with Dog PK



| Model Application

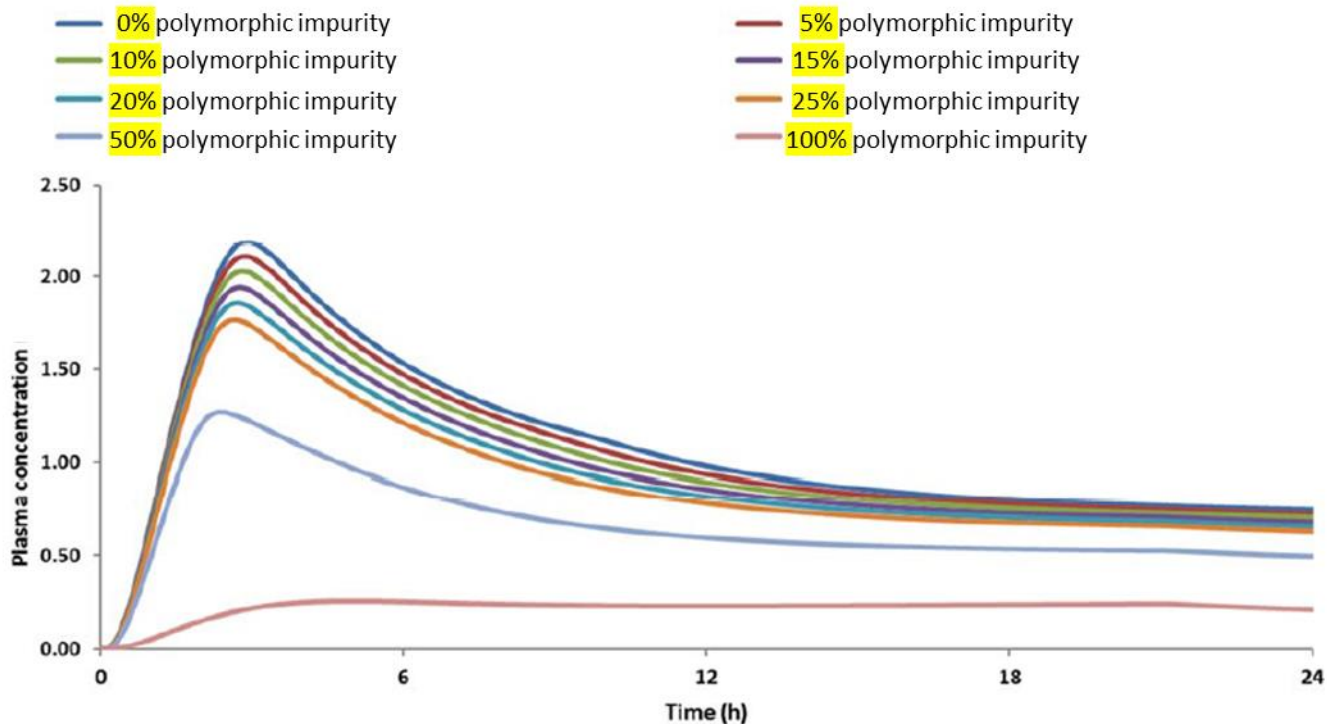


Assess the clinical
impact of polymorphic
impurity

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.

Thank you