EUROPEAN MEDICINES AGENCY

Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices For Drug Product Quality: Regulatory and Industry Perspectives

Pfizer - Case Study 9

A Retrospective Case Study on Fluconazole

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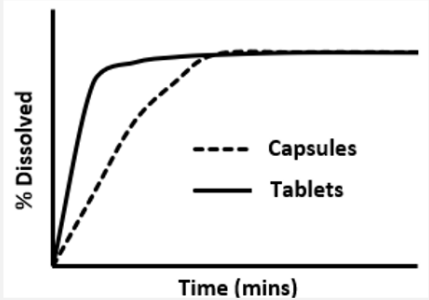
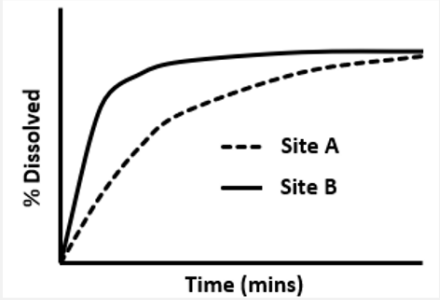
Key Objectives of Fluconazole PBBM Case Study 9

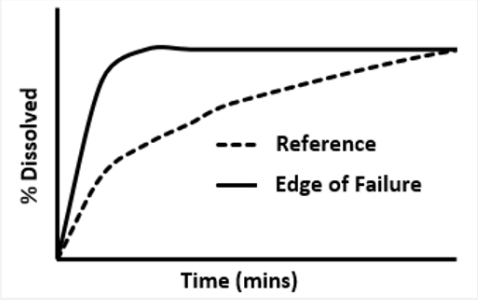
Can PBPK modeling add value for BCS 1 compounds understanding?



- ✓ Explore whether PBPK is appropriate to demonstrate ***virtual BE between different oral dosage forms*** of fluconazole to support the ***grant of biowaivers?***



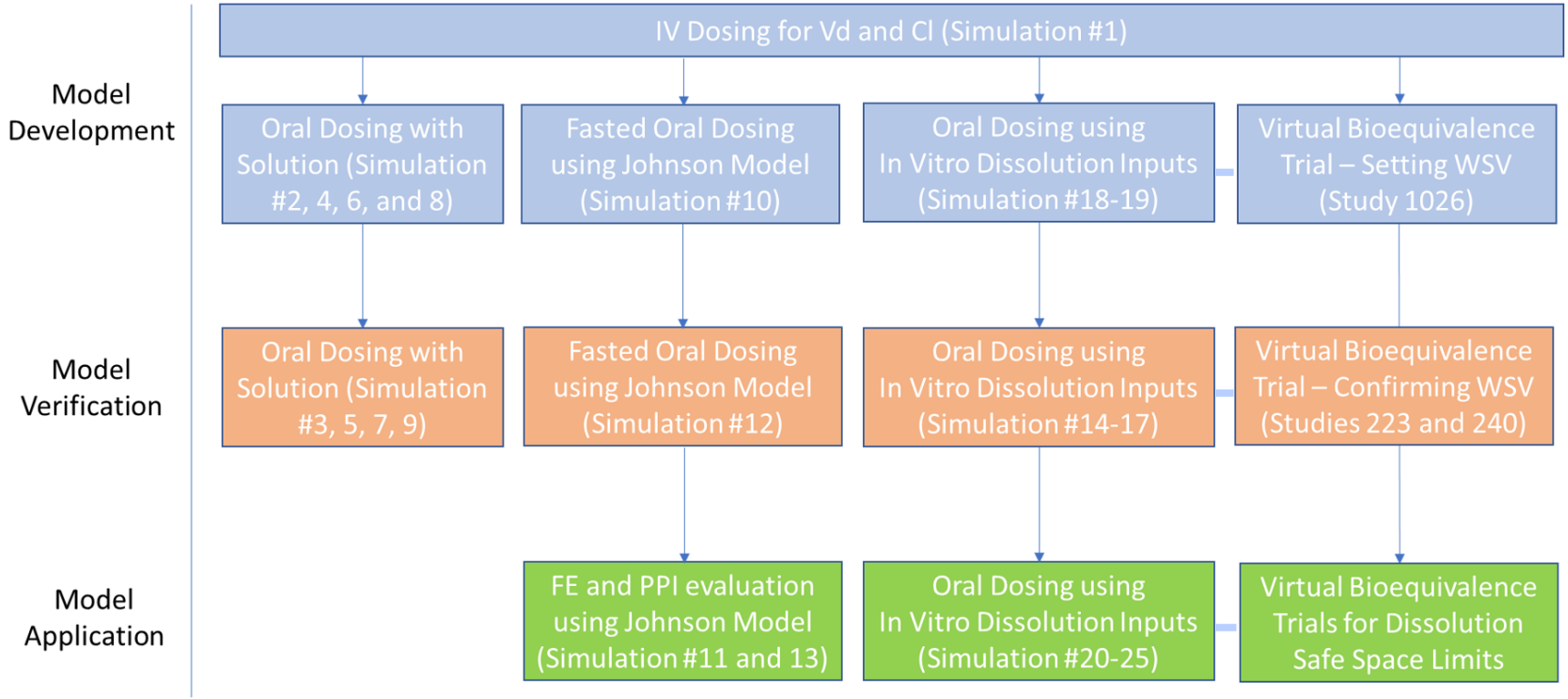
- ✓ Explore whether ***PBPK modeling could increase the level of confidence*** to demonstrate BE between same drug products with ***significantly differing*** (e.g., f2 less than 50) ***dissolution profiles?***



- ✓ Explore whether a verified PBPK model provides the ability to ***define the boundaries of the in vitro dissolution safe space*** in which fluconazole formulations are anticipated to be bioequivalent to one another

Step-wise Modeling workflow for Fluconazole PBBM

The approach followed for modeling fluconazole are provided as a step-wise flowchart is outlined briefly here



Key Outcomes of the Fluconazole PBBM Case study

- The PBBM approach for fluconazole was ***developed and verified*** to adequately predict the ***PK of fluconazole across various formulation types and dissolution inputs***.

- The model was verified to replicate the outcomes of numerous BE studies conducted in-house
  1. BE between a ***tablet and a capsule*** formulation
  2. BE between ***two capsule formulations*** dosed as a ***single unit vs multiple units of lower strength***
  3. BE between two capsule formulations that ***exhibited f2 values below 50*** during site transfer

- Additionally, virtual bioequivalence (VBE) was utilized to extend the ***lower limit of the dissolution safe space for fluconazole capsules (Q=80% of 75 mins)***, significantly longer than the typical limit of (Q=80% of 30 mins) for rapidly dissolving ***BCS 1 compounds for biowaiver applications***.

- The model also well predicted the PK of fluconazole under ***fed and antacid co-administration*** compared to the observed *in vivo* data.

- These outcomes demonstrate the potential advantage of ***including PBBM as part of BCS 1 compound drug product development***.

Simulation ID	Clinical Study ID	n	Dose	AUC_{inf} P/O ratio	C_{max} P/O ratio
1	A0560206	8	50 mg	0.98	0.80
2	A0560201	2	0.25 mg/kg	1.17	0.98
3	A0560201	2	0.5 mg.kg	1.88	1.16
4	A0560201	2	0.75 mg/kg	1.43	1.10
5	A0560201	4	1 mg/kg	1.55	1.04
6	A0560201	2	1.5 mg/kg	1.40	1.21
7	A0560201	2	2 mg/kg	1.32	1.09
8	A0560201	2	2.5 mg/kg	1.60	1.14
9	A0560201	2	3 mg/kg	1.48	1.08
10	A0560203	12	50 mg	1.43	0.98
11	A0560203	12	50 mg	1.52	1.05
12	A0560242	14	100 mg	1.00	1.17
13	A0560242	14	100 mg	1.00	1.16
14	A0560223	12	150 mg	1.00	1.08
15	A0560223	12	150 mg	1.05	1.02
16	A0560240	14	200 mg	1.00	0.90
17	A0560240	14	200 mg	1.01	0.89
18	A0561026	23	50 mg	1.05	1.00
19	A0561026	23	50 mg	1.07	1.10
20	Literature Study[a]	28	150 mg	1.05	0.95
21	Literature Study[a]	28	150 mg	1.05	0.95
22	Literature Study[a]	28	150 mg	1.05	0.95
23	Literature Study[a]	28	150 mg	1.05	0.95
24	Literature Study[a]	28	150 mg	1.03	0.80
25	Literature Study[a]	28	150 mg	1.05	0.93
26	Literature Study[a]	28	150 mg	1.05	0.89
27	Literature Study[a]	28	150 mg	1.05	0.86
28	Literature Study[a]	28	150 mg	1.04	0.83

[a]: Zoltec 150 mg Capsule PK profile was used as the observed data (Perira et.al)

Overview of PBBM simulations

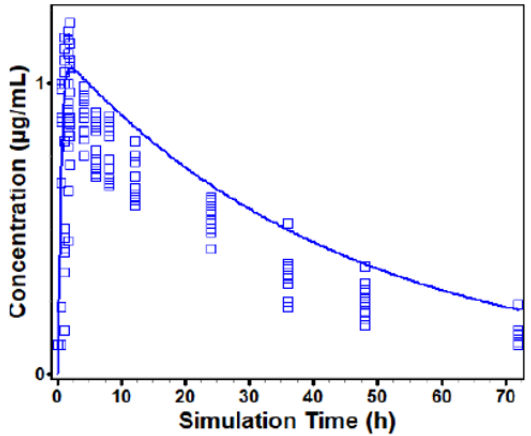
- 19 simulations based on 7 clinical trials
  - IV, PO solutions, IR capsules, CR dispersed
- 6 simulations based on literature study
  - CR dispersed showing a range of dissolution profiles
- 3 simulations based on hypothetical formulations/ dissolution profiles

- Separate data sets used for model-development, verification, application.

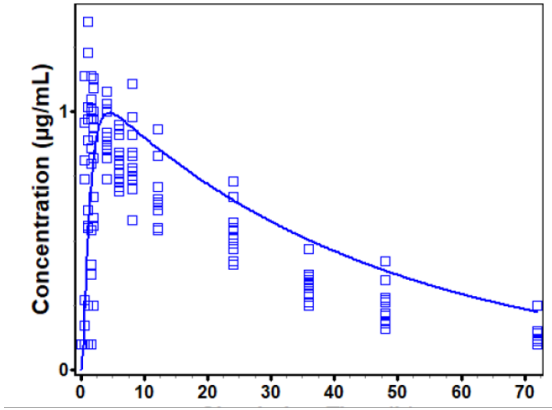
Results
Food effect

Simulation ID	Clinical Study ID	n	Dose	AUC_{inf} P/O ratio	C_{max} P/O ratio
10	A0560203	12	50 mg	1.43	0.98
11	A0560203	12	50 mg	1.52	1.05

Simulation 10. A0560203 Oral Capsules 50 mg Fasted



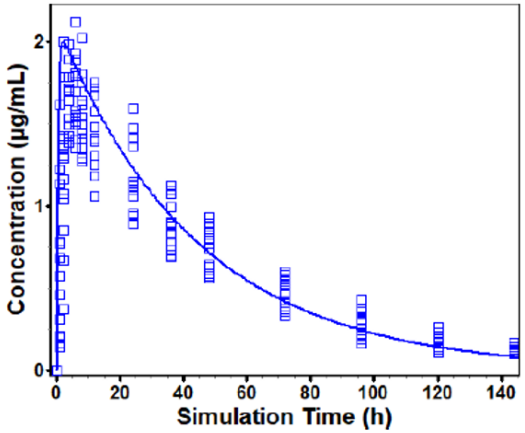
Simulation 11. A0560203 Oral Capsules 50 mg Fed



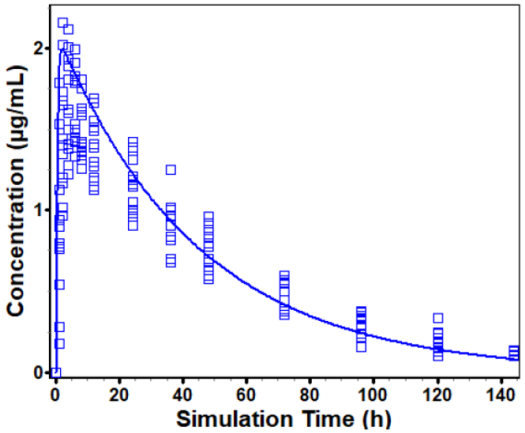
Results
Antacid effect

Simulation ID	Clinical Study ID	n	Dose	AUC_{inf} P/O ratio	C_{max} P/O ratio
12	A0560242	14	100 mg	1.00	1.17
13	A0560242	14	100 mg	1.00	1.16

Simulation 12. A0560242 Oral Capsules 100 mg Fasted



Simulation 13. A0560242 Oral Capsules 100 mg Fasted with Antacid

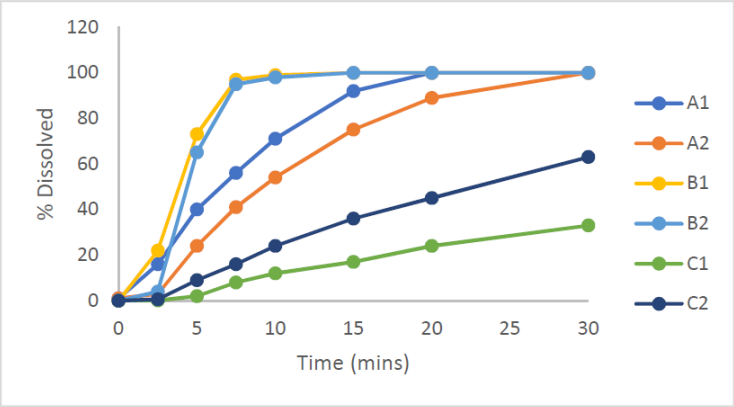


Results
Dissolution safe space

Simulation ID	Clinical Study ID	n	Dose	AUC_{inf} P/O ratio	C_{max} P/O ratio
20	Literature Study[a]	28	150 mg	1.05	0.95
21	Literature Study[a]	28	150 mg	1.05	0.95
22	Literature Study[a]	28	150 mg	1.05	0.95
23	Literature Study[a]	28	150 mg	1.05	0.95
24	Literature Study[a]	28	150 mg	1.03	0.80
25	Literature Study[a]	28	150 mg	1.05	0.93

[a]: Zoltec 150 mg Capsule PK profile was used as the observed data (Perira et.al)

Figure 3. Dissolution profiles extracted from literature (Marcelo et.al)



Results
Dissolution safe space

- VBE indicates formulation C2 is bioequivalent to commercial formulation A1, whereas C1 is not

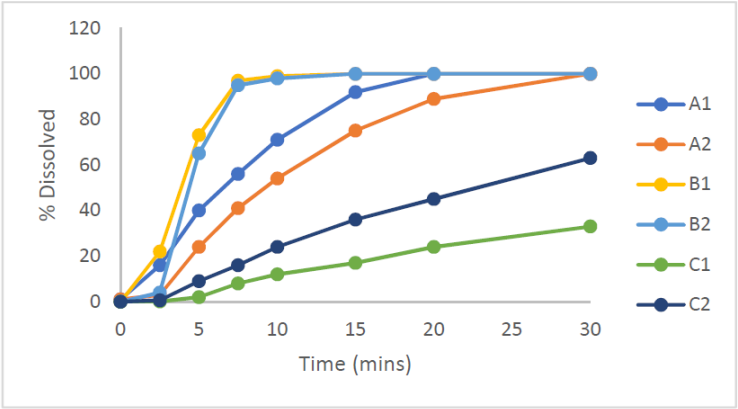


Table 9. Virtual Bioequivalence Study Results – Formulation A1 vs. Formulation C2 (N=28, 150 mg Capsules)

Trial Number	PASS/FAIL	T/R Ratio C_{max}	Lower 90% CI	Upper 90% CI	T/R Ratio AUC_{inf}	Lower 90% CI	Upper 90% CI
1	PASS	94.57	86.31	103.62	99.99	89.3	111.96
2	PASS	91.82	83.4	101.09	98.37	87.41	110.72
3	PASS	101.8	94.03	110.23	99.17	87.66	112.19
4	PASS	96.91	89.25	105.24	100.6	90.79	111.39
5	PASS	90.14	82.26	98.77	99.48	90.2	109.72
6	PASS	98.53	91.41	106.22	97.56	87.27	109.06
7	PASS	94.9	87.01	103.51	100.6	88.26	114.62
8	PASS	100.5	93.42	108.07	99.4	91.41	108.09
9	PASS	93.38	86.44	100.88	100.2	88.02	114.1
10	PASS	91.82	83.6	100.84	98.99	86.31	113.54

Table 10. Virtual Bioequivalence Study Results – Formulation A1 vs. Formulation C1 (N=28, 150 mg Capsules)

Trial Number	PASS/FAIL	T/R Ratio C_{max}	Lower 90% CI	Upper 90% CI	T/R Ratio AUC_{inf}	Lower 90% CI	Upper 90% CI
1	PASS	88.39	81.61	95.74	99.46	88.87	111.31
2	FAIL	77.13	70.78	84.06	96.43	85.89	108.26
3	FAIL	83.19	76.81	90.11	98.27	87.13	110.83
4	FAIL	76.38	70.67	82.55	92.3	83.67	101.82
5	FAIL	78.97	72.67	85.81	97.6	88.57	107.55
6	FAIL	80.73	74.69	87.26	96.29	86.43	107.28
7	FAIL	82.79	76.42	89.7	94.94	83.33	108.17
8	FAIL	85.62	79.45	92.28	99.12	90.83	108.18
9	FAIL	81.71	76.81	86.93	99.01	86.94	112.75
10	FAIL	83.89	76.55	91.93	96.84	83.85	111.85

Results
Dissolution safe space

- Dissolution safe space further narrowed based on VBE for hypothetical dissolution profiles

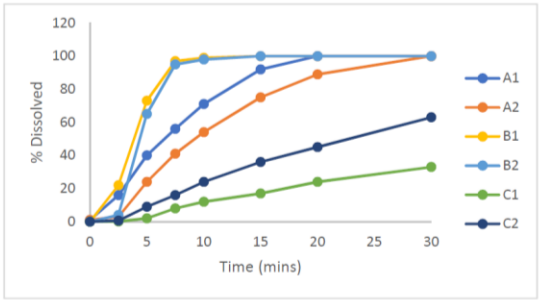
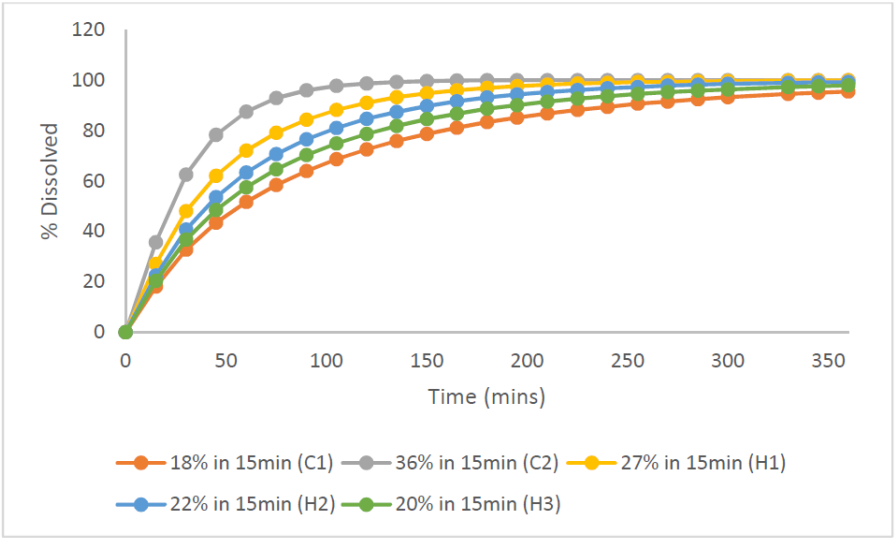


Figure 4. Hypothetical dissolution profiles to identify the Lower Bound of Dissolution Safe Space

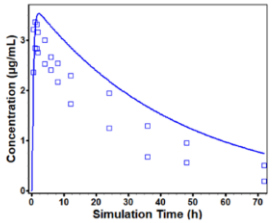


Regulatory concern: Confidence in the model

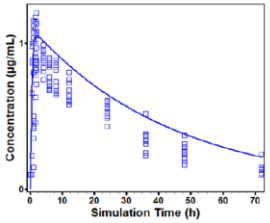
Several simulations overestimated C_{max}/ AUC without explanation

Development

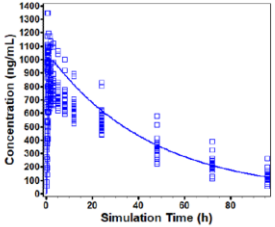
Simulation 8. A0560201 Oral Solution 2.5 mg/kg



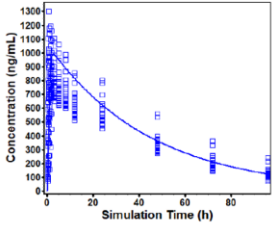
Simulation 10. A0560203 Oral Capsules 50 mg Fasted



Simulation 18. A0561026 Oral Capsules 50 mg

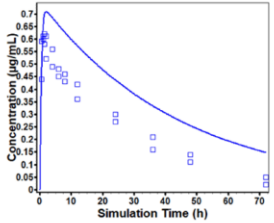


Simulation 19. A0561026 Oral Capsules 50 mg

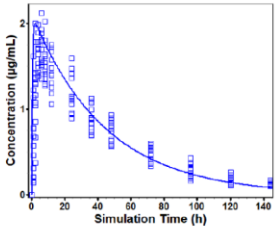


Verification

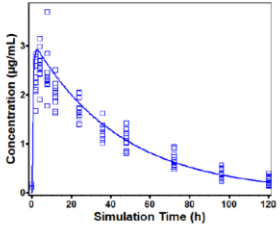
Simulation 3. A0560201 Oral Solution 0.5mg/kg



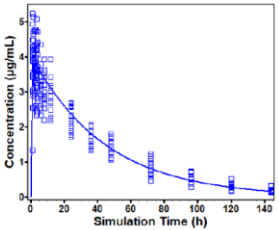
Simulation 12. A0560242 Oral Capsules 100 mg Fasted



Simulation 14. A0560223 Oral Capsules 150 mg



Simulation 17. A0560240 Oral Capsules 4*50 mg



Regulatory concerns:
Unclear basis for model development and verification

- No modification of the model to improve pred/obs results outside predefined criteria (pure bottom-up approach)
- Uncertainty regarding some of the model input parameters. No sensitivity analysis
- In the absence of data, PSD was estimated for fitting to the Johnson model
- Virtual BE trials
  - VBE for model development?
  - Intrasubject CV in VBE markedly lower than for the corresponding clinical trials
  - Higher number of subjects in the VBE for dissolution safe space
- General concern for this case study: The PK studies were not available for assessment

Conclusion:
Would the presented PBBM support regulatory decisions?

- Bioequivalence shown between different oral formulations?
- Bioequivalence shown in spite of significantly differing in vitro dissolution profiles (f2 < 50)?
- Support relaxed criteria for in vitro dissolution (quality control/ batch release)?

Bioequivalence study is normally necessary to support the above claims.

Based on the data provided with the case study, the PBBM represents limited value, and would probably not be considered sufficient as substitute for clinical data. However, during a normal regulatory procedure, concerns might have been resolvable.

Thank you

Any questions?

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