OIP development in practice

Overcoming barriers to bioequivalence

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IR Solid Oral Dosage forms

Orally Inhaled Products

90% CI for T/R: 80.00 – 125.00 %

Are the same BE criteria appropriate to both oral and inhalation products?

Pictures: manufacturingchemist.com

Asthma Inhalers. Image Credit: Bochimsang12 / Shutterstock, www.news-medical.net

Study standardisation

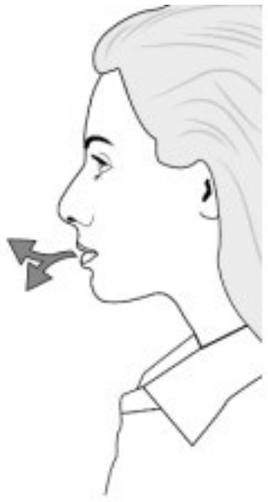
T/R

Can we apply the same level of standardisation to OIPs?

4

Inhalation technique

Join the study!



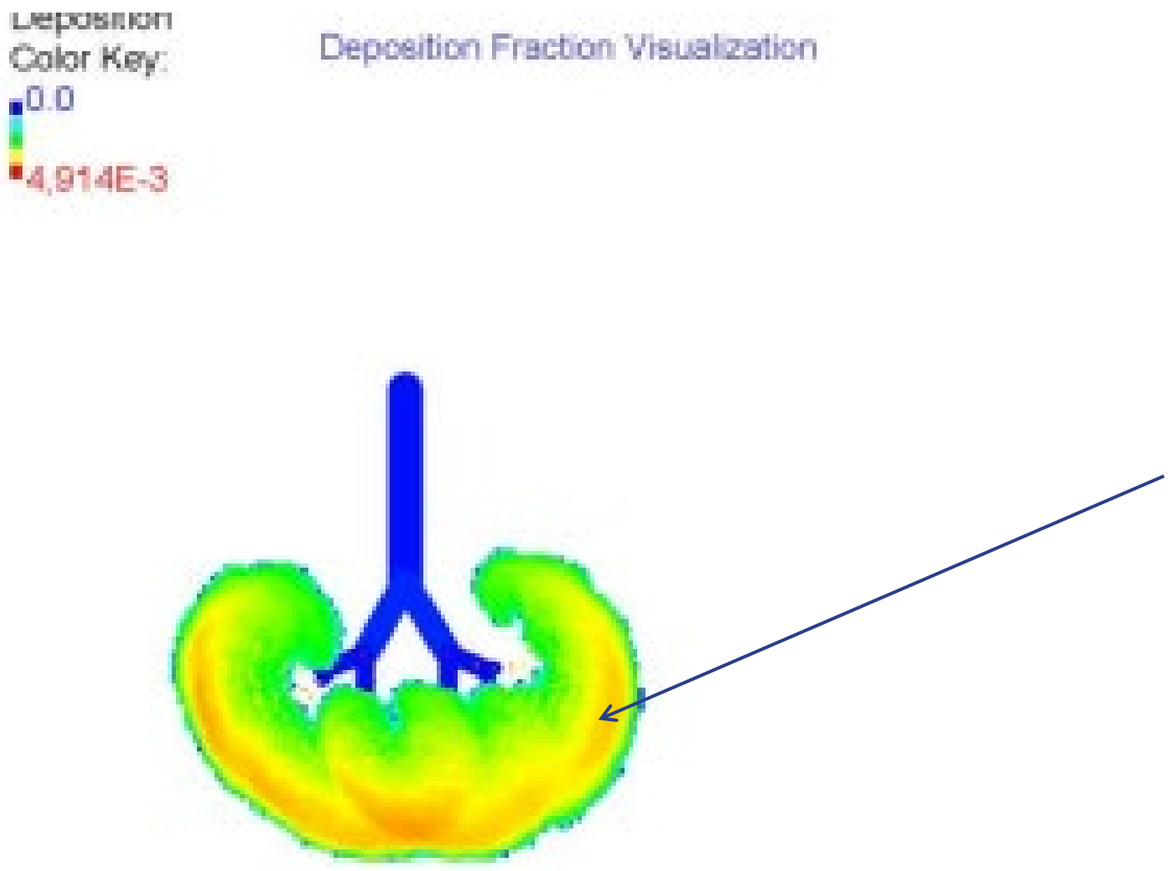
1. Breathe out fully

2. Breathe in quickly and deeply as you can

3. Hold your breath for 5 seconds.

Ref: Amidil AmiHaler. SmPC

Factor associated with lung deposition:



Inhalation technique

- inspiration flow rate,
- inspiratory effort,
- length
- depth
- volume
- breath– hold time

Ref: Baloira et al (2021),

Case study 1

- Training using **In-Check Dial Device**
- Subjects carefully screened based on proper inhalation technique
- Training conducted prior to each period

Although intensive training is provided, variability still exists

Case study 1

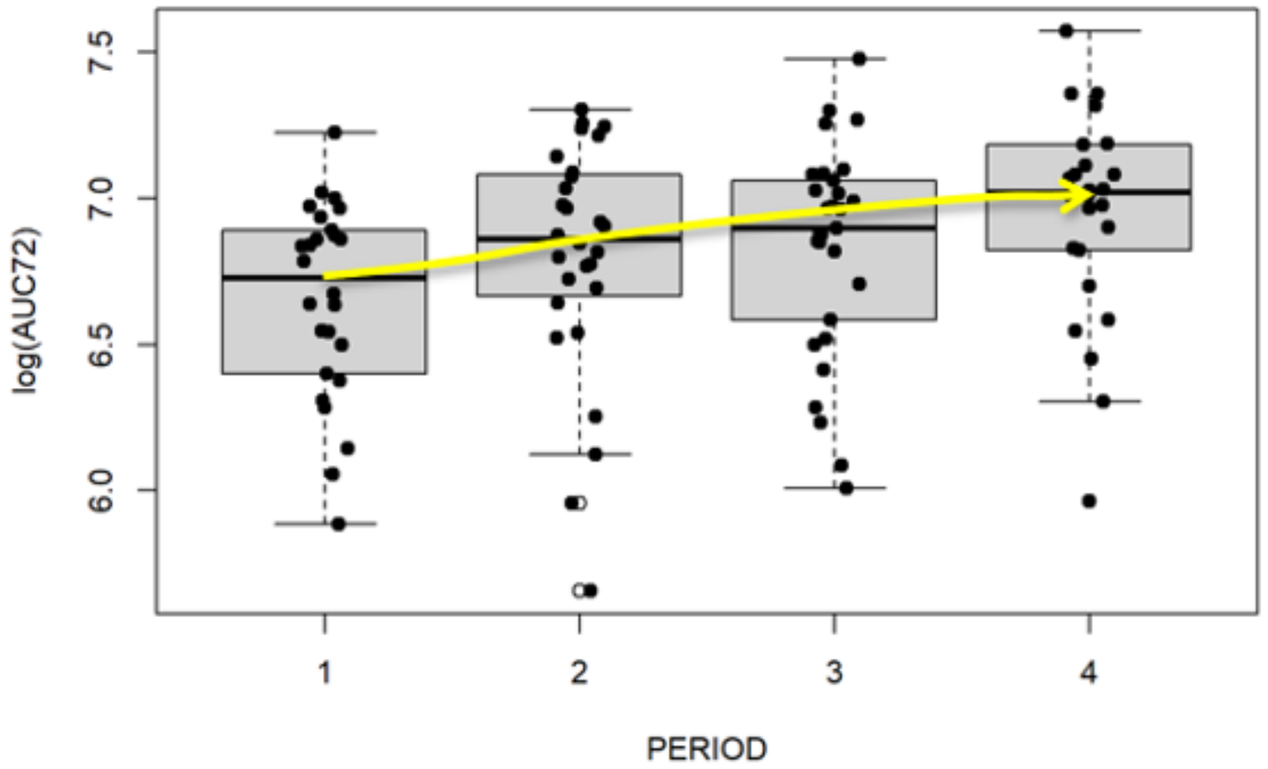
Period 3

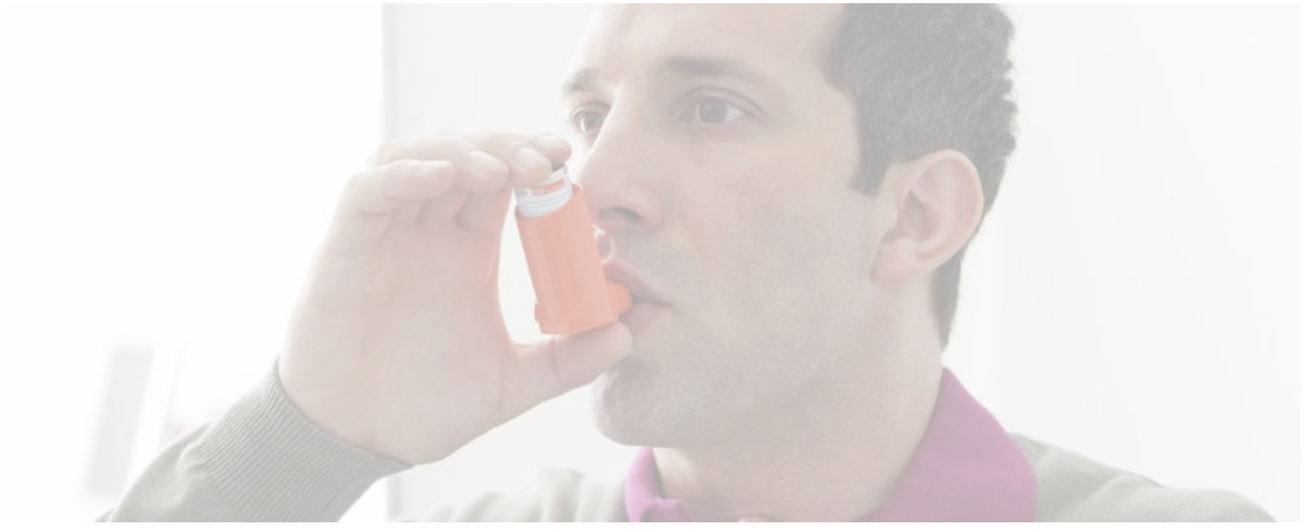
Subject No.	Attempt	Flow Rate (L/min)	Proper Inhalation Technique?	If the technique is poor, specify the Applicable Reason(s)
9	1	60	N	Participant did not breathe in long, steady or deeply. Participant did not hold breath in for at least 3-4 seconds.
9	2	90	N	Participant did not hold breath in for at least 3-4 seconds.
9	3	85	N	Participant did not hold breath in for at least 3-4 seconds.
9	4	90	N	Participant did not hold breath in for at least 3-4 seconds.
9	5	90	N	Participant did not hold breath in for at least 3-4 seconds.
9	6	85	N	Participant did not hold breath in for at least 3-4 seconds.
9	7	65	N	Participant did not hold breath in for at least 3-4 seconds.
9	8	95	N	Participant did not hold breath in for at least 3-4 seconds.
9	9	100	N	Participant did not hold breath in for at least 3-4 seconds.
9	10	85	N	Participant did not hold breath in for at least 3-4 seconds.
9	11	85	Y	
9	12	90	Y	

- Example observation: **Subject 9 needed 12 attempts in Period 3** (sic!) to achieve the training goal, the flow rate ranges **60-100 L/min**
- Imagine subject's pressure during „real" drug administration

Case study 2

- **Period-effect** visible for AUC72
- Hypothesis: subjects became more familiar with the real product inhalation
- **Feeling of the drug** (e.g. bitter taste in the mouth) cannot be fully replicated using training devices





Case study 3

Consequences of poor inhalation technique

- 2-arm, replicate design
- Outstanding results in **Cmax** and **AUC72** in Period 2
- Potential influence of **paused inhalation** (1st administration of Ref)

Subject 18

PERIOD	AUC72	CMAX	TMAX	observations???
1	549.05	164.0	0.25	no observations
2	**285.81**	**98.5**	0.25	paused inhalation
3	406.79	168.0	0.25	no observations
4	632.52	132.0	0.20	no observations

Lesson 1:

No matter how rigorous the training, inhalation technique remains a significant source of variability

Case study 4

- Disappointing results for Cmax
- About 24% difference between arms
- Does it mean the product is flawed?

Parameter (Unit)	Statistic	Result
AUC_{0-72} (pg*h/mL)	% GMR (90% CI)	90.68 (78.00 , 105.43)
C_{max} (pg/mL)	% GMR (90% CI)	76.19 (62.91 , 92.27)

Case study 4

The same batch (Reference!) in replicate

Comparison	Parameter (Unit)	Statistic	Result
R1 (2nd) (vs R1 (1st)	AUC_{0-72} (pg*h/mL)	% GMR (90% CI)	90.68 (78.00 , 105.43)
	C_{max} (pg/mL)	% GMR (90% CI)	76.19 (62.91 , 92.27)

Case study 4

Unsatisfied ~~product~~ sampling

- Sampling: **2**, 4, 6, 8, 10 (min), etc…
- **85%** of Cmax observed at the first sampling point of **2 min**…
- Study was repeated with improved sampling scheme:
  5% of Cmax observed at the first sampling point of **1 min**…

You may still miss the true peak concentrations

Lesson 2

Even the best rocket may be insufficient to accurately capture Cmax

Case study 5

- Very unfavourable results in **AUCt and AUCinf**
- Very high difference between arms
- Enormous ISCV

Parameter	*Trt*	*Geometric Least-squares Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	138.64	**A vs B**	132.46	95.54 - 183.66	40
*(hr*pg/mL)*	**B**	104.66				
AUC_{inf}	**A**	272.24	**A vs B**	160.82	89.75 - 288.19	70
*(hr*pg/mL)*	**B**	169.28				

16

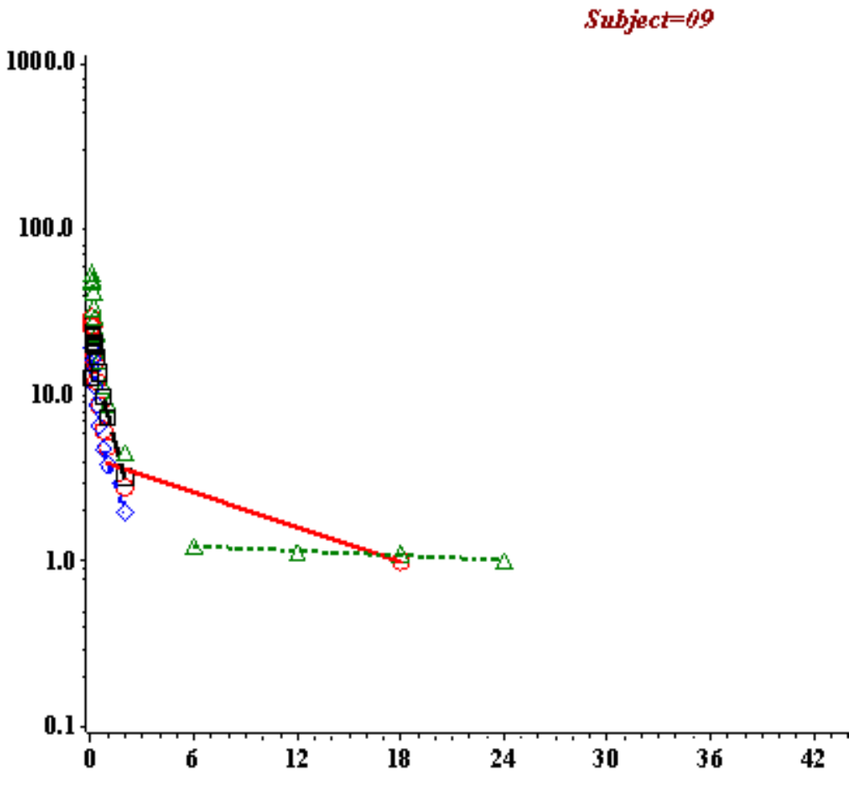
Case study 5

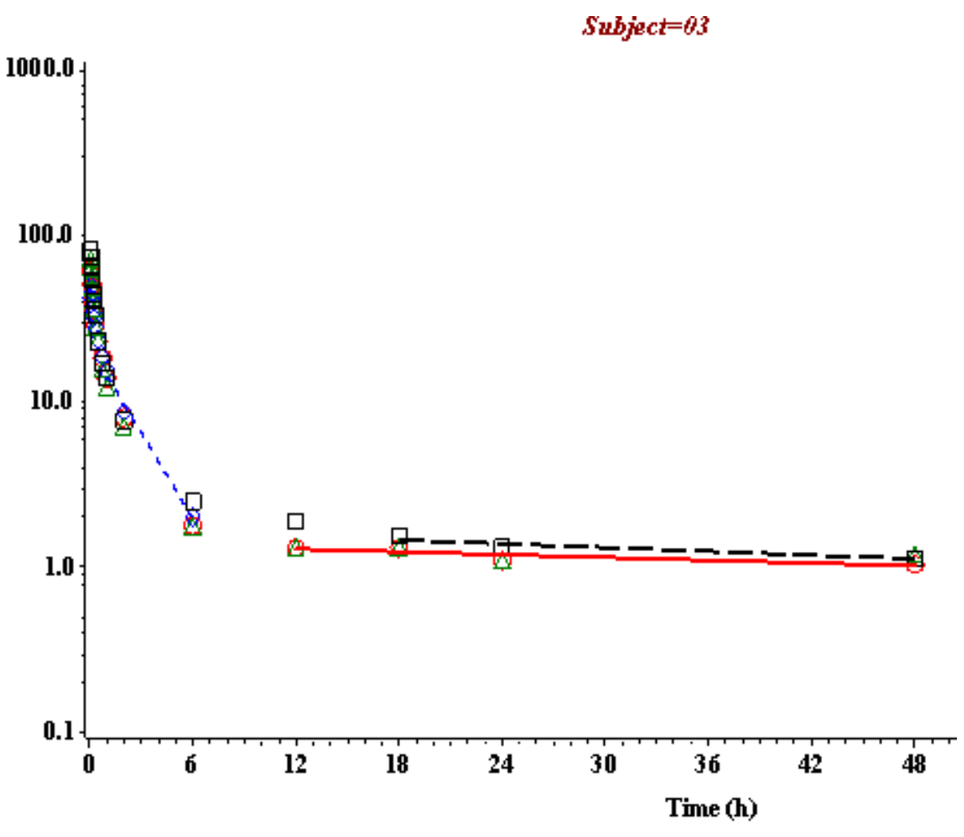
Why was the issue observed only for AUCt and AUCinf?

	GMean_N_ch	GMean_Ch	P_E	Lower_CI	Upper_CI	ISCV
AUC3min	2.52	2.05	103.50	87.32	122.67	20.0
AUC5min	5.83	4.70	105.26	89.21	124.19	19.5
AUC7min	8.97	7.13	107.60	91.55	126.48	19.0
AUC9min	11.52	9.12	108.81	92.89	127.45	18.6
AUC12min	14.59	11.59	109.18	93.49	127.50	18.2
AUC15min	16.99	13.54	109.43	93.77	127.70	18.2
AUC20min	20.15	16.11	109.67	94.00	127.96	18.1
AUC30min	24.90	20.00	110.23	94.53	128.53	18.1
AUC45min	29.96	24.27	110.50	95.02	128.50	17.7
AUC1	33.79	27.61	110.20	94.96	127.88	17.5
AUC2	44.29	36.71	110.20	95.28	127.45	17.1
AUC6	67.16	58.63	108.76	93.38	126.67	17.3
AUC12	80.46	76.93	108.11	90.73	128.81	17.8
AUC18	87.85	89.11	107.85	91.64	126.94	16.5
AUC24	102.85	100.09	107.83	92.40	125.84	15.7
AUC48	145.54	147.57	97.21	86.64	109.07	8.2
AUC72	186.13	196.95	108.61	94.78	124.45	7.6
AUCt	138.64	101.48	132.46	95.53	183.67	39.5
AUCinf	276.29	168.20	160.83	89.75	288.21	69.7
Cmax	104.85	84.32	106.98	91.06	125.67	19.0

Case study 5

- Insufficient LLOQ (**1 pg/ml** – sic!)
- Last quantifiable concentration time: 2.00 – 72.00 h (!)
  Start time for linear regression (TLIN): 0.75-24.00 h
- Substantial differences in parameters which are dependent on the elimination

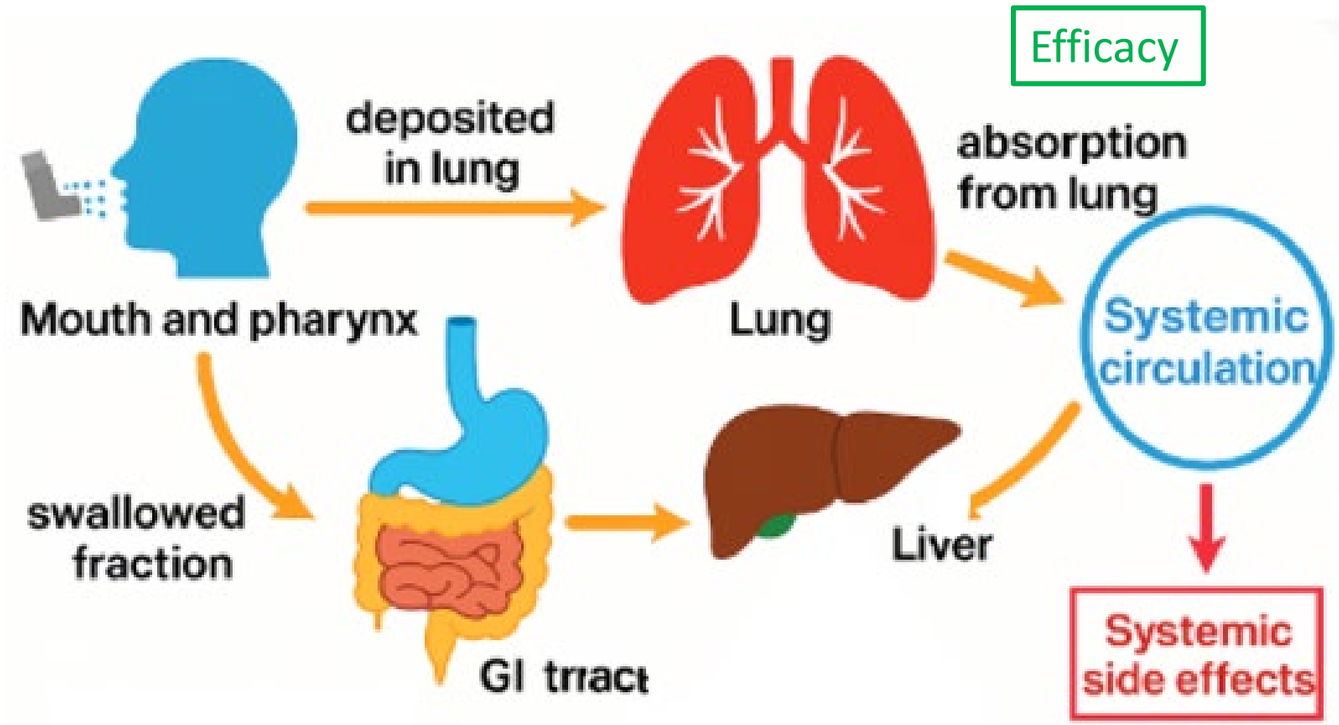




Lesson 3

LLOQ might determine 'to be or not to be' for your BE

Oral contribution concept



When **oral contribution** is **negligible (<5%)**

→ 1 study

- non-charcoal (total absorption - **safety** and **efficacy**)

When **oral contribution** is **not** negligible **(> 5%)**

→ 2 studies:

- non-charcoal (total absorption - **safety**) and
- **charcoal** (absorption only from lung - **efficacy**)

CPMP/EWP/4151/00 Rev. 2 guideline

Case study 6

- Comparison **charcoal (B) vs non-charcoal (A)** conditions for **the same batch** of the **Reference**
- ~ **12%** differences between arms
  – the **oral contribution is not negligible** (>5%)
- Both studies: non-charcoal and charcoal should be conducted with Test product

Parameter	*Trt*	*Geometric Least-squares Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*
AUC_t	**A**	171.419	**A vs B**	112.77	97.06 - 131.03
*(hr*pg/mL)*	**B**	152.003			
AUC_{inf}	**A**	185.270	**A vs B**	112.36	96.63 - 130.65
*(hr*pg/mL)*	**B**	164.891			

21

Case study 6

However…

This was a **model drug for charcoal biowaiver**
(has a proved **negligible oral contribution** due to a high first pass metabolism)

Intrinsic study variability
(study procedures, inhalation technique, minor time shifts, etc…) can easily exceed the 5% limit.

22

Case study 6

Intrinsic study variability

- **Study procedures** (including… **charcoal administration**!) can impact BE study result
- Subjects complained that **charcoal is unpleasant**, some of them dropped out of the study just before period with charcoal….

23

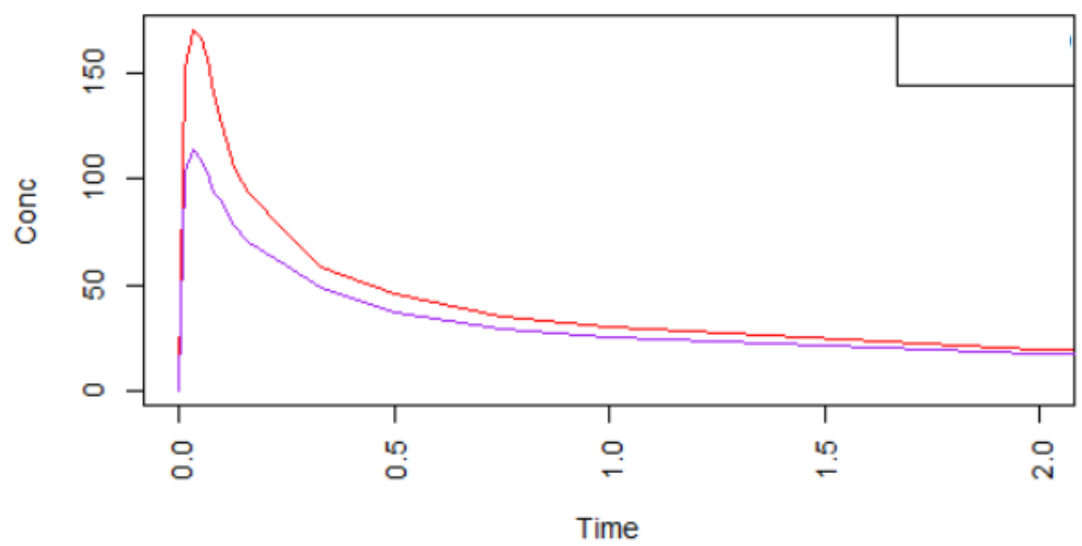
Lesson 4

The 5% limit in oral contribution is highly challenging, as such differences can arise from study variability or chance

Case study 7

- **Unsatisfied** study results especially in terms of Cmax
- 3rd study with the same drug – sampling scheme adjusted, subjects well trained, LLOQ sufficient
- What else could have gone wrong?

	N	GMean_	GMean_	P_E	Lower_CI	Upper_CI	ISCV
Cmax		147.47	110.15	128.46	97.2	169.78	45.3

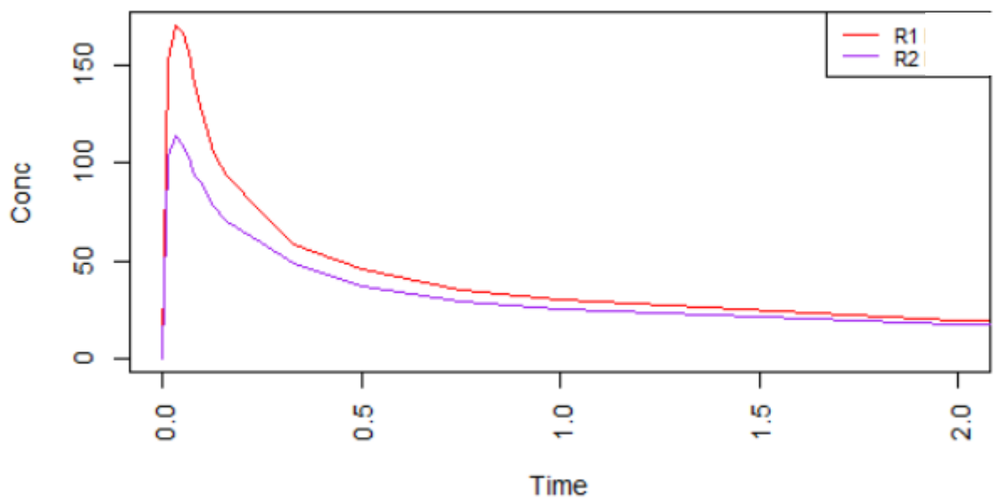


25

Case study 7

Surprisingly…

- **Two different batches** of the same Reference product
- Batch-to-batch variability is a very known phenomenon
- OIP guidelines: There may even be situations where it **may be difficult** to demonstrate BE between batches of the same reference product
- Therefore, the Ref biobatch should be **representative**



26

But…
what if those two batches had **almost the same *in vitro* characteristics?**

APSD profile

FPD

Expiry date

Reference	Relative FPD	Relative Delivered dose	Exp. Date
Ref Batch 1/ Ref Batch 2	0.99	1.02	03.2021 04.2021

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27

Lesson 5…
or maybe a rhetorical question:

Are BE criteria derived from solid oral dosage forms truly suitable by default for every OIP?

Important message

BE studies for OIPs are influenced by a wide range of factors, some of which **cannot be fully standardised**, such as:

- **Inhalation technique** and its period-to-period variability
- **Bioanalysis** method limitations (LLOQ)
- Ultra-rapid (<1 min) or variable **absorption** from lung
- **Study procedures** that can introduce variability
- Mock selection of Reference **biobatch**
- And many, many others….

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Final thought

BE studies for OIPs are far more
complex, risky, expensive and unpredictable
than those for oral dosage forms

The same BE criteria, vastly different challenges.

It’s more than just meeting numbers - it demands precision, expertise, knowledge, and…
a bit of luck.

30

The greater the obstacle, the more glory in overcoming it.

Molière