Detection of data manipulation in bioequivalence trials

BioBridges 2023

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Timeline

2014: Training for authorities, inspector for WHO, rumours about reinjected PK profiles under false subject ID often with interim analysis, sometimes with T and R swapped. This would make a BE study pass regardless of how badly matching the formulations are. Cannot be detected on site by inspectors.

2014/15: Started writing Buster and SaToWIB, software which detects the pattern that this practice will leave.

2015-2020: Software became popular with EU authorities for screening purposes.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 September 2016
EMA/633693/2016

EMA recommends suspension of medicines over flawed studies at Semler Research Centre

Bioequivalence studies performed at the site cannot be used to support medicines approval in the EU

U.S. FOOD & DRUG ADMINISTRATION

VIA E-MAIL AND UNITED PARCEL SERVICE

Mr. Umesh Mishra, CEO
Panexcell Clinical Lab Pvt. Ltd.
R-374, TTC MIDC, Rabale
Navi Mumbai, 400 701
INDIA

Dear Mr. Mishra:

This letter addresses significant objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your firm between November 18 and 22, 2019, by FDA personnel Lori Gioia; Amanda Lewin, Ph.D.; and Gajendiran Mahadevan, Ph.D., representing the FDA. In addition, based on significant objectionable conditions observed during the inspection, FDA's own data analyses, and other information, FDA issued a General Correspondence Letter to you on March 12, 2021 (referred to as "FDA's General Correspondence Letter"), requesting that you provide specific responses to those concerns indicating in FDA's assessment that you created falsified data, which you then submitted to FDA. This letter also addresses your April 12, 2021, response to FDA's General Correspondence Letter.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 November 2022
EMA/915838/2022

Synchron Research Service: re-examination confirms suspension of medicines over flawed studies

On 15 September 2022, EMA's human medicines committee (CHMP) confirmed its recommendation to suspend the marketing authorisations of several generic medicines tested by Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, India. This concludes the re-examination requested by the marketing authorisation holders for some of the medicines concerned.

The CHMP adopted its initial recommendation in May 2022, after irregularities were found in how the CRO carried out bioequivalence studies, which raised serious concerns about the company's quality management system and the reliability of data from that site. Bioequivalence studies are conducted to show that a generic medicine releases the same amount of active substance in the body as the reference medicine. The CHMP concluded that for the majority of the medicines investigated no adequate bioequivalence data were available from other sources and therefore recommended that they be suspended. For a small number of authorised generic medicines, adequate bioequivalence data were available from other sources, and these medicines were allowed to remain on the EU market.

Publication after intense discussions with regulators

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Detection of data manipulation in bioequivalence trials

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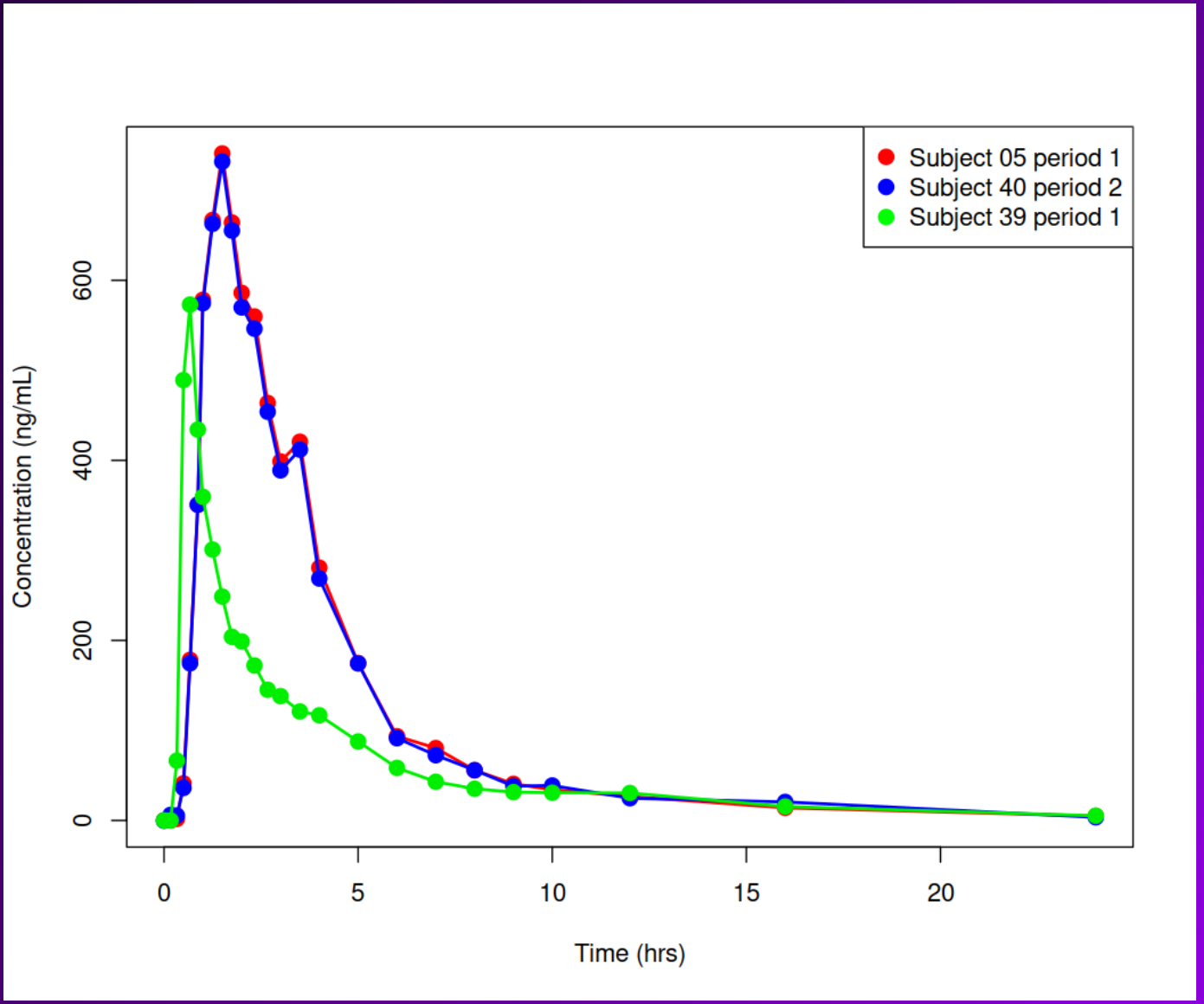
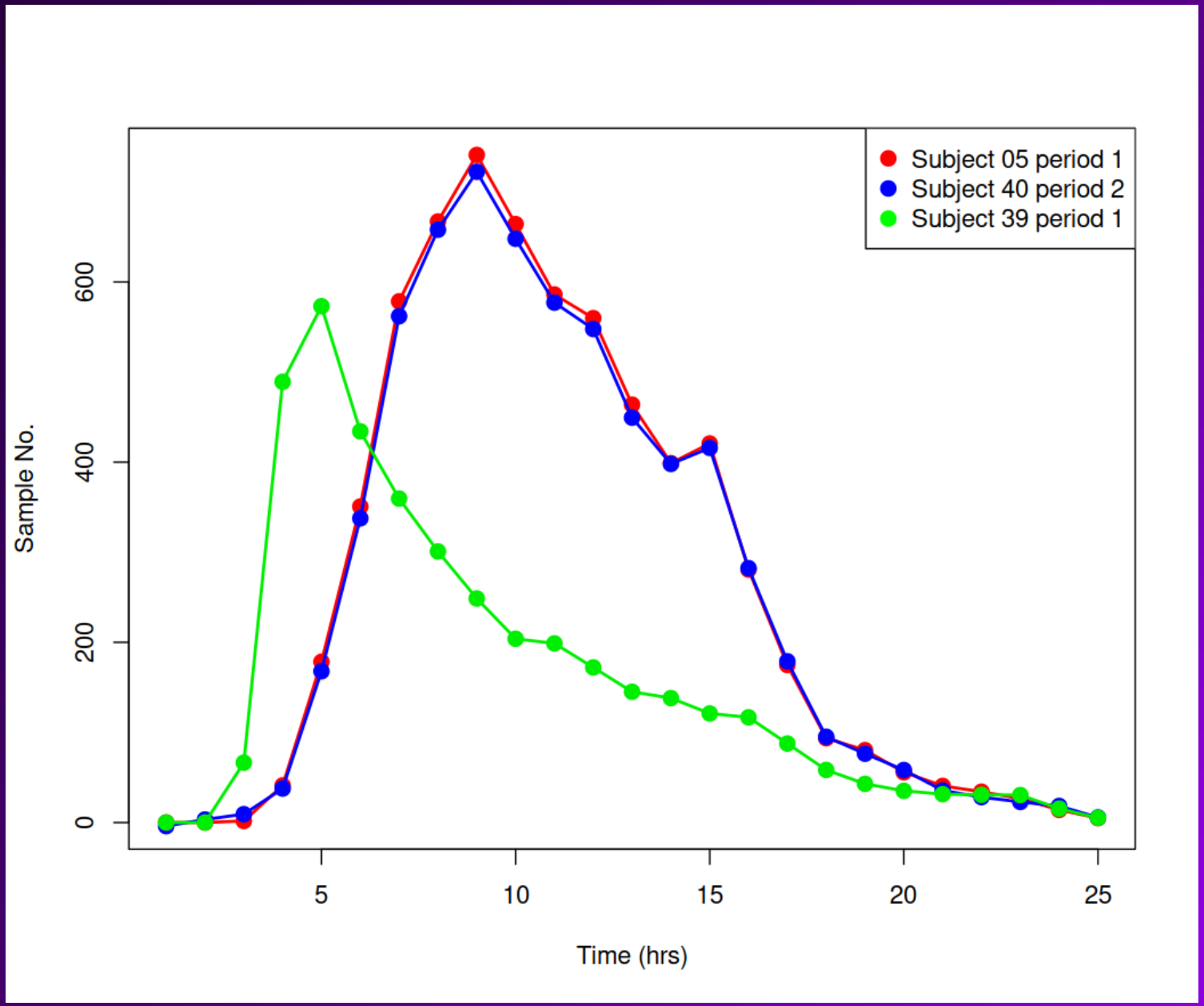
ABSTRACT

In recent years regulators have documented how pharmaceutical companies or clinical research organisation can manipulate bioequivalence trial data for non-approvable formulations by performing an interim analysis followed by re-analysis of pharmacokinetic profiles under new subject aliases, with a switch of Test and Reference and/or dilutions. The net effect is that point estimates for failing products will be forced artifically towards 1 and that trials will pass the test for bioequivalence. This is not detectable by any pharmacopoeial method, and is not addressed by common assessment practices at agencies. This paper aims at demonstrating how the signals of such fraudulent study conduct can be detected. The approaches presented are called "Buster" and "SaToWIB" routines; these are computer programs that have been used extensively by regulators to detect signals of fraud but they have not been described in the public domain.

The idea, SaToWIB (actual fraud case)

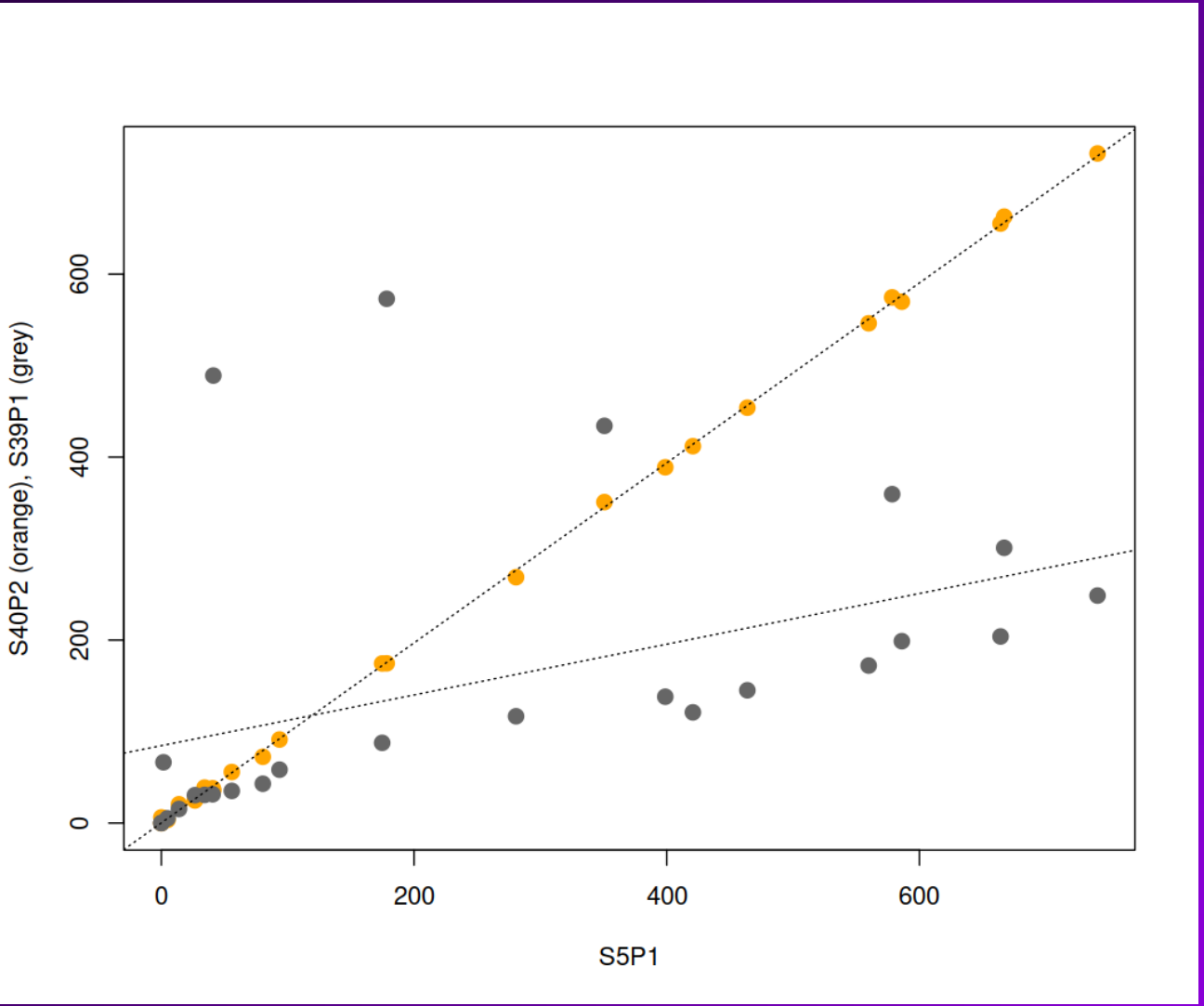



Subject 05 period 1
Subject 40 period 2
Subject 39 period 1
Sample No.
0
200
400
600
5
10
15
20
25
Time (hrs)

Linear regression on concentrations

Note: Slope indicates the dilution (ratio),

1-r^2 indicates the degree of match



SaToWIB in a nutshell

1. Compare all PK-profiles against each other
2. Use a comparison score such as linear regression ($1-r^2$) or method 32 (see EJPS)
3. Sort the list so that best matches come first.
4. Voilá – there's your list of best candidates of reinjected profiles.
5. Inspect, judge, graph, form an opinion.

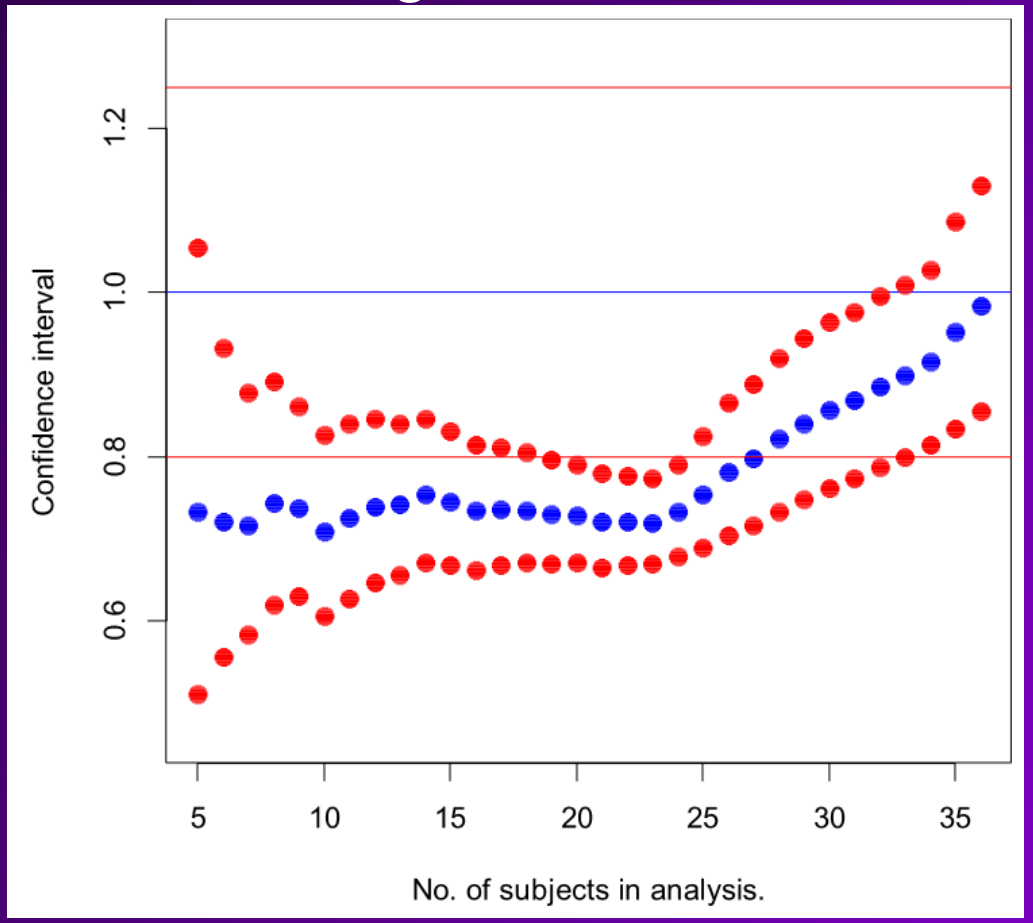
The sorted list

Profile1	Profile2	Score	Rank	Ratio
S18P1	S27P2	0.03891	1	0.9561
S21P1	S28P2	0.03990	2	1.0051
S5P1	S25P2	0.04041	3	0.9901
S2P2	S33P2	0.04182	4	0.9639
S9P2	S30P1	0.04187	5	1.0264
S4P1	S26P2	0.04239	6	1.0189
S2P1	S33P1	0.04487	7	1.0273
S15P2	S34P1	0.04557	8	1.0024
S7P2	S31P1	0.04609	9	1.0282
S10P1	S35P1	0.04671	10	2.0087
S23P2	S36P1	0.04716	11	0.9593
S19P2	S29P2	0.04827	12	1.0492
S21P2	S28P1	0.04924	13	1.0083
S19P1	S29P1	0.04966	14	1.0107
S7P1	S31P2	0.05015	15	0.9962

Threshold?
Validation?

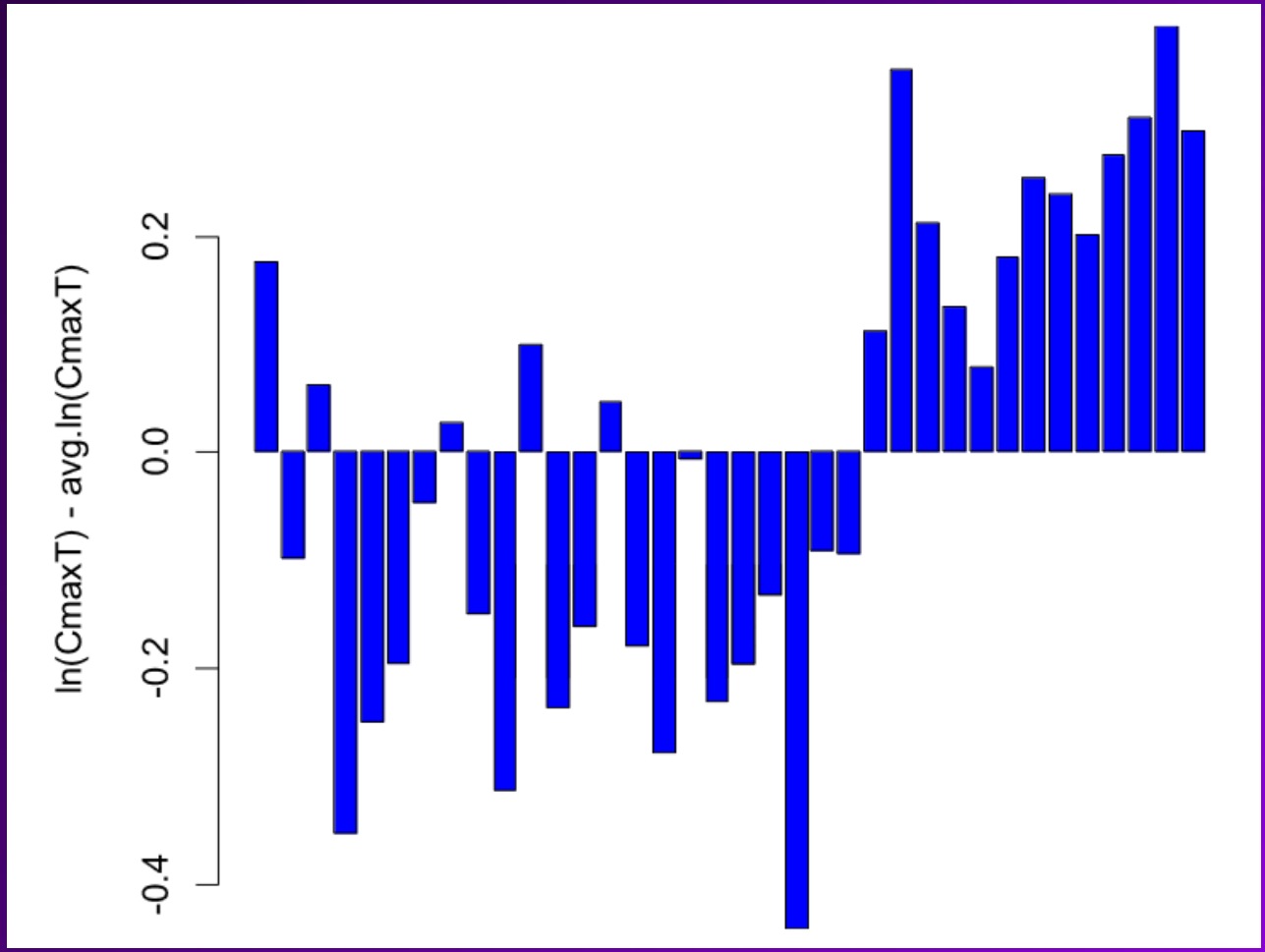
Buster

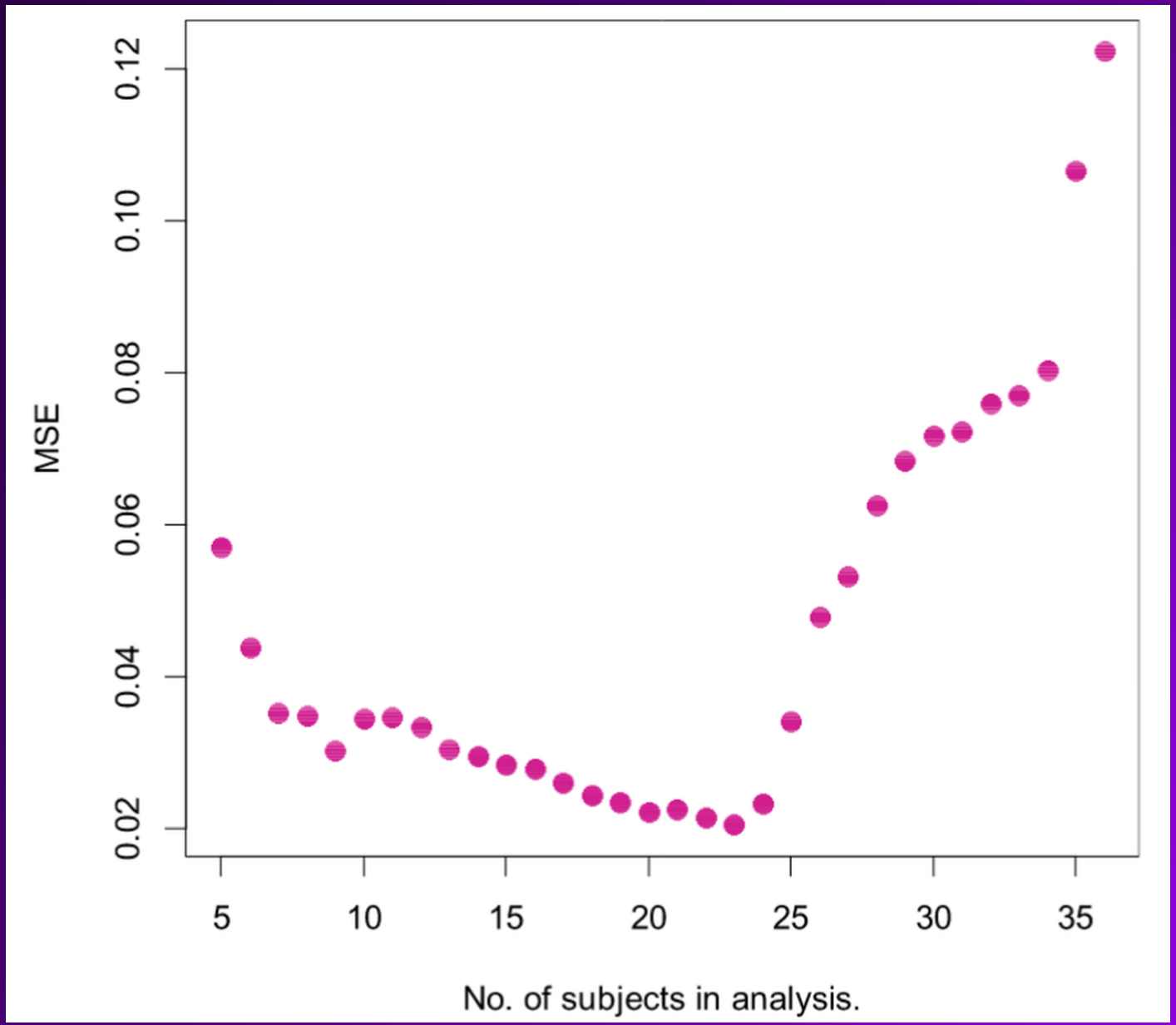
If there is interim analysis, followed by profile reinjection to “correct” a deviant point estimate then there may be a trend in e.g. the cumulative CI.



Note:
Chronology

And there will be signals in residuals, T or R levels etc.




MSE
0.02
0.04
0.06
0.08
0.10
0.12
5
10
15
20
25
30
35
No. of subjects in analysis.

But one big issue is

When is a trend in Buster significant?
When is a match in SaToWIB significant?

Bear in mind the bioanalytical A+P varies from CRO to CRO, and within and between runs, and may vary with concentration.

Tried to initiate collaborations with regulators, but got no answers.

Two months ago

NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Spain:

Details on the draft list of products concerned (pending applications and authorised medicinal products) are annexed to this notification.

The Spanish Agency of Medicines and Medical Devices (AEMPS) has conducted a GCP inspection of the bioequivalence (BE) facilities in Synapse Labs Pvt. Ltd., a contract research organisation (CRO) located at Majestic Plaza, S. No. 21/5, Nr. Nyati Empire, Kharadi-Mundhwa Bypass, Kharadi, Pune – 411014, Maharashtra (India) and Krushna Complex, Kharadi-Mundhwa Bypass, Kharadi, Pune-411014, India).

The findings reported during the inspection cast serious doubts on the validity and reliability of the data of BE studies (clinical and bioanalytical part) conducted at the CRO. The inspection examined [redacted] studies over the 2009 - 2019 period and Synapse quality management system (QMS) over the 2009-2023 period. Five (05) critical findings (CF) and one (01) major finding were identified:

- The CRO failed to demonstrate the adequacy of the Computerized Systems/Bioanalysis and Data Management to ensure bioanalytical and clinical data integrity. Overall, up to 2023, the CRO lacked robust QMS measures, procedures and control over the data integrity of the data generated (4 CF).
- Significant pharmacokinetics anomalies were observed in over 20 studies conducted from 2013 to 2018 (i.e. multiple pairs of subjects with overlapping plasma time-concentration profiles). This fact, in absence of other acceptable justification would be considered coherent with profile duplication (1 CF).

360 pages of pure nightmare

The marketing authorisation holders (MAHs) and applicants are invited to comment on the impact of the above on their marketing authorisation(s) or application(s). Demonstration of bioequivalence to the EU reference medicinal product (RMP) is a requirement of Article 10 of Directive 2001/83/EC, MAHs and applicants are therefore requested to provide evidence of bioequivalence (e.g. bioequivalence trials) with the EU reference medicinal product, in order to demonstrate a positive benefit-risk balance of the concerned medicinal products.

Some companies book new slots for repeat trials.

Some companies do nothing.

Some companies use Buster/SaToWIB analyses to argue absence/presence of overlapping profiles.

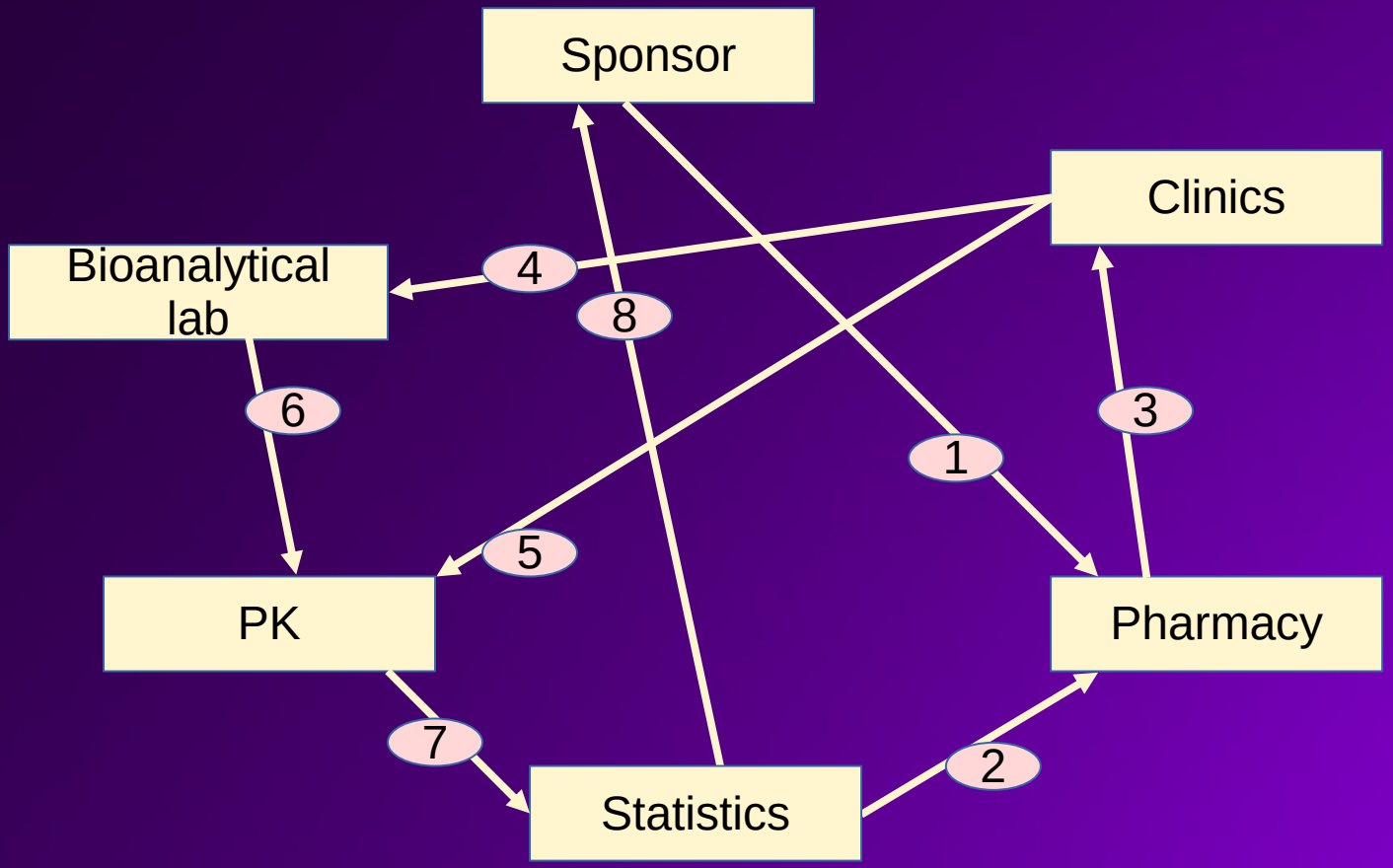
All this can be detected prior to submission. So why didn’t we learn the lesson?

Monitoring (clinical) is mandatory and everybody seems to be monitoring dosing. But why not do a check on PK data prior to submission?

cLEAN? Not mandatory = not done.

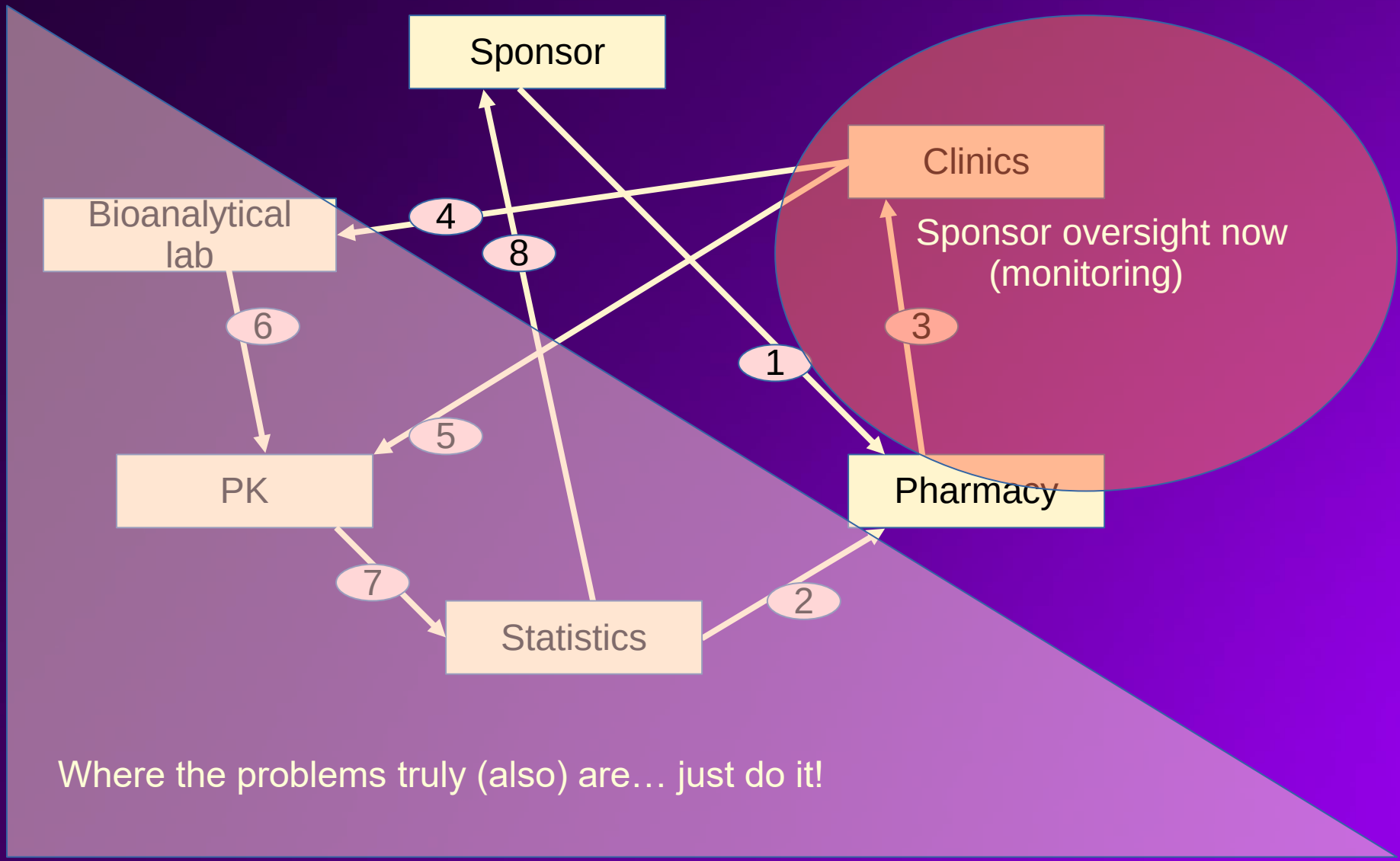
Flow in BE, common themes

Local variations exist



1. IMP
2. Rand. code
3. Labeled IMP
4. Plasma
5. TPDs
6. Blinded PK data
7. Blinded NCA outcome
8. Results

Oversight … where?



Where the problems truly (also) are… just do it!

Bioanalytical data = result tables

Index	Sample Name	Sample Type	Acquisition Date	File Name	Analyte Pea	Analyte Cc	Area Ratio	IS Peak Area	Use Record	Record Mod	Calculate	Accuracy (%)
1	Std Blank 1	Double Blank	08/08/18 12:00 AM	AbxD01.wiff	0	0	#DIV/0!	0		0	N/A	N/A
2	Std Zero	Blank	08/08/18 12:04 AM	AbxD02.wiff	0	0	0	122415		0	N/A	N/A
3	ESCIT_J8_STD1	Standard	08/08/18 12:08 AM	AbxD03.wiff	6531	0.2	0.04941	127054	1	0	0.206	103.00
4	ESCIT_J8_STD2	Standard	08/08/18 12:13 AM	AbxD04.wiff	13461	0.4	0.10864	131738	1	0	0.383	95.75
5	ESCIT_J8_STD3	Standard	08/08/18 12:17 AM	AbxD05.wiff	32009	1	0.28494	123500	1	0	0.9304	93.04
6	ESCIT_J8_STD4	Standard	08/08/18 12:22 AM	AbxD06.wiff	66391	2	0.58194	118239	1	0	1.9842	99.21
7	ESCIT_J8_STD5	Standard	08/08/18 12:26 AM	AbxD07.wiff	149472	4	1.02724	115485	1	0	4.5388	113.47
8	ESCIT_J8_STD6	Standard	08/08/18 12:31 AM	AbxD08.wiff	257203	8	2.32261	115887	1	0	7.7638	97.05
9	ESCIT_J8_STD7	Standard	08/08/18 12:35 AM	AbxD09.wiff	527641	16	4.64908	118193	1	0	15.589	97.43
10	ESCIT_J8_STD8	Standard	08/08/18 12:40 AM	AbxD010.wiff	771933	20	5.69453	133365	1	0	20.204	101.02
11	Std Zero 2	Double Blank	08/08/18 12:44 AM	AbxD010.wiff	0	0	#DIV/0!	0		0	N/A	N/A
11	ESCIT_J8_S18_P1_Smpl001	Unknown	08/08/18 12:49 AM	AbxD011.wiff	0	N/A	0	137860		0	No Peak	N/A
12	ESCIT_J8_S18_P1_Smpl002	Unknown	08/08/18 12:53 AM	AbxD012.wiff	0	N/A	0	136714		0	No Peak	N/A
13	ESCIT_J8_S18_P1_Smpl003	Unknown	08/08/18 12:58 AM	AbxD013.wiff	0	N/A	0	129496		0	No Peak	N/A
14	ESCIT_J8_S18_QCLOW	Quality Control	08/08/18 01:02 AM	AbxD014.wiff	21082	0.6	0.16897	121368	1	0	0.6324	105.40
15	ESCIT_J8_S18_QCHIGH	Quality Control	08/08/18 01:06 AM	AbxD015.wiff	519390	16	2.66063	123000	1	0	14.747	92.17
16	ESCIT_J8_S18_P1_Smpl004	Unknown	08/08/18 01:11 AM	AbxD016.wiff	107864	N/A	1.26546	113762		0	2.223	N/A
17	ESCIT_J8_S18_P1_Smpl005	Unknown	08/08/18 01:15 AM	AbxD017.wiff	17121	N/A	0.19965	136356		0	0.362	N/A
18	ESCIT_J8_S18_P1_Smpl006	Unknown	08/08/18 01:20 AM	AbxD018.wiff	52687	N/A	0.58804	128992		0	1.04	N/A
19	ESCIT_J8_S18_P1_Smpl007	Unknown	08/08/18 01:24 AM	AbxD019.wiff	144870	N/A	1.8125	133475		0	3.177	N/A
20	ESCIT_J8_S18_P1_Smpl008	Unknown	08/08/18 01:29 AM	AbxD020.wiff	154405	N/A	1.84175	134430		0	3.228	N/A

Screening proposal

1. Process chromatographic data: Assess run pass criteria, standard curve, re-calculation of PK values by subject, period, time.
= A list of concentrations by subject, time, period.
2. Verify concentrations against reported concentrations.
3. Verify NCA (Cmax and AUC by subject, period, treatment, sequence)
4. Run Buster and SaToWIB.

Outcomes, examples

1. No Buster trends, no profiles matches.
2. Clear Buster profiles, pairwise SaToWIB matches with T and R swapped = “The switch”.
3. No Buster trends but occasional (few) SaToWIB matches.

Ad 3: Remove the (last) duplicates and re-run stats to decide if the study justifies a repeat trial.

New flavours of trouble

Needs no randomisation code: Switch T and R for half the subjects at random. A very high probability of success as the expected PE is 1. You will see an elevated MSE (CV) as compared to non-manipulates studies (but you have nothing to compare with). SaToWIB and Buster will be clean.

New flavours of trouble

Re-use profiles across studies for different sponsors. Especially straightforward when the number of samples per period is the same. SaToWIB and Buster are clean.

I have unfortunately seen this happen! Sponsors will not realise it.

Screening for this may require centralised trial data repositories (agencies!).

Concluding remarks

I heard this all too often:

“It is unacceptable to cheat.”

“Regardless of how much we regulate there will always be cheaters.”

It is a recurring issue. Waiting for guidance that will make the issues go away is a problem, not a solution.

“Insanity is doing the same thing over and over, but expecting a different result.” (Attributed to A. Einstein)

Options exist for the industry. Screening with Buster / SaToWIB-esque tools is not difficult. Give me a good reason not to do it.

Thank you.

Thanks to: Olivier Le Blaye, Stephanie Croft, Helmut Schütz, Isabella Berger and many others.

Please get in touch.

anfu@fuglsangpharma.com