ANALYTICAL DATA INTEGRITY: LOOKING BEYOND THE OBVIOUS

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Disclaimer

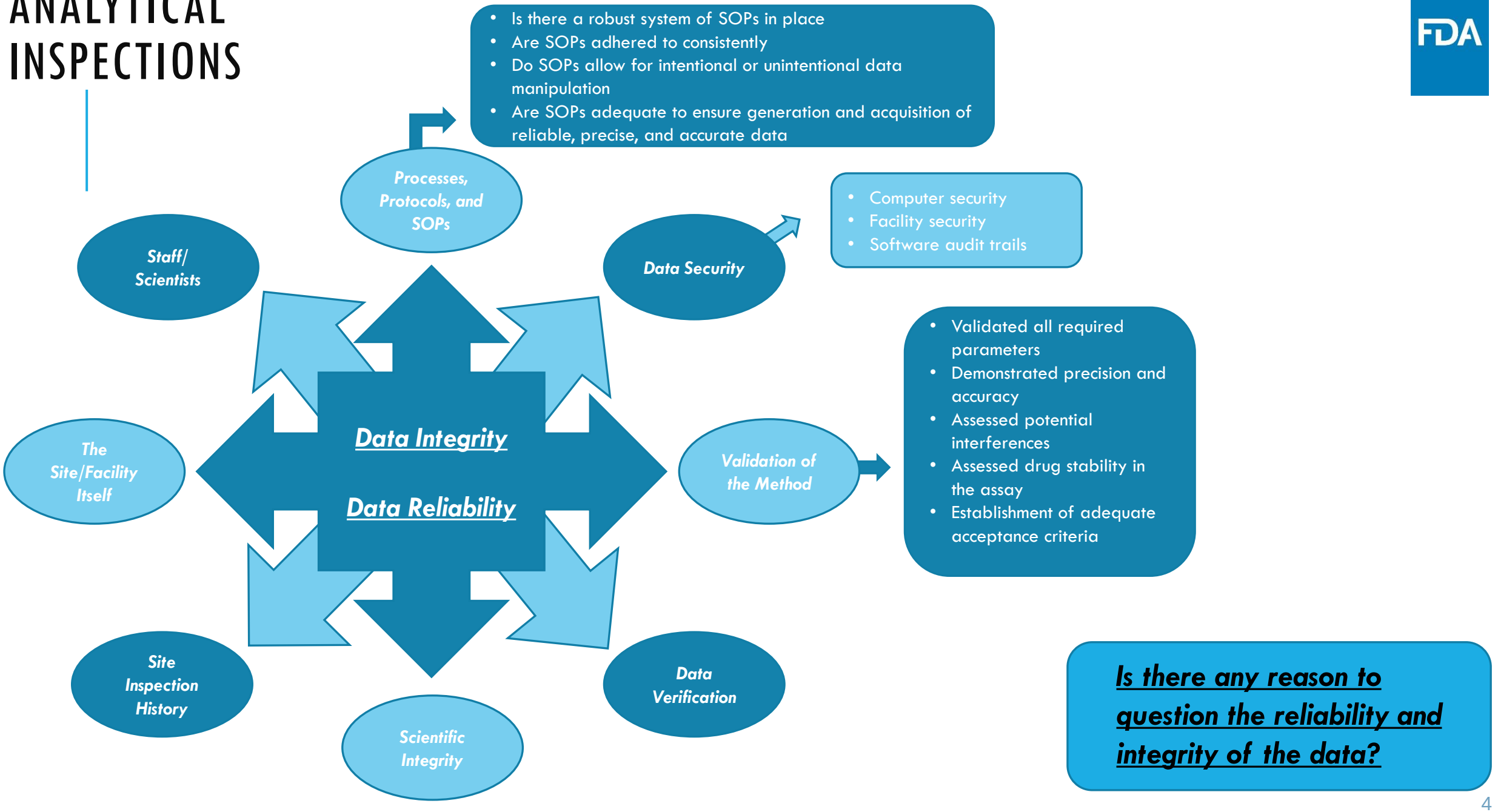
The opinions and information in this presentation are those of the author, and do not necessarily represent the views and/or policies of the U.S. Food and Drug Administration.

All data in this presentation are modified, and were crafted specifically as example scenarios

LEARNING OBJECTIVES

- What We Do: Overview of Analytical Inspections
- What We Look For: Identifying Potential Data Integrity Issues
- What We Find: Some Examples
  - PK and Concentration Anomalies in Bioequivalence Studies
  - "Outlier" Exclusion and Run Failure in P&A Assessments
  - Chromatography
  - Audit Trails/Software Security

ANALYTICAL INSPECTIONS



- Is there a robust system of SOPs in place
- Are SOPs adhered to consistently
- Do SOPs allow for intentional or unintentional data manipulation
- Are SOPs adequate to ensure generation and acquisition of reliable, precise, and accurate data

- Computer security
- Facility security
- Software audit trails

- Validated all required parameters
- Demonstrated precision and accuracy
- Assessed potential interferences
- Assessed drug stability in the assay
- Establishment of adequate acceptance criteria

Is there any reason to question the reliability and integrity of the data?

PK AND CONCENTRATION ANOMALIES IN BIOEQUIVALENCE (BE) STUDIES

PK AND CONCENTRATION ANOMALIES IN BE STUDIES

- **Prior to inspections, submitted bioanalytical data is reviewed**
- **If potential data anomalies in a study prior to the inspection are identified……**
- **Goal onsite: investigate to verify/resolve potential anomalies**

During the inspection, we ask the firm to provide us with the following information:

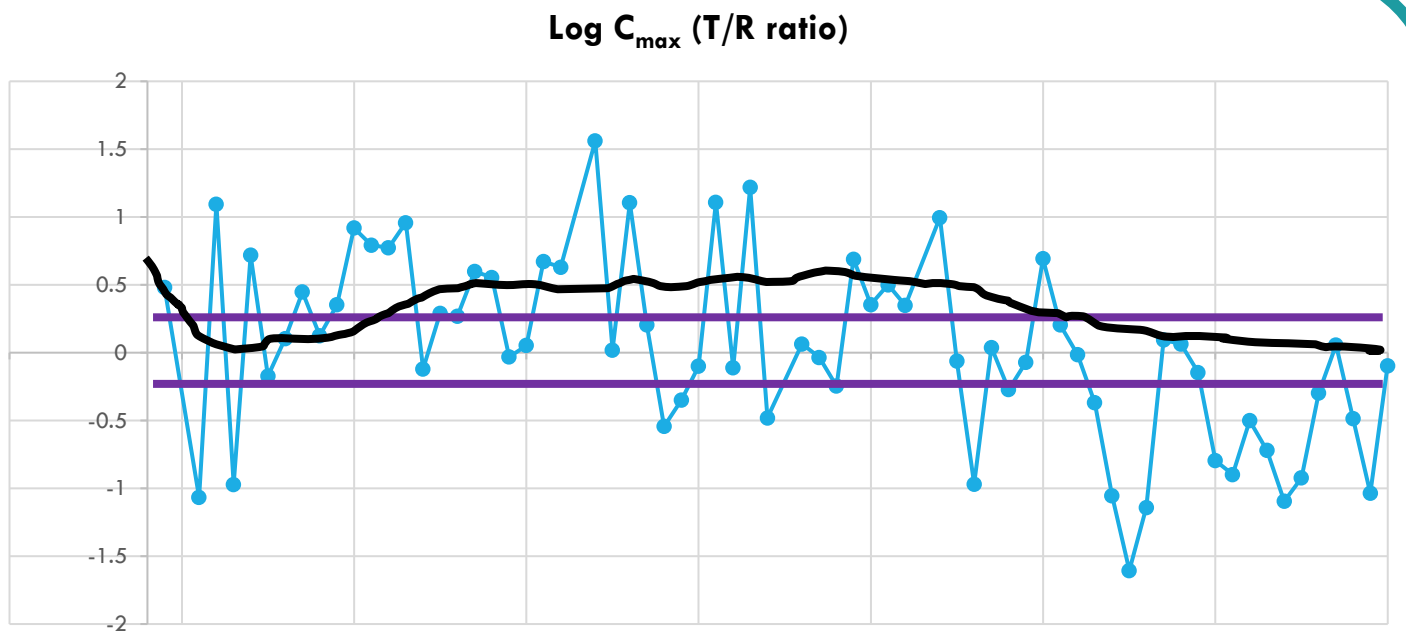
1) ***Full PK data analysis using all subjects***
2) ***Concentration profiles for all subjects***

PK AND CONCENTRATION ANOMALIES IN BE STUDIES

1) **For potential PK anomalies: look at the distribution of the T/R ratio**

- **The T/R ratio of the C_{max} trended above the acceptable BE range prior to the midpoint of the study**
- **Distinct downward trend of the T/R ratio of the C_{max} after the midpoint of the study**

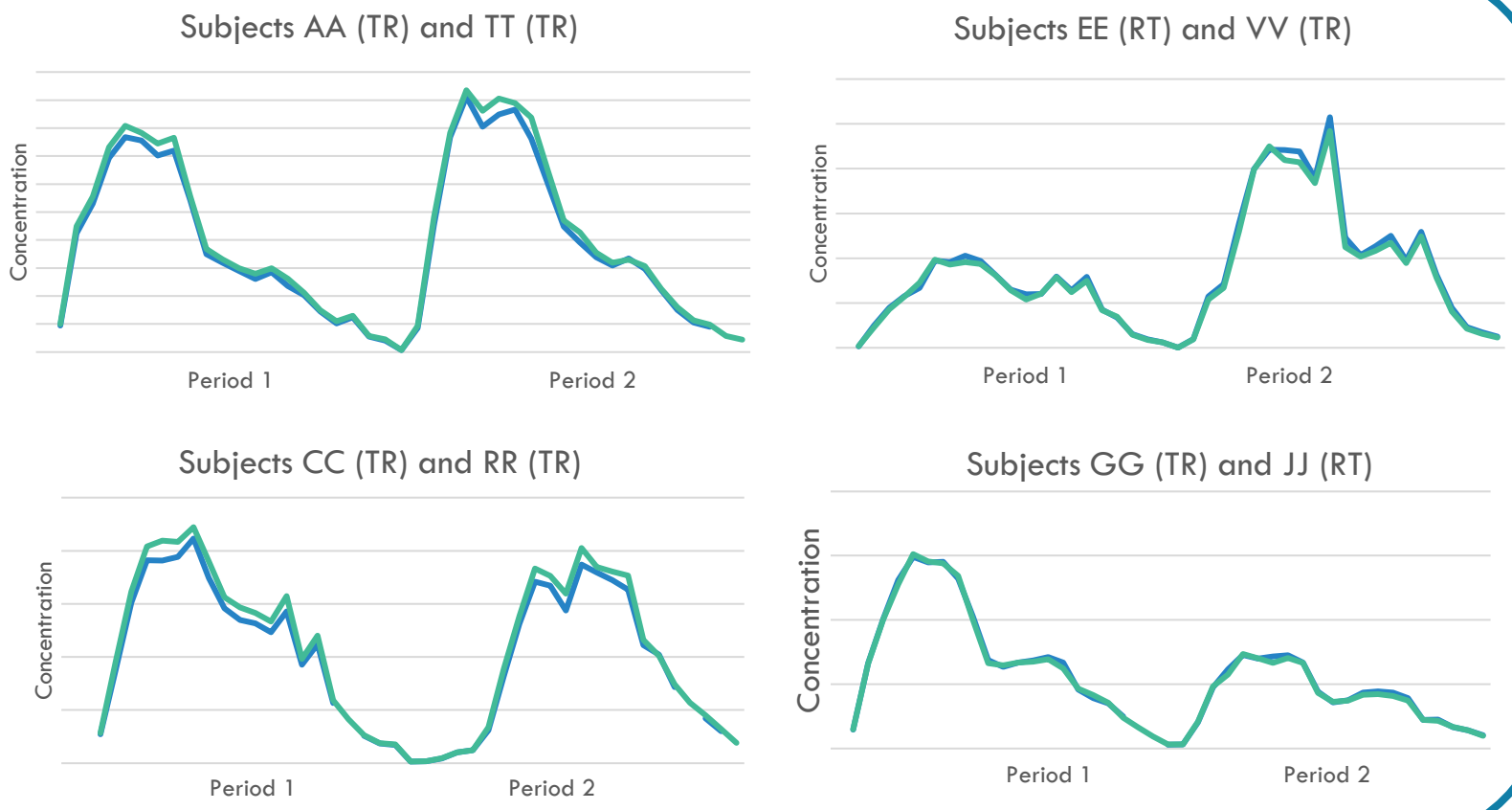
- **Final T/R ratio = 1.03**



Ratio	Lower Limit	Upper Limit	Decision
1.03	0.9	1.2	Equivalent

PK AND CONCENTRATION ANOMALIES IN BE STUDIES

2) Overlapping or nearly overlapping concentration profiles between subjects; not expected in a randomized study population



Just one subject pair? Could be a coincidence!!

18 subject pairs???

Is there documentation to explain the anomalies? (e.g., accidental switching of tubes)

Is there documentation to indicate intent to alter results?

PK AND CONCENTRATION ANOMALIES IN BE STUDIES

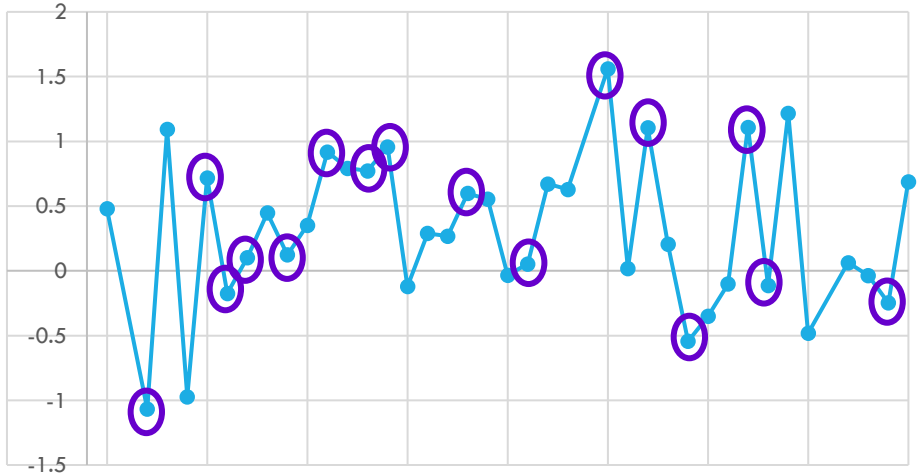
- **Are PK and concentration anomalies related?**

- **Group 1 – ratio of 1.4**
- **Group 2– ratio of 0.7**

} *Partition into two distinct populations*

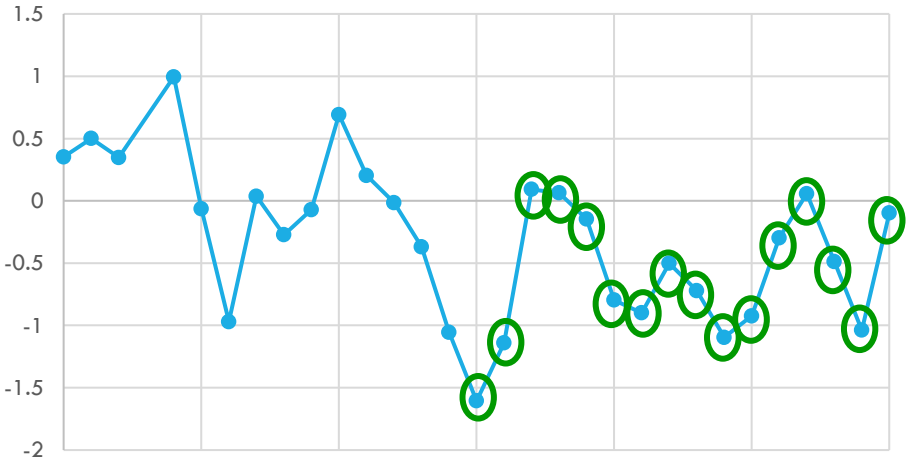
- **Entire study – ratio of 1.03**

Group 1



Ratio	Lower Limit	Upper Limit	Decision
1.4	1.2	1.6	Not Equivalent

Group 2



Ratio	Lower Limit	Upper Limit	Decision
0.7	0.5	0.9	Not Equivalent

PK AND CONCENTRATION ANOMALIES IN BE STUDIES

1. PK results: would not expect such marked differences between groups from a random population
2. Overlapping subject concentration profiles: not expected from a random population
3. Data found on site: confirm unintentional error; verify intent to alter data

What can you do?

- Look for anomalous trends in your data
- Understand what is physiologically improbable
- Understand the characteristics of your drug – what is expected in a random population?
- Look at the data as a whole – ask if it makes sense!

“OUTLIER” EXCLUSION AND “RUN FAILURE” IN P&A ASSESSMENTS

DATA INTEGRITY AND PRECISION AND ACCURACY

Exclusion of "outliers" from P&A data:

Language in SOPs allowing for exclusion of a specific number of outliers

If not a true, documented error (e.g., double pipetting) are you negating true inherent assay variability?

In this example, 135 was excluded as an outlier

Note: with 135 included, ***intra-assay precision meets acceptance criteria*** for the LPC (10.5%)

However: the precision of %inhibition fails (25.5%)

Thus: 135 was excluded; all precision is met

Food for thought: if precision of the LPC meets acceptance criteria with 135 included, is it a true outlier, or just inherent variability in a plate-based assay?

More food for thought: The ***inter-assay*** precision for %inhibition of the LPC was ***unacceptable***, even with exclusion of this "outlier"

	LPC	I-LPC	%inhibition
	105	76	28
	107	78	27
	109	86	21
	135	79	41
	106	78	26
	106	81	24
Mean	111	80	28
SD	11.7	3.5	7.1
%CV	***10.5***	4.4	***25.5***
	LPC	**I-LPC**	**%inhibition**
	105	76	28
	107	78	27
	109	86	21
		79	
	106	78	26
	106	81	24
Mean	107	80	25
SD	1.5	3.5	2.8
%CV	***1.4***	4.4	***10.9***

DATA INTEGRITY AND PRECISION AND ACCURACY

Exclusion of P&A data:
This run "failed" intra-run P&A; unacceptable precision of the LQC

- Calibration curve was acceptable
- No documented errors
- No equipment malfunctions

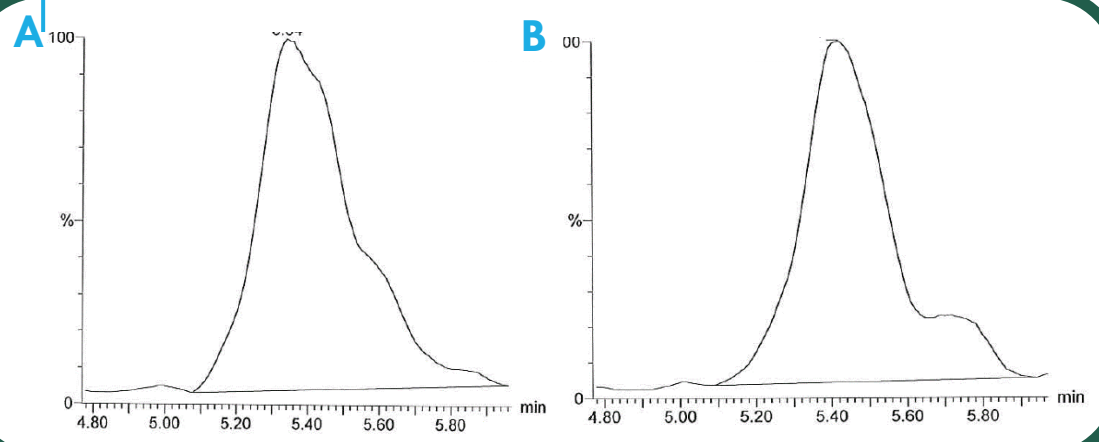
Excluded from ***inter-run*** P&A statistics
No justification
Skews the true P&A of the assay

	LLOQ	LQC	MQC	HQC
	0.05	0.14	1.9	22
	0.04	0.1	1.9	22
	0.05	0.16	2	22
	0.05	0.14	1.9	22
	0.05	0.16	1.8	23
	0.05	0.12	1.9	23
Mean	0.05	0.14	1.9	22
SD	0.004	0.02	0.06	0.5
%CV	8.4	***17.1***	3.33	2.31
%Accuracy	96.7	91.1	95	93.1

Ask yourself these questions…..
Is the data being excluded falsely skewing results or negating inherent variability?
Does excluding data alter the integrity of the true P&A results?

CHROMATOGRAPHY

DATA INTEGRITY AND CHROMATOGRAMS



More concerning:

When all samples labeled poor chromatography are C_{max} samples

When repeat analysis results look like this…….

- ***Repeat value is ~3-fold higher than original***
- ***Multiple samples affected***
- ***T/R ratios changed***

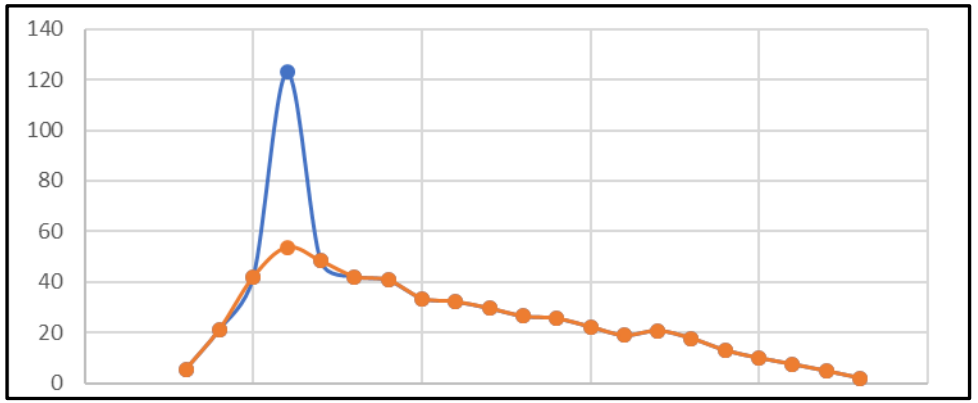
Poor Chromatography:

Do you know which of these two samples was labeled as poor chromatography? A or B or both?

Sample B

The firm could not confirm why Sample B was considered poor chromatography, but Sample A was not

Apply objective, consistent criteria for chromatography
If you show 5 analysts a chromatogram, will they all agree?



AUDIT TRAILS AND SOFTWARE SECURITY

DATA INTEGRITY AND AUDIT TRAILS

25-12-2019 04:04:42	Security	N/A	Unsuccessful user login attempt as
25-12-2019 04:04:34	Security	N/A	Unsuccessful user login attempt as
25-12-2019 04:04:34	Security	N/A	3 login failures! Notification sent to responsible person
25-12-2019 04:04:28	Security	N/A	Unsuccessful user login attempt as
25-12-2019 04:04:21	Security	N/A	Unsuccessful user login attempt as
25-12-2019 03:31:31	Security	N/A	User successfully logged out
25-12-2019 03:19:46	Security	N/A	User successfully logged in
25-12-2019 03:19:36	Security	N/A	Unsuccessful user login attempt as
25-12-2019 03:19:36	Security	N/A	3 login failures! Notification sent to responsible person
25-12-2019 03:19:29	Security	N/A	Unsuccessful user login attempt as
25-12-2019 03:19:22	Security	N/A	Unsuccessful user login attempt as

Multiple failed login attempts:

1. 7 failed login attempts within 1 hour
2. This notification is a default setting in Analyst
   a) *No notification if not configured*
3. However, Analyst CAN be configured to alert management when there are multiple failed login attempts
4. Management should be aware of/monitor this type of activity

Record #	Date and Time	Module	Change Reason	Change Description	ESig
160	6/15/2017 9:31:58 AM	Results table - Saved	N / A	_run03.rdb" was saved	No
139	6/14/2017 9:19:44 AM	Results table - Saved	N / A	_run03.rdb" was saved	No
138	6/14/2017 9:19:03 AM	Results table - Saved	N / A	_run03.rdb" was saved	No
137	6/14/2017 9:17:45 AM	Results table - Saved	N / A	_run03.rdb" was saved	No
122	6/14/2017 9:00:38 AM	Results table - Saved new table	N / A	_run03.rdb" was	No

Overwriting results tables after re-integration:

1. Results were saved 4 times after the initial integration; original integrations were not saved or printed; no record of results
2. Analyst can be configured to prevent overwriting of data; requires use of new filename
3. Also, note that no change reasons or E-signatures were required
4. Understand how to configure Analyst/other software for the most security/data integrity

The integration parameters for peak 1" for "SE-blank-male-1"

changed: Area threshold changed from "350.00" cps to "400.00" cps. Area changed from "1262" to "0" counts (100% decrease).

Using "unknowns" to optimize integration parameters:

1. Area threshold change reduced the peak area of an unknown selectivity sample to zero
2. Manipulation of data to make a validation parameter meet acceptance criteria

KNOWLEDGE CHECK #1:

Which of the following statements is not true?

A. *In a randomized population, study subjects would be expected to have nearly identical or overlapping profiles*

B. *Values can be excluded from precision and accuracy statistics if there is a contemporaneously documented technical error*

C. *Audit trails are an integral part of ensuring the integrity of bioanalytical data*

D. *Clear, objective criteria for identifying poor chromatography should be provided in an SOP*

A

In a randomized population, study subjects would <u>NOT</u> be expected to have nearly identical or overlapping profiles

KNOWLEDGE CHECK #2:

Which of the following data anomalies could indicate a data integrity issue?

A. Saving a results table multiple times using the same file name

B. Inclusion of all data values in precision and accuracy statistics, even when one or two look weird

C. The presence of two distinct PK populations within a random subject population

D. Multiple system login failures with no acknowledgement or actions by firm management

A, C, and D

The situations in A, C, and D would be red flags; warrant further investigation

SUMMARY

- The presence of PK anomalies, particularly when they are not reflective of normal physiological responses, may indicate a data integrity issue
- Exclusion of data from P&A evaluation should be the exception, not the rule
- Should be justified with clear, objective criteria
- ALL P&A data should be reported, even if excluded
- Characterization of samples having poor chromatography should be based on clear, objective criteria
- Understand the software being used and optimize security and audit trails to ensure data integrity

THANK YOU!!!