

PARALLELISM ACCEPTANCE CRITERIA: DRIVEN BY CONTEXT OF USE

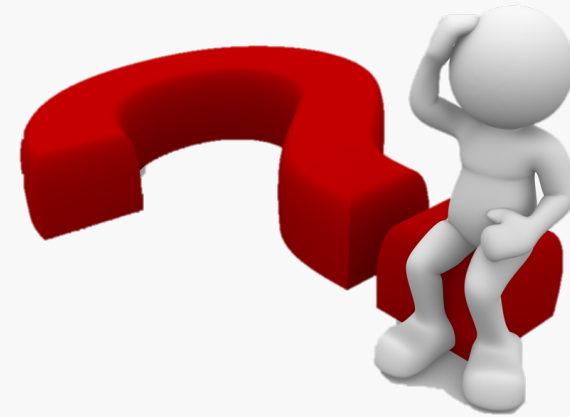
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16th Sept 2020

EVERY STEP OF THE WAY

Session Description and Objectives

- This session will focus on the need to have a good acceptance criteria method to evaluate parallelism and the values to chose.
- Which acceptance criteria method should we use to evaluate parallelism?
- How to decide the acceptance criteria values to apply to the chosen method?



Parallelism Acceptance Criteria Methods

- Before we can talk about the acceptance criteria values, we need to see how to look at the data.
- As a CRO, we see several different methods.



The three main acceptance criteria (methods) :

- ☑ Overall %CV
- ☑ Neat reference
- ☑ Artificial MRD

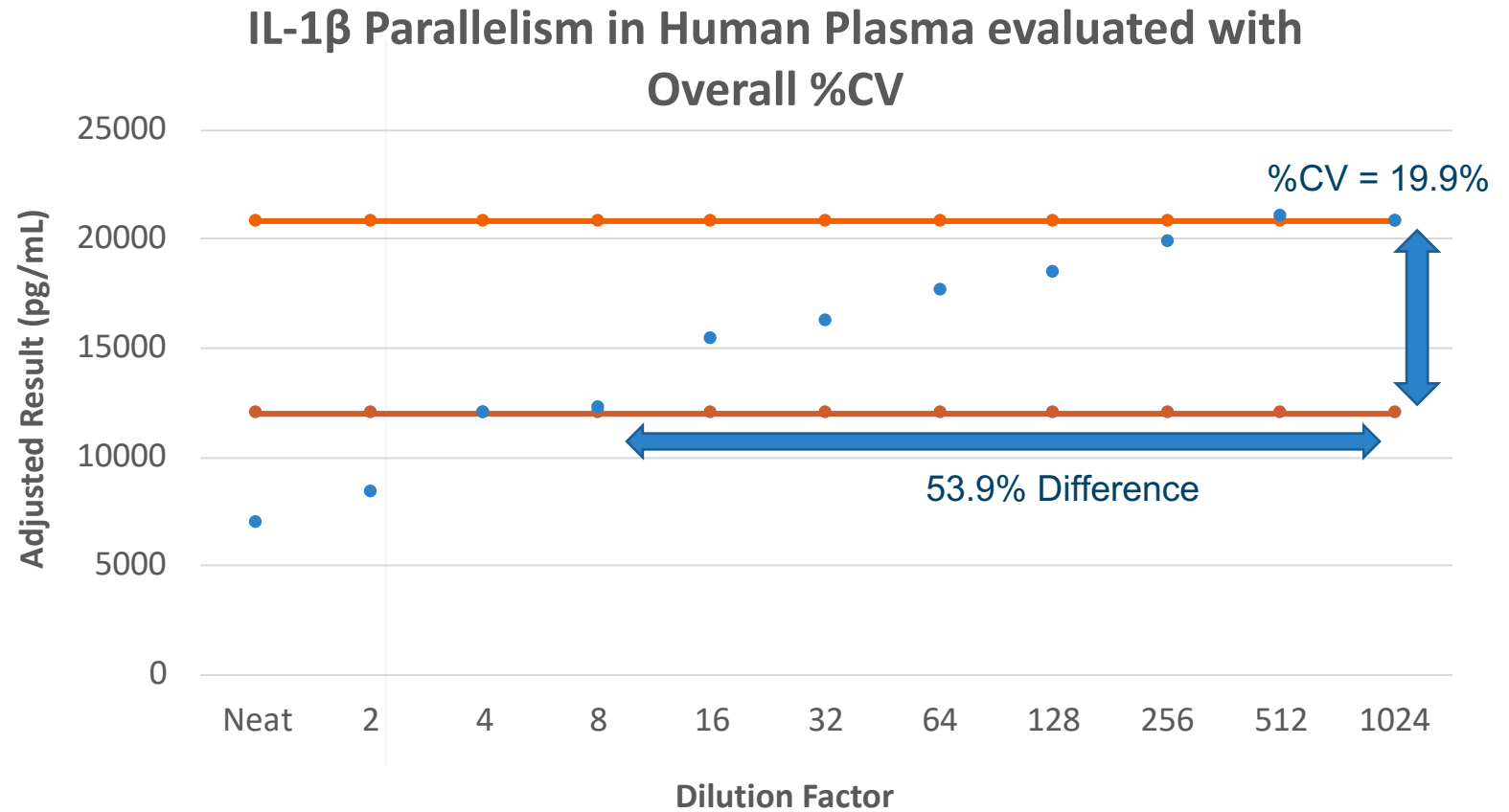
Parallelism Acceptance Criteria Methods



Overall %CV

Parallelism Acceptance Criteria Methods: Overall %CV

Dilution factor (Fold)	Adjusted Result (pg/mL)	%Difference between dilutions
Neat	6998.76	18.1%
2	8393.89	35.4%
4	11998.76	1.6%
8	12193.89	23.6%
16	15460.08	5.1%
32	16277.31	8.1%
64	17645.92	4.5%
128	18463.33	7.4%
256	19888.24	5.5%
512	21010.11	-0.8%
1024	20843.34	



Overall %CV criteria set at 20%



Acceptable
Range:
4 to 1024-fold



Acceptable Range:
1.7-fold Increase

Parallelism Acceptance Criteria Methods



Neat reference

Parallelism Acceptance Criteria Methods: Neat reference

Dilution factor (Fold)	Adjusted Result (pg/mL)
Neat	6998.76
2	8393.89
4	11998.76
8	12193.89
16	15460.08
32	16277.31
64	17645.92
128	18463.33
256	19888.24
512	21010.11
1024	20843.34

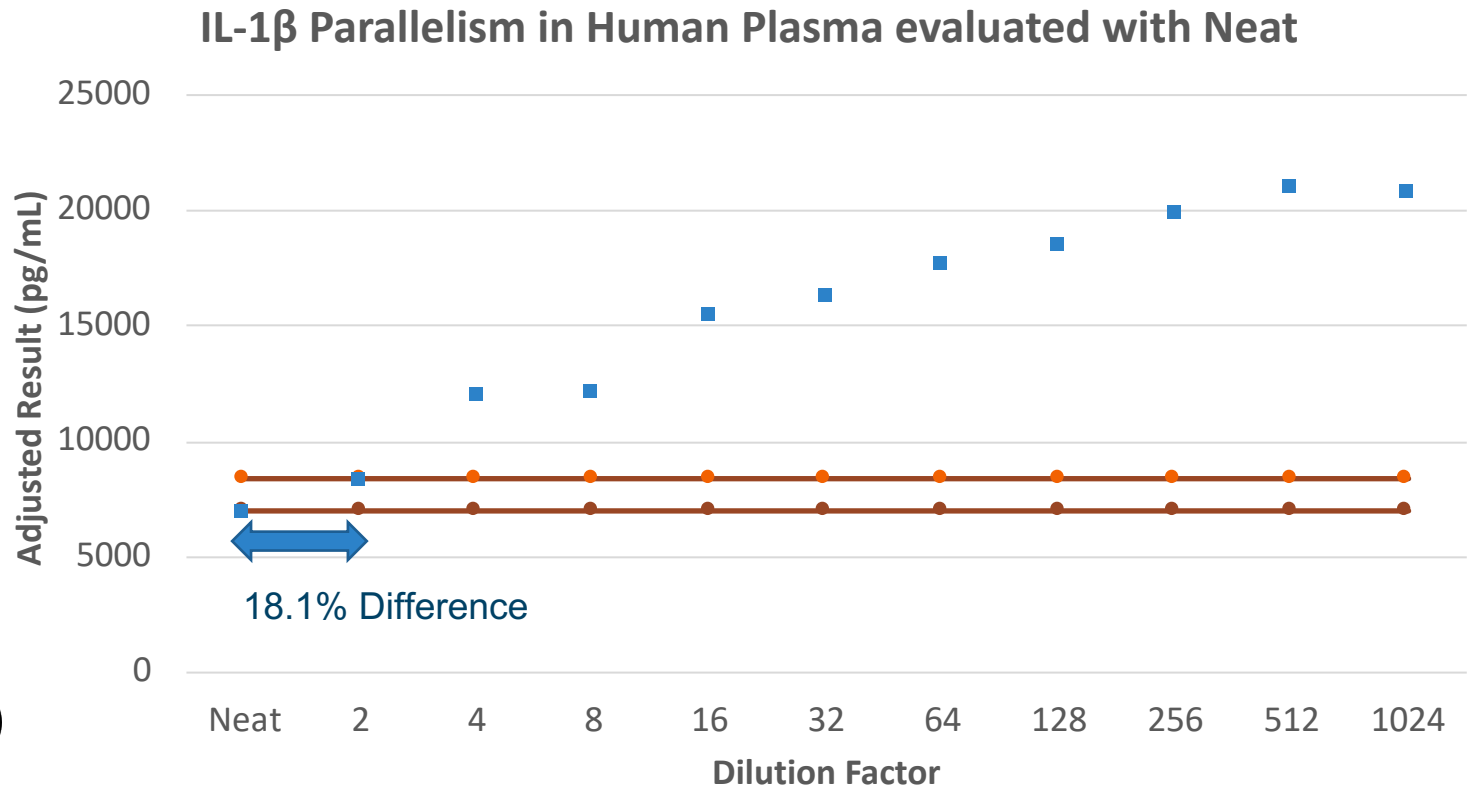
%Difference between dilutions

18.1%

52.6%

54.1%

20% CV = 28.3 % Difference



%Diff criteria set at 28.3%



Acceptable Range: Neat to 2-fold



Acceptable Range: 1.2-fold Increase

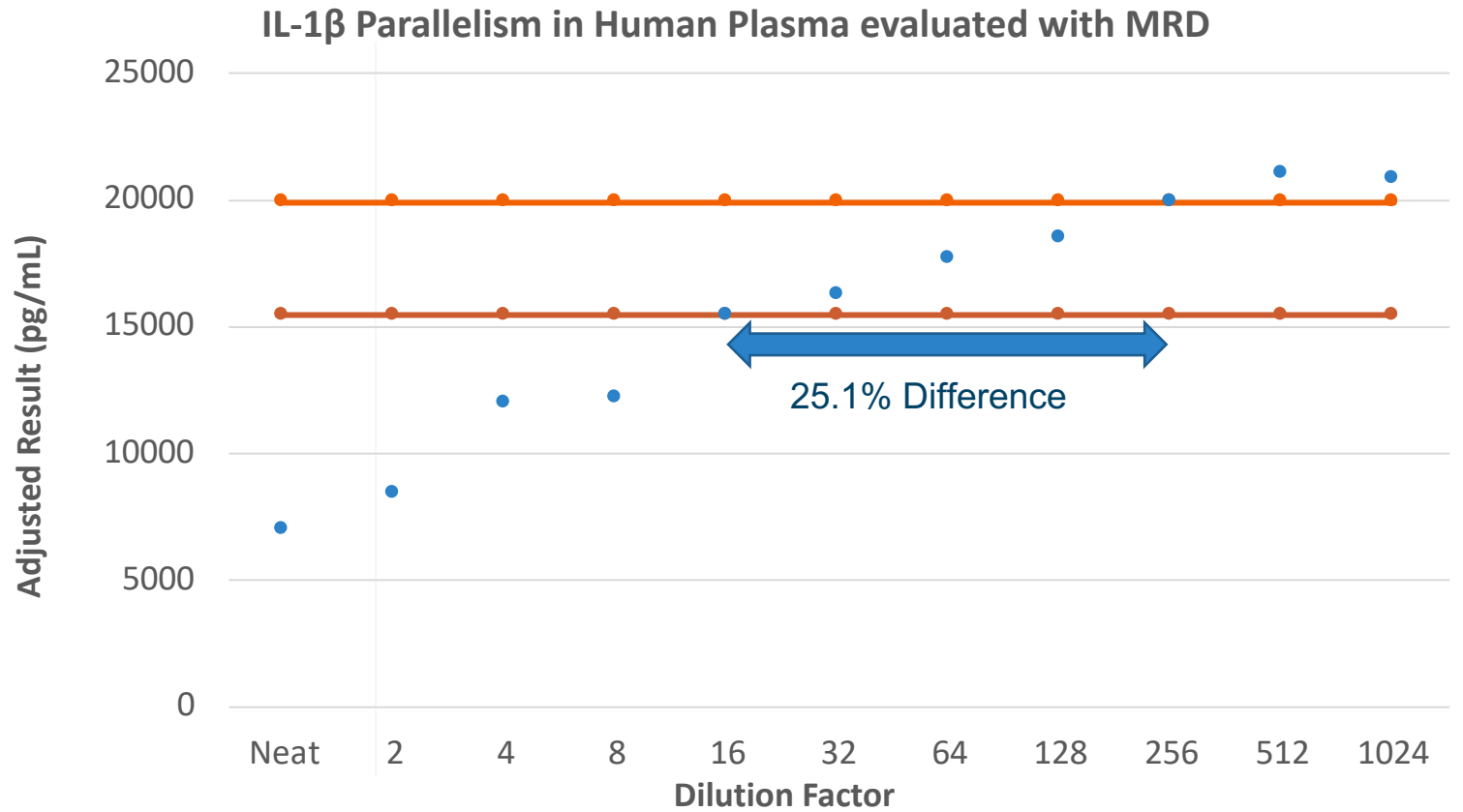
Parallelism Acceptance Criteria Methods



Artificial MRD

Parallelism Acceptance Criteria Methods: Artificial MRD

Dilution factor (Fold)	Adjusted Result (pg/mL)	%Difference between dilutions
Neat	6998.76	
2	8393.89	
4	11998.76	
8	12193.89	
16	15460.08	
32	16277.31	5.1%
64	17645.92	13.2%
128	18463.33	17.7%
256	19888.24	25.1%
512	21010.11	30.4%
1024	20843.34	29.7%



%Diff criteria set at 28.3%



Acceptable Range:
16 to 256-fold

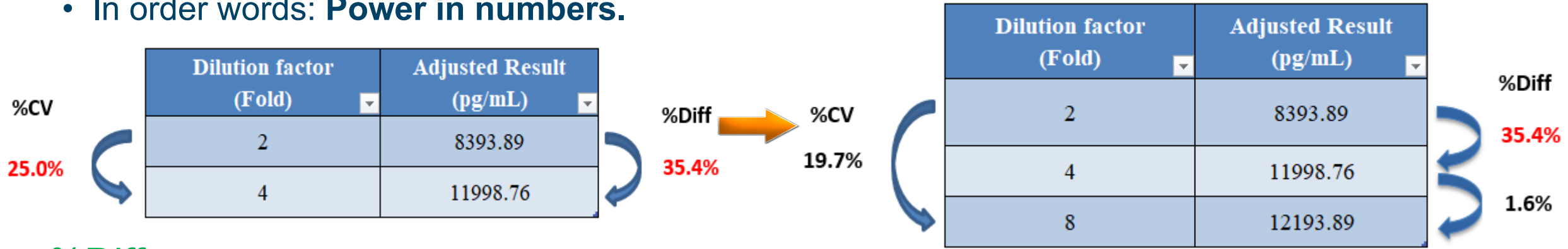


Acceptable Range:
1.3-fold Increase

Parallelism Acceptance Criteria Methods Summary

- Overall %CV:

- “The Coefficient of Variability (CV) is a dimensionless number defined as the standard deviation of a set of measurements divided by the mean of the set”.
- In order words: **Power in numbers.**



- %Difference:

- The %difference is an indication of the variance between only two values.
- It will not allow to “recover” a non parallel dilution factor.

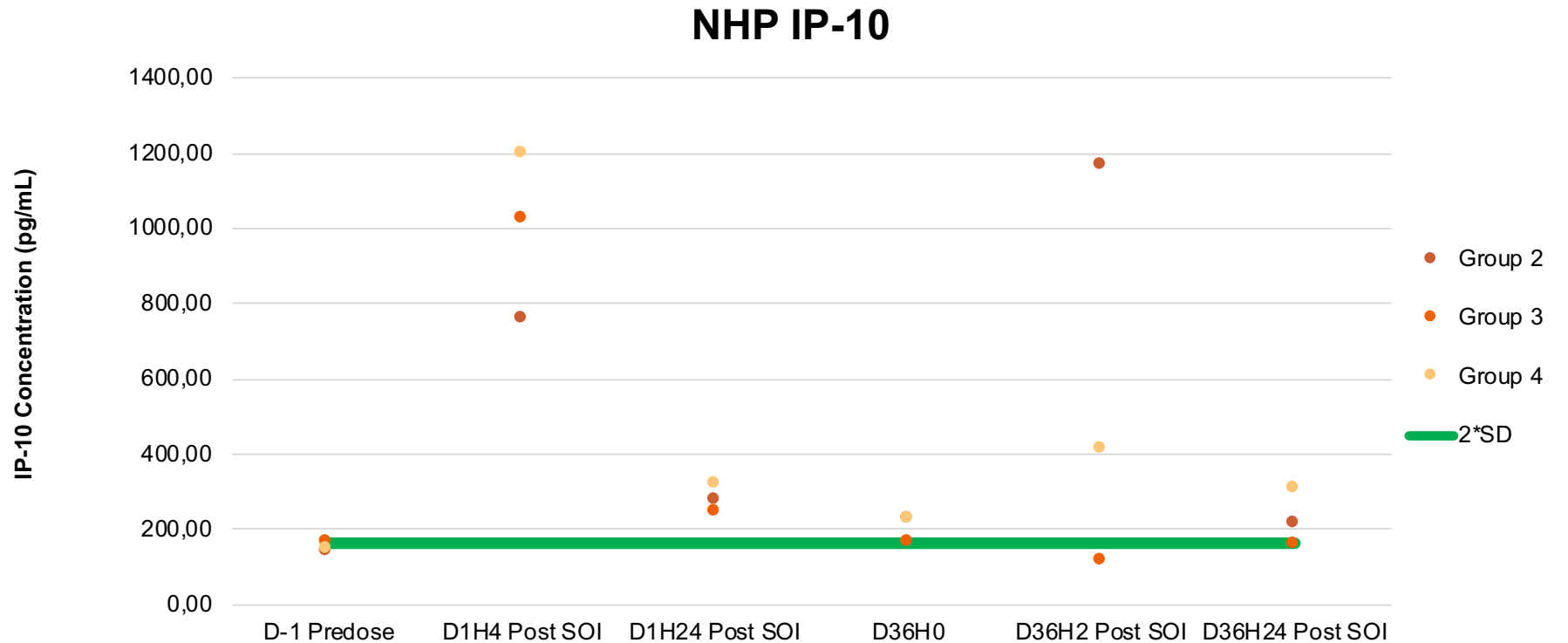
Parallelism Acceptance Criteria Values

**Which
acceptance
criteria
should I use?**



Parallelism Acceptance Criteria Values

- Monkey assay
Validated for IP-10
relative quantitation
- **Green Line =**
2X control group
Standard Deviation
- **11 points above line**
- **Criteria: %Diff 25%**

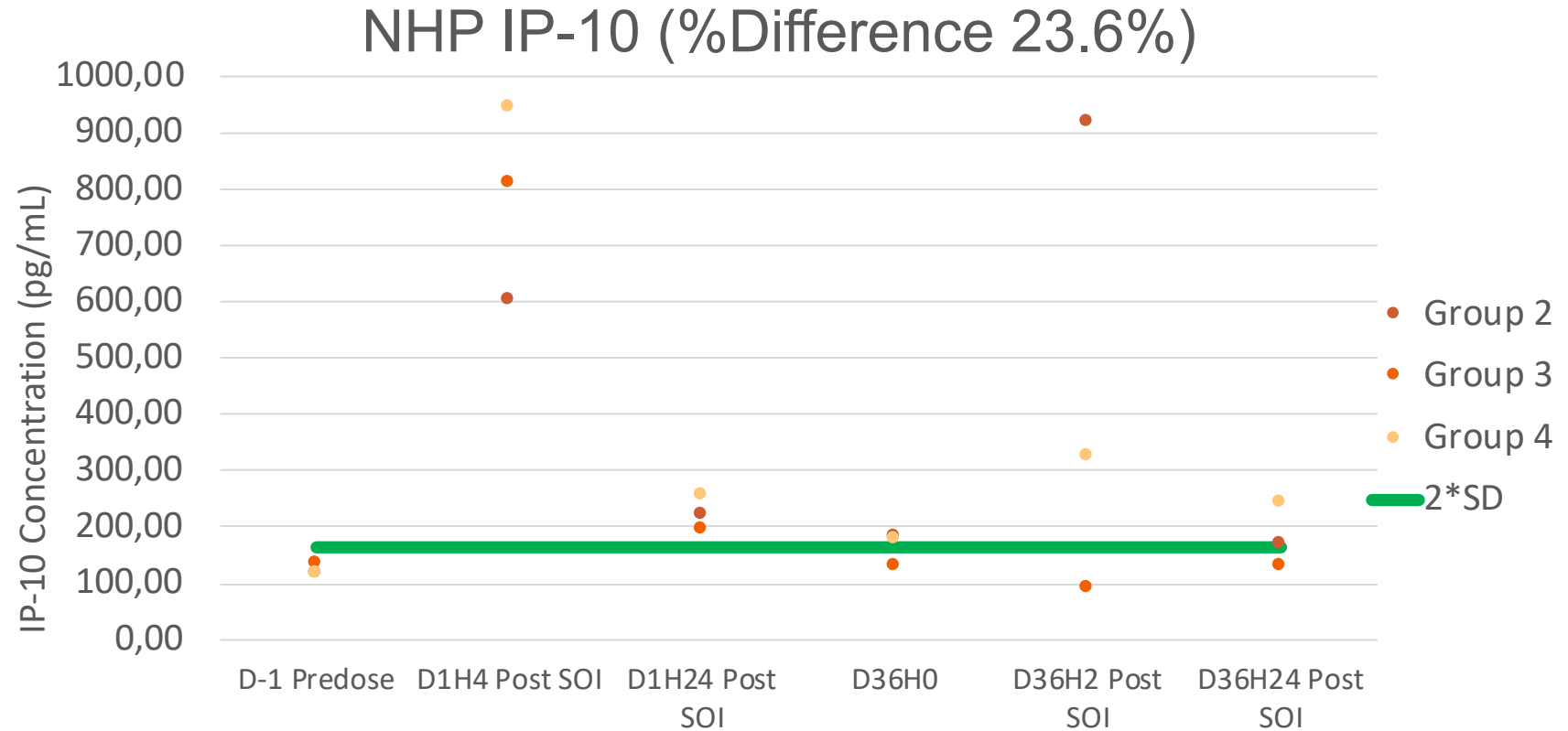


Parallelism Acceptance Criteria Values

Dilution factor
8
16

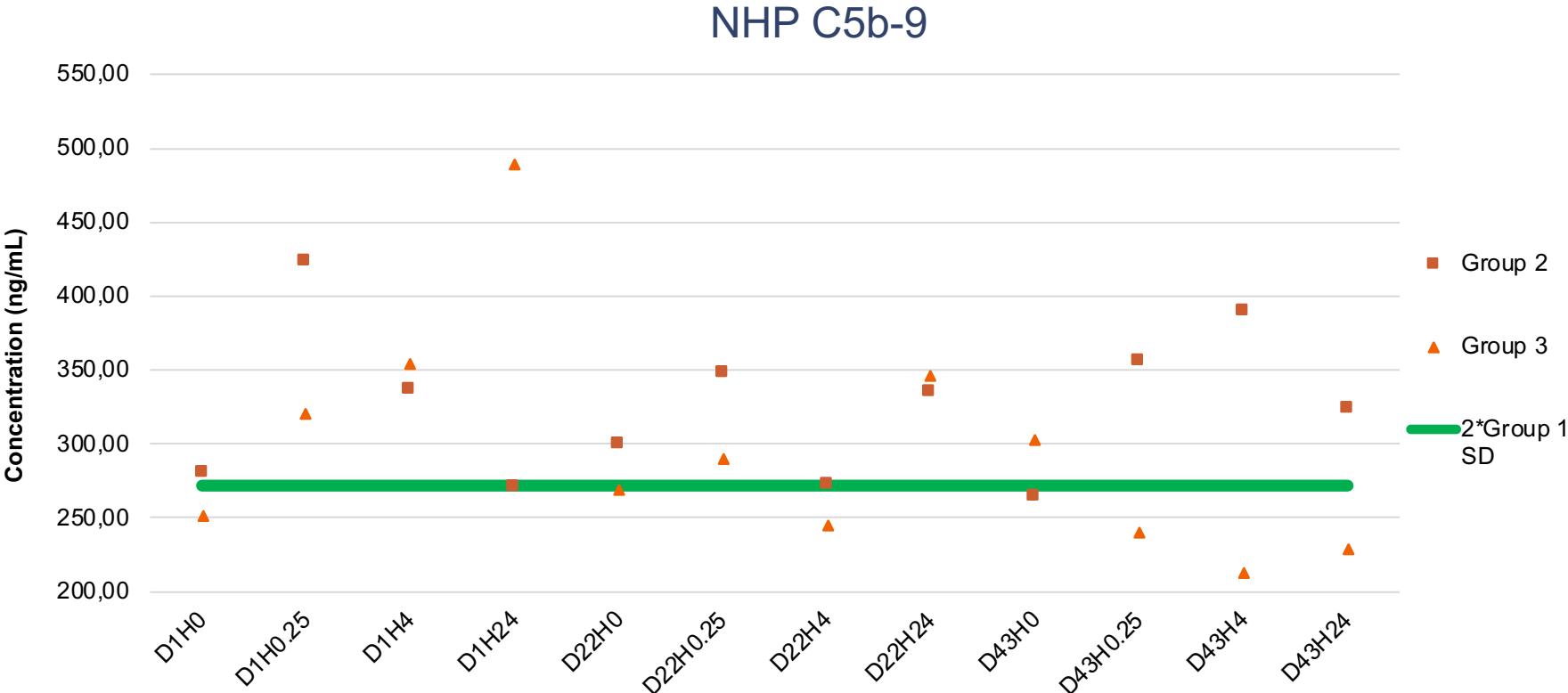
23.6%

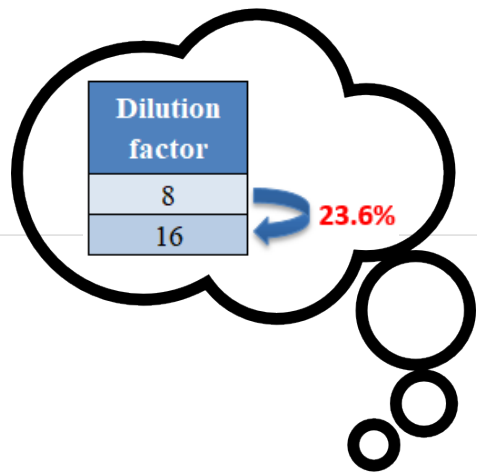
- What would happen if controls were diluted 16-fold and dosed groups 8-fold?
- **10 points above line (vs 11 Points)**
- **Criteria: %Diff 25%= Acceptable**



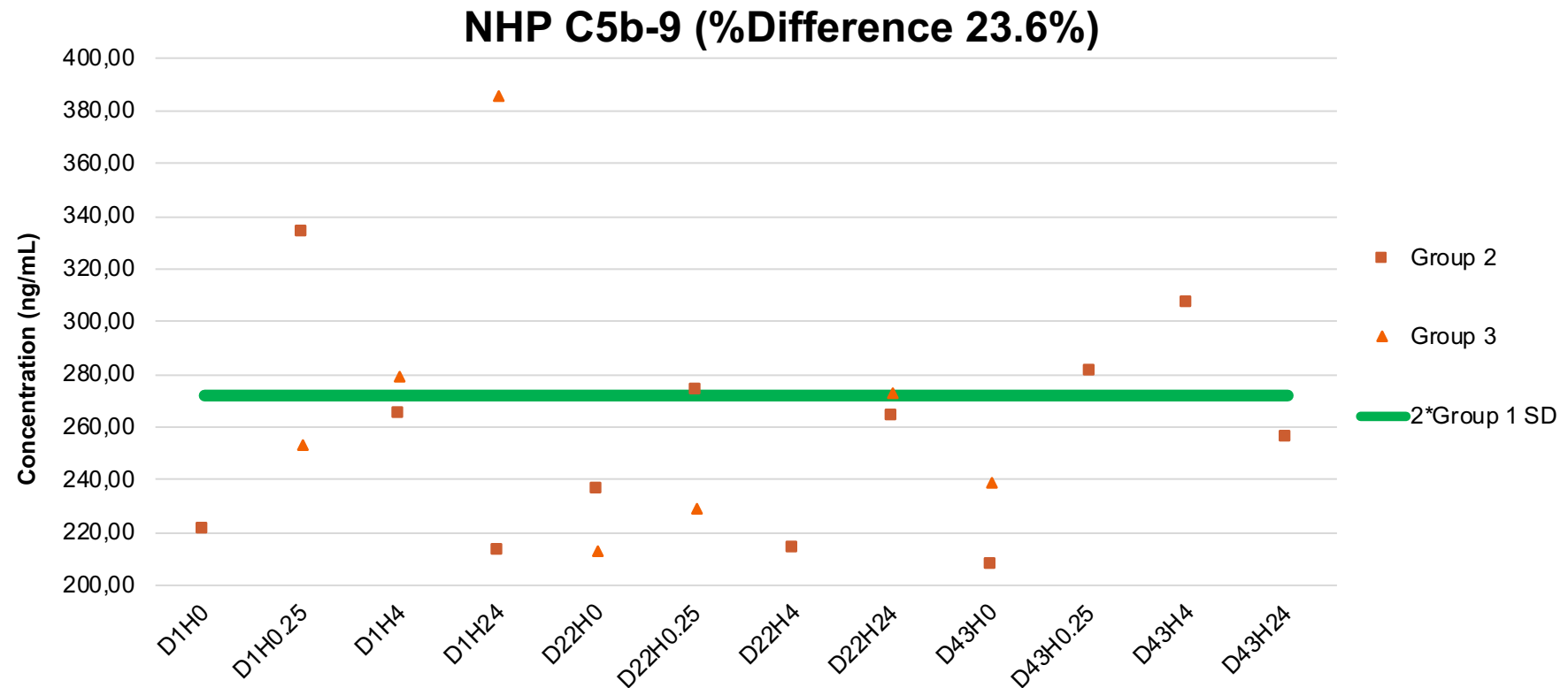
Parallelism Acceptance Criteria Values

- Monkey assay
Validated for C5b-9
relative quantitation
- **Green Line** =
2X control group
Standard Deviation
- **15 points above line**
- **Criteria: %Diff 25%**





Parallelism Acceptance Criteria Values



- What would happen if control are diluted 16-fold and dosed groups 8-fold?
- **5 points above line (vs 15 Points)**
- **Criteria: %Diff 25%= Not Acceptable**

Parallelism Acceptance Criteria Methods: Summary

- Disconnect between validation scientist and end user.
- You need to develop and assay for its intended use.

Dilution factor (Fold) ▾	Adjusted Result (pg/mL) ▾	%Difference between dilutions
Neat	6998.76	
2	8393.89	
4	11998.76	
8	12193.89	
16	15460.08	
32	16277.31	5.1%
64	17645.92	13.2%
128	18463.33	17.7%
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512	21010.11	30.4%
1024	20843.34	29.7%

%Diff criteria set at 25%



Acceptable
Range:
16 to 256-fold

Summary

- Artificial MRD is a better approaches to evaluate parallelism then Overall %CV.
- Different method exist to evaluate parallelism but none are perfect. Full characterization and evaluation against COU is critical.
- Your context of use should drive the acceptance criteria you use to evaluate your parallelism.

Acknowledgments

- Sophie Cotton
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Questions

For additional questions, do not hesitate to contact me.

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