



Detecting Differences in APSD: Efficient Data Analysis (EDA) vs. Stage Groupings

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on behalf of the
IPAC-RS Cascade Impactor Working Group

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Overview

1. FDA currently uses a grouped-stage approach for detecting changes in APSD
2. IPAC-RS Cascade Impactor Working Group proposed an alternative (EDA) approach

EDA is based on two metrics:

- **Ratio** (LPM / SPM)
- **Sum** (LPM + SPM) = **ISM**

of Large Particle Mass (LPM) and Small Particle Mass (SPM) of Impactor Sized Mass (ISM)

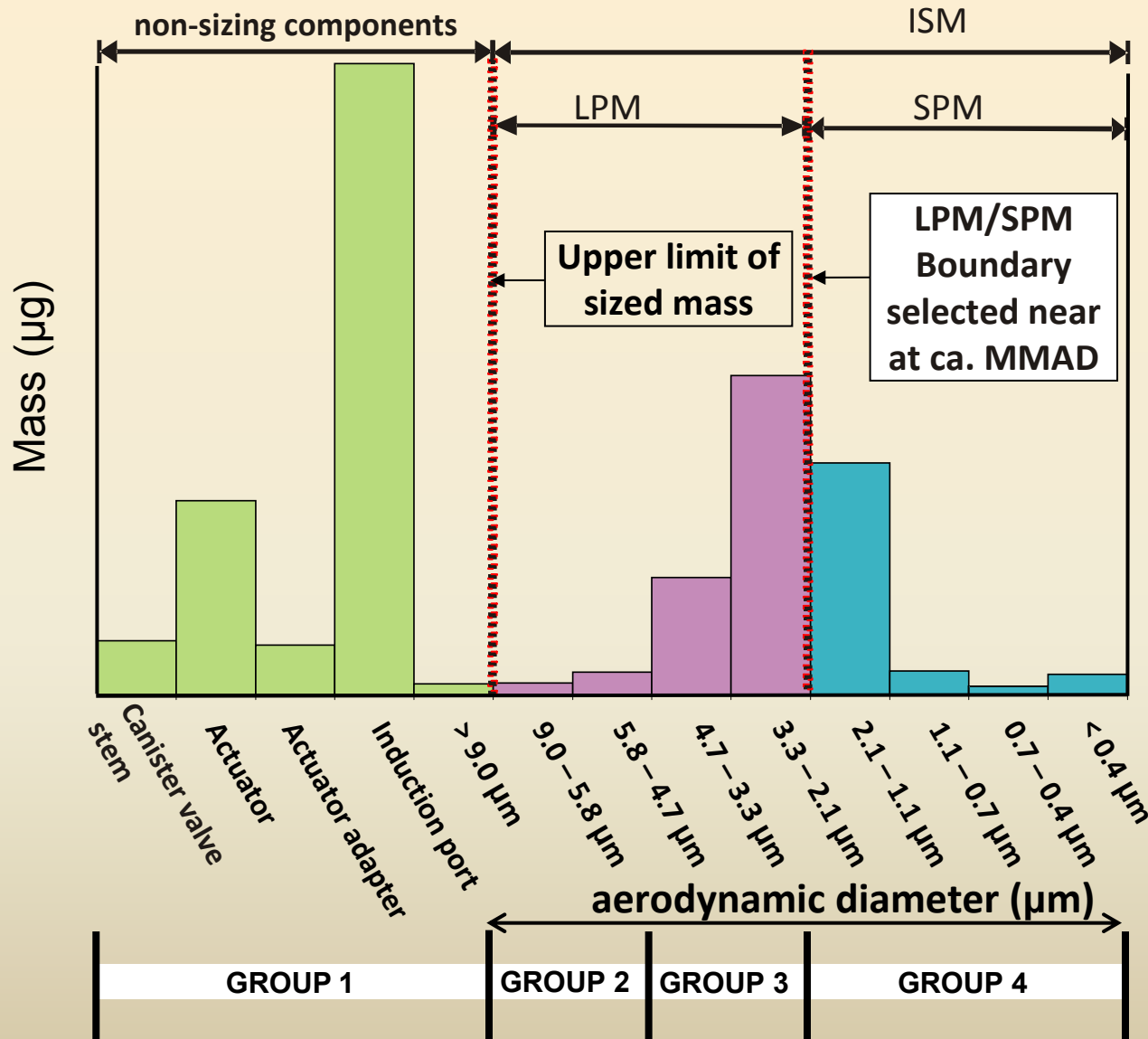
- Presented here is a comparison of the decision making capability of the two approaches using simulations and operating characteristic curves

Purpose

- To compare the decision making capability of EDA versus grouped stages in general and/or for a specific product
- Some aspects of this assessment could be useful in justifying an EDA approach in a filing

EDA Concept

(Generalized Example based on ACI @ 28.3 L/min)



Ratio

LPM / SPM

Sum (ISM)

LPM + SPM

Typical grouped stages shown for comparison

Differences Between EDA and Typical Grouped Stage Approaches

Based on Full-Resolution Impactor Data

Grouped Stages

3 (sized) stage groupings

3 metrics

(each grouping assessed separately, but combined into a single outcome)

Each metric can be affected by both shift and mass amount in APSD

Results in confounding and introduces “noise”

EDA

2 (sized) stage groupings

2 metrics

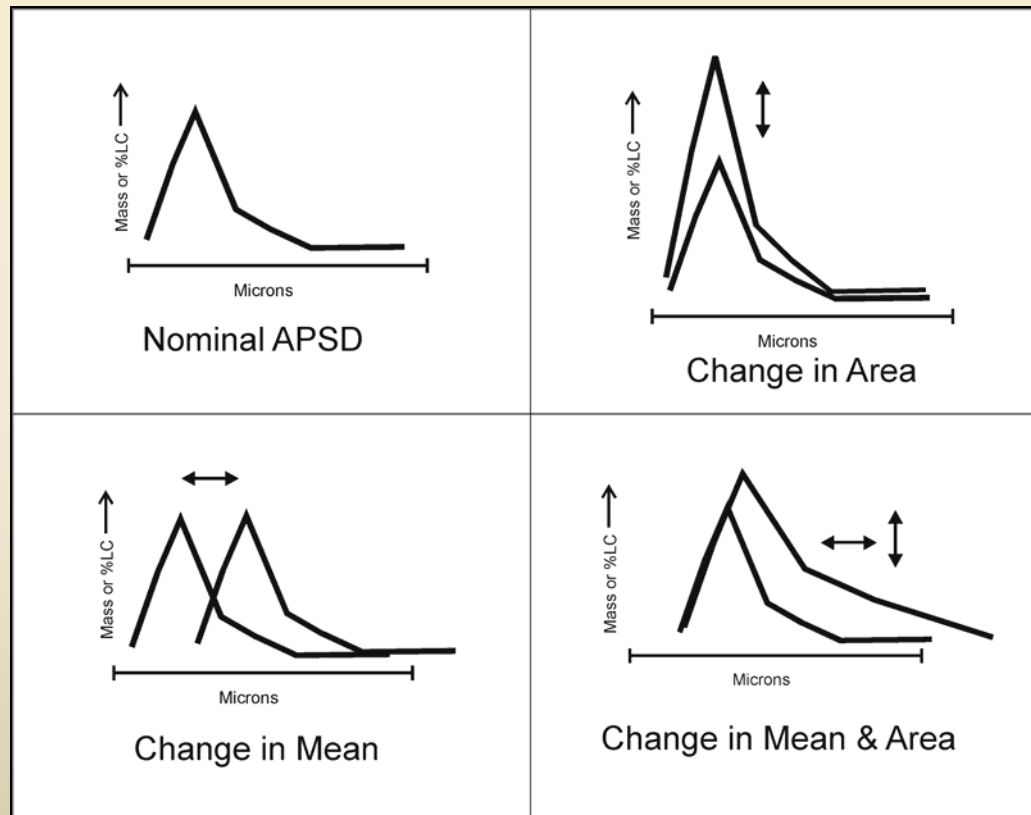
(for each metric, both groupings assessed simultaneously)

Ratio metric affected by only shift in APSD

ISM metric affected by only mass amount in APSD

ISM and LPM/SPM in Relation to APSD

- Combination of ISM and LPM/SPM enables all realistic changes of APSD shift to be detected



Comparison of Decision Capability

- Compared ability of two approaches to make correct decisions about changes in APSD
- Not for the purpose of assessing product quality
- Based on a body of real, blinded data (IPAC-RS database)
- Presentation illustrates one of eight products assessed (all were consistent)
- Values for acceptance limits determined to allow “apples-to-apples” comparison of the two approaches
- Assessment based on mass from sized components
 - Three groupings for grouped-stage approach
 - Two groupings for EDA (LPM and SPM)
 - Both approaches use same data

Comparison of Decision Capability (2)

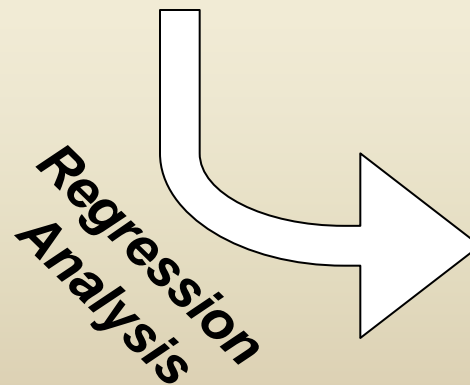
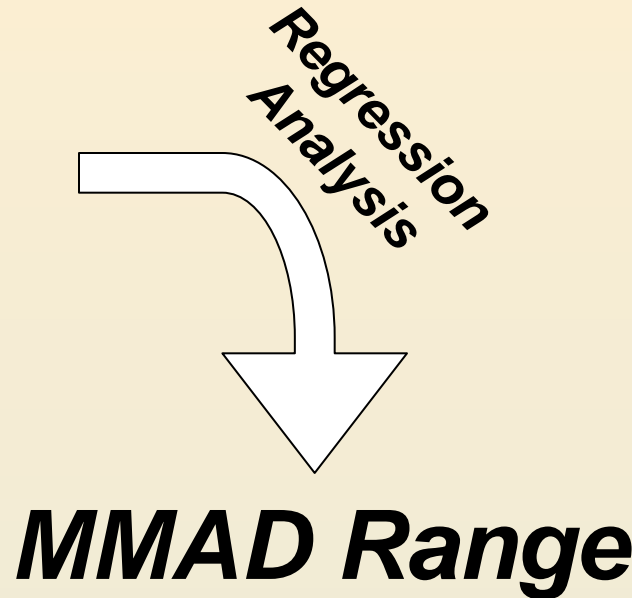
- Total mass on sized components of impactor (ISM) has no impact on relative decision making capability of two approaches
 - ISM is exactly equal to sum of grouped stages
 - Respective sums of upper and lower limits for grouped stages translate directly into upper and lower limits for ISM
 - A decision made based on ISM acceptance limits will be the same as the (combined) decision based on acceptance limits for each of the grouped stages
- Therefore, a comparison of decision making capability can be based on how effectively each method can detect shifts in APSD (i.e., on Ratio and grouped-stage outcomes)

Shifts in APSD and Changes in MMAD

- Shifts in APSD can be directly measured by changes in MMAD
- The same set of calculated MMADs was used in the assessment of each approach
- A range of MMADs was established for which stage groupings were discriminating
- This range was then used to compare the performance of the two approaches

Basis for Capability Comparison

Stage
Grouping
Acceptance
Limits



Stage Grouping Acceptance Limits for Decision Capability Assessment

- Group 1 is mass of non-sized components
- Size ranges for Groups 2, 3, 4 based on “reasonable” stage groupings*
- Acceptance limits based on 1st and 99th percentiles of distribution of these stage grouping values
- Acceptance limits for each group generally consistent with typical “rule of thumb” limits likely acceptable by FDA

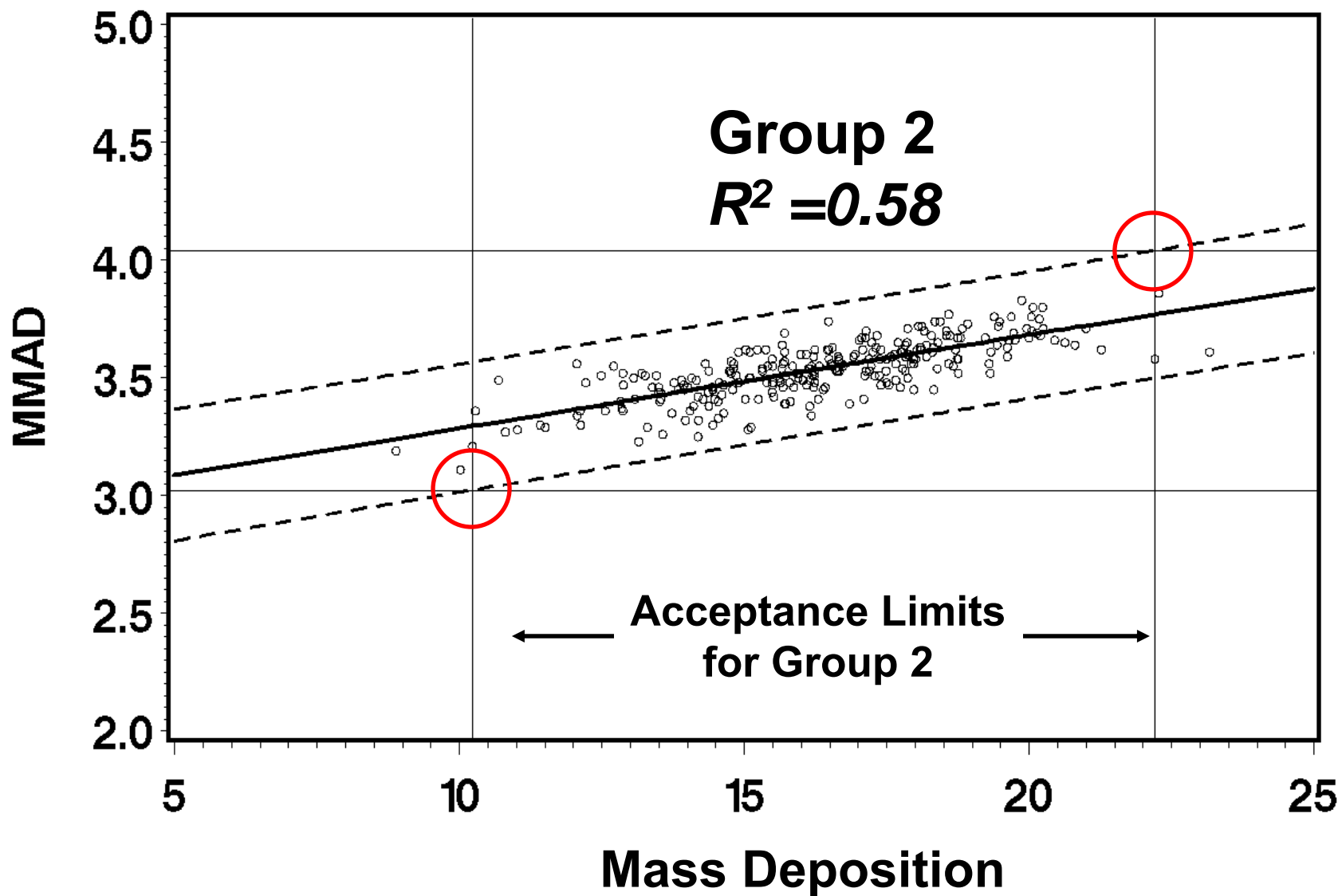
Grouped Stages (Sized)	Mass Deposition		
	Mean	1 st Percentile	99 th Percentile
Group 2 (10.0 - 4.7 µm)	16.31	10.23	22.21
Group 3 (4.7 - 2.1 µm)	49.06	39.57	55.87
Group 4 (<2.1 µm)	8.03	5.08	12.32

* Tougas, T.P., Christopher, D., Mitchell J.P., Strickland, H., Wyka, B., Van Oort, M., and Lyapustina, S. (2009), “Improved quality control metrics for cascade impaction measurements of orally inhaled drug products (OIPs),” AAPS PharmSci Technol, 10(4), pp. 1276-85.

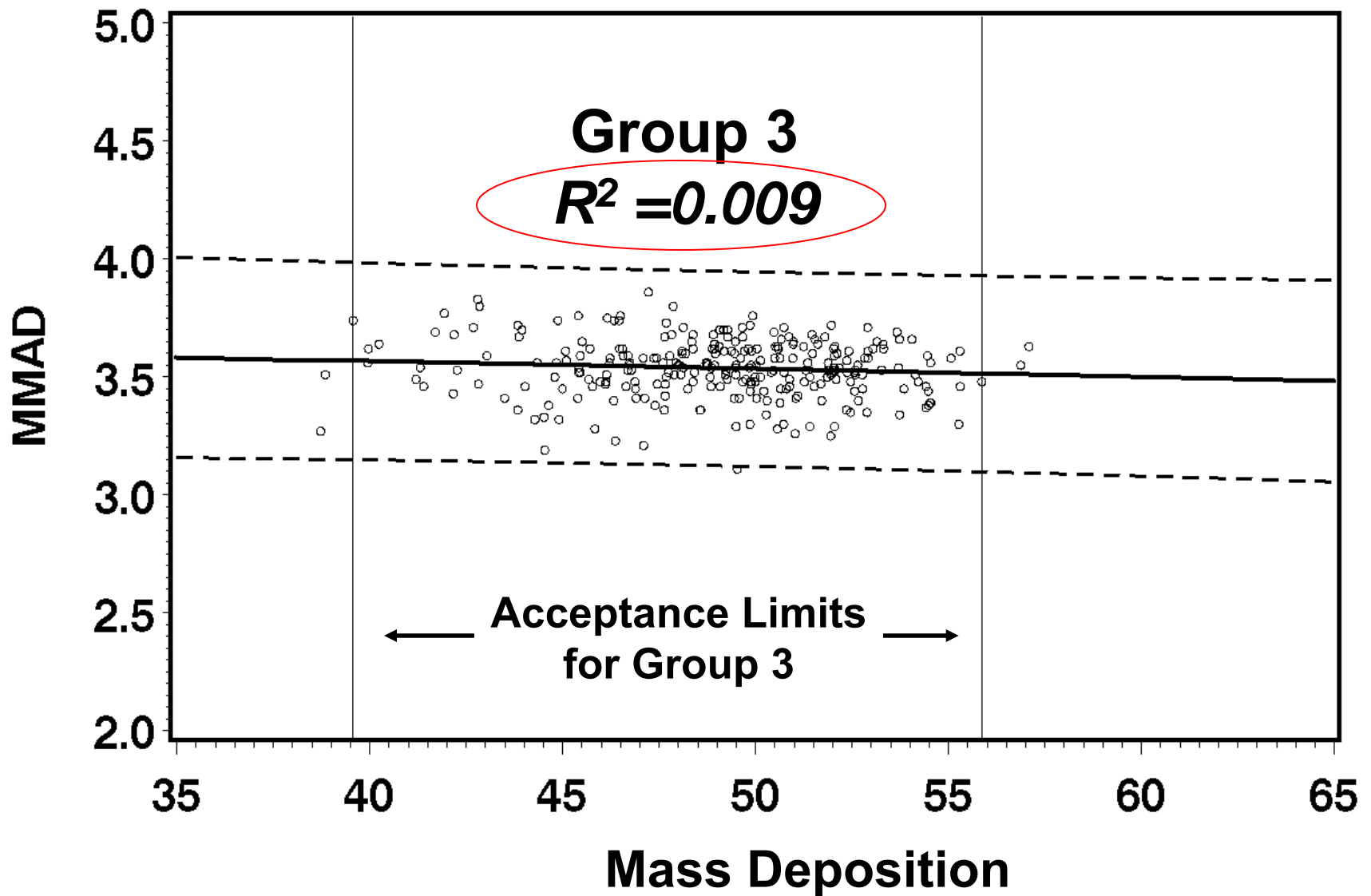
Stage Grouping Relationship with MMAD

- The relationship of stage groupings to MMAD was established using a suitable regression model with 99.9% prediction intervals
- Intersection of the prediction interval with acceptance limits determined the relevant range of MMADs over which stage groupings were discriminating (shown in following plots)

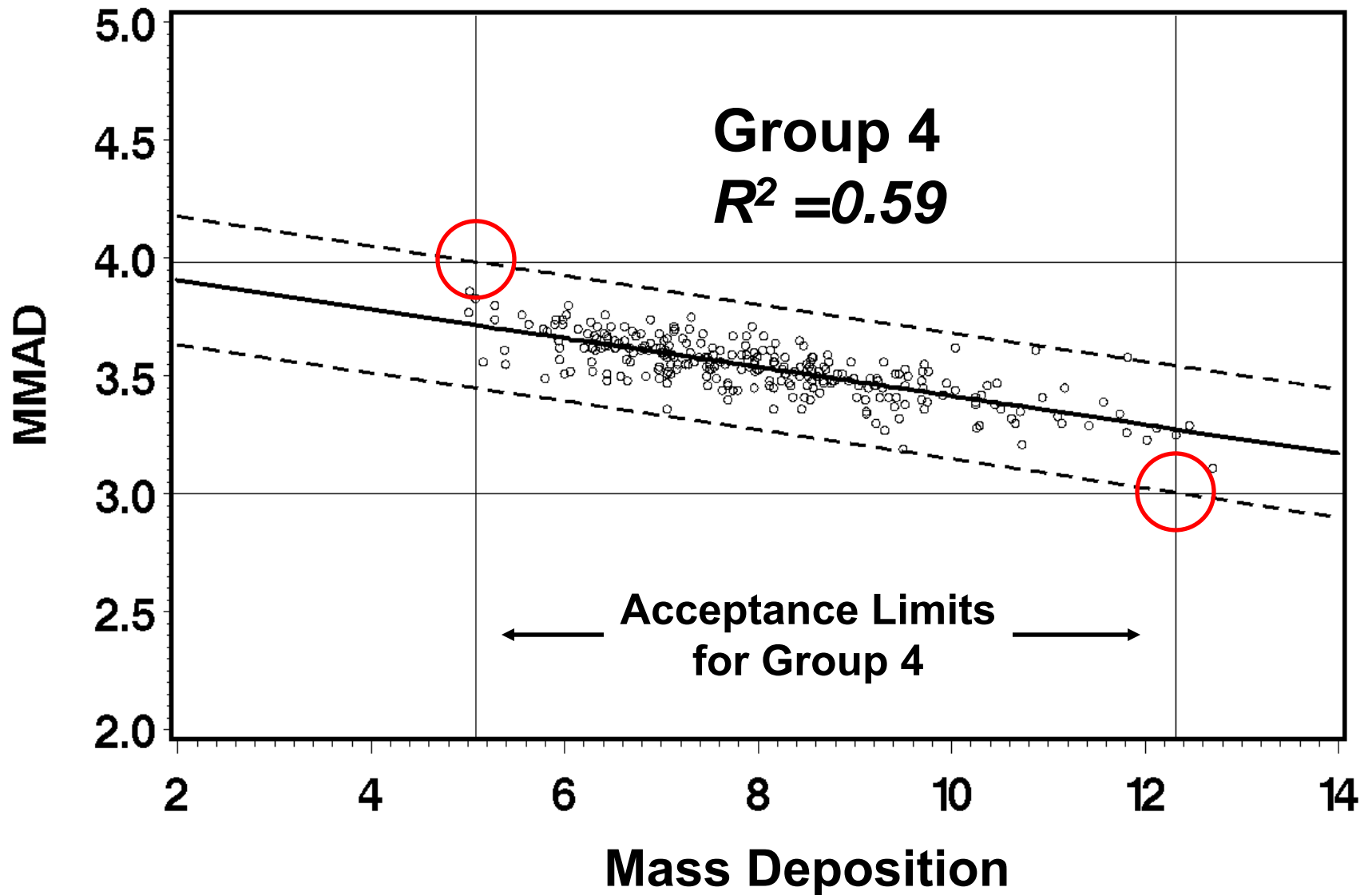
Stage Grouping Relationship with MMAD



Stage Grouping Relationship with MMAD



Stage Grouping Relationship with MMAD



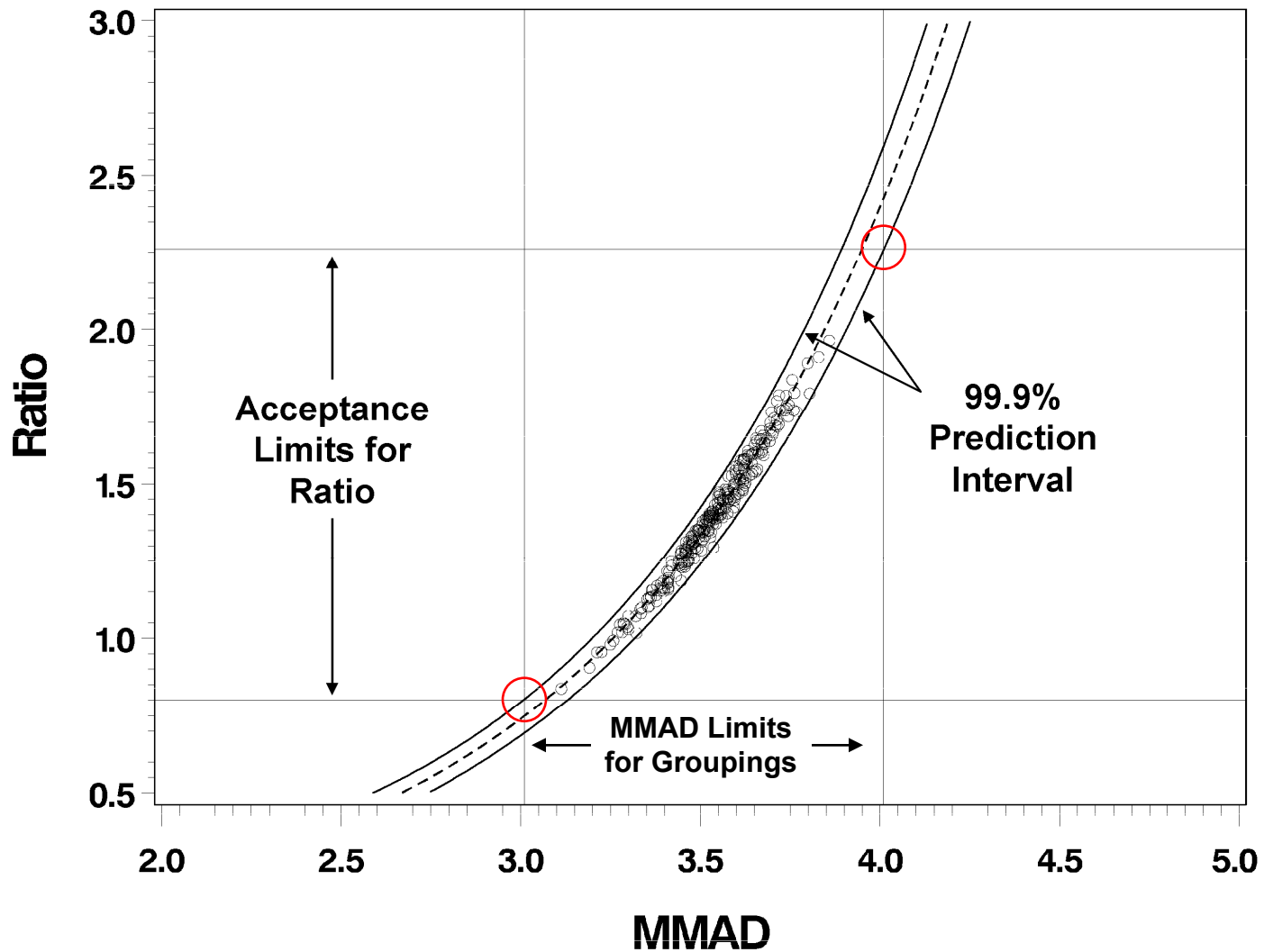
Stage Grouping Relationship with MMAD

- Because of low correlation of Group 3, only Groups 2 and 4 used to establish relationship with MMAD
- Group 2 and 4 results averaged to establish common range of 3.01–4.01 μm for MMAD which was then used in determining acceptance limits for Ratio
- Allows “apples-to-apples” comparison of decision capability of the two approaches

EDA

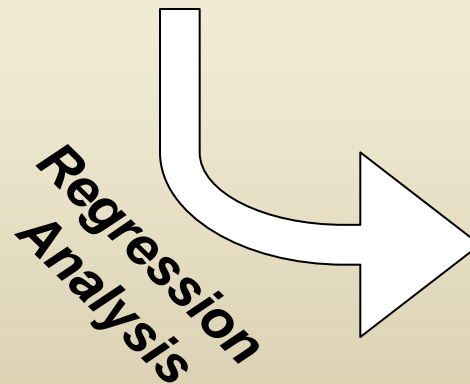
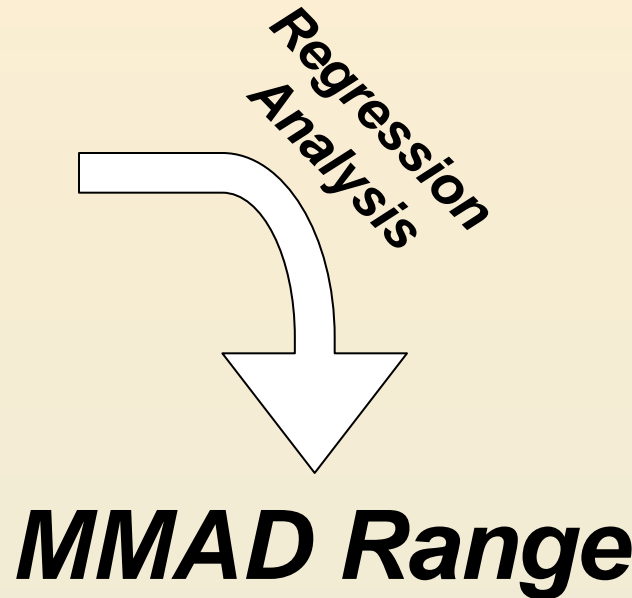
- LPM / SPM Ratio calculated for each set of CI results using appropriate boundary (based on median MMAD)
- Fitted suitable regression model with 99.9% prediction intervals (same method as for groupings) to establish relationship between Ratio and MMAD
- Determined acceptance limits for Ratio by intersection of prediction interval with previously established MMAD limits used for stage groupings
- Allows direct link from stage grouping acceptance limits to corresponding acceptance limits for Ratio
- Comparable acceptance limits associated with common range of MMAD limits allows “apples-to-apples” comparison of decision making capability

EDA Ratio vs. MMAD



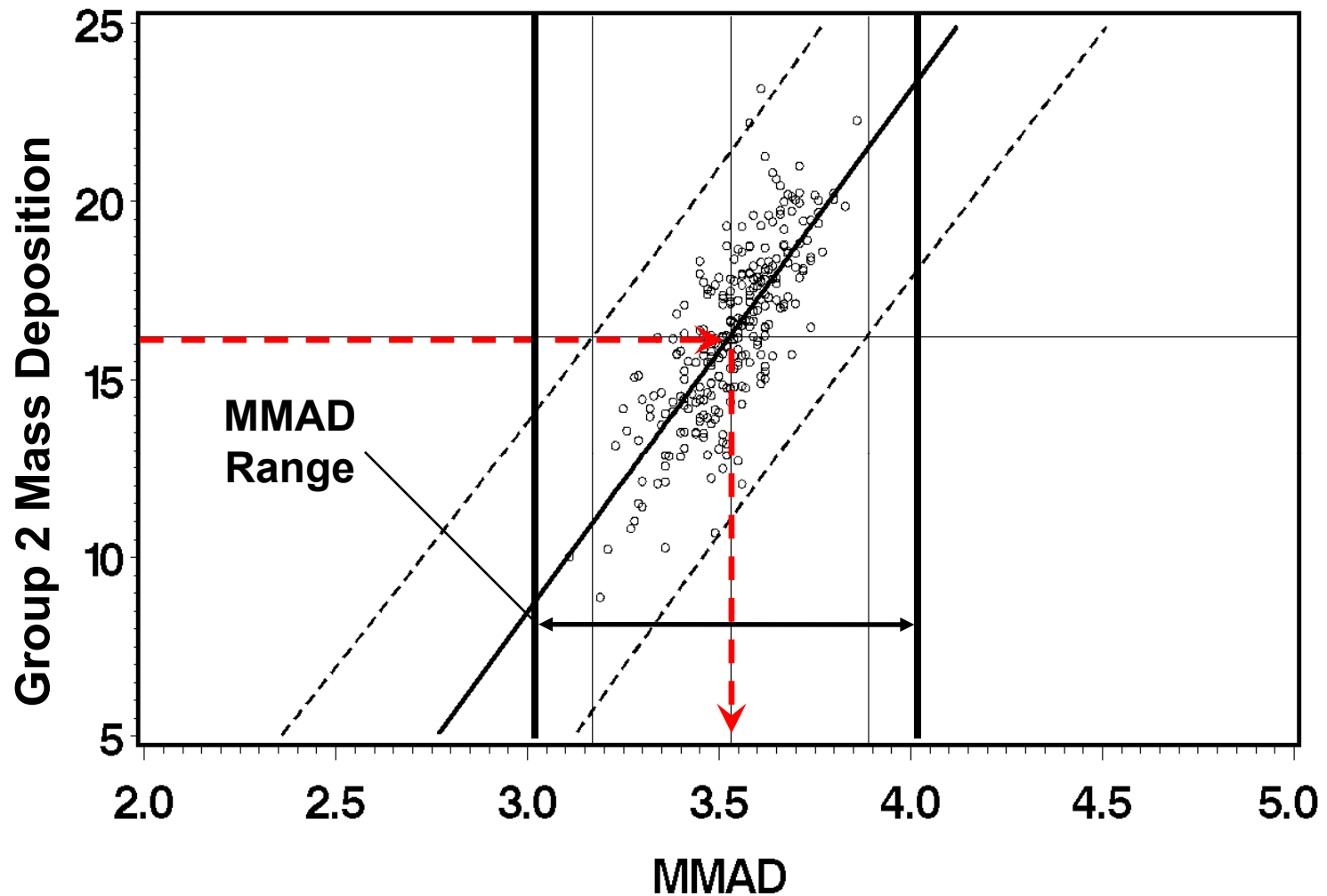
Basis for Comparable Comparison

Stage
Grouping
Acceptance
Limits



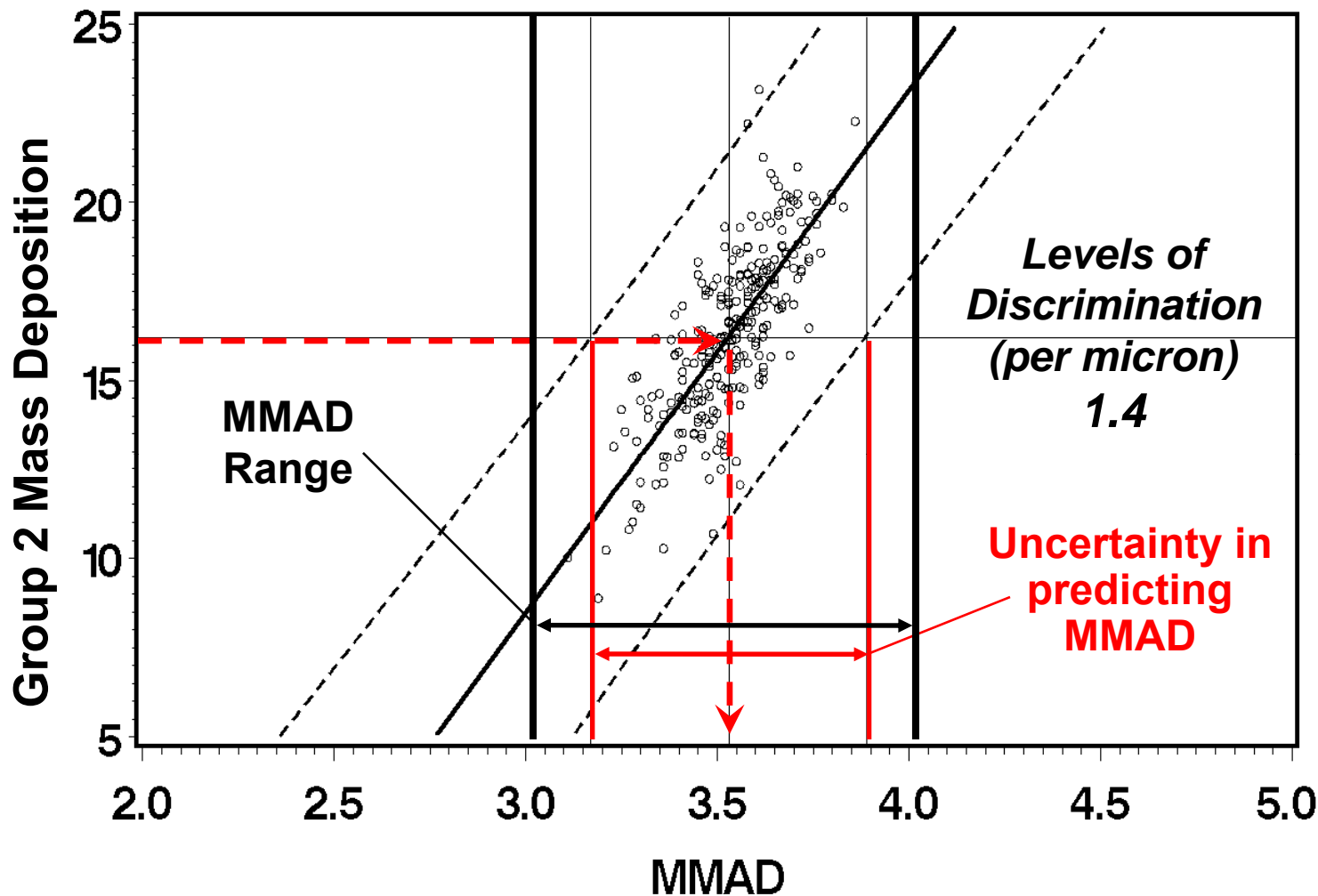
Levels of Quality – Grouped Stages

Measurement System Analysis (MSA)



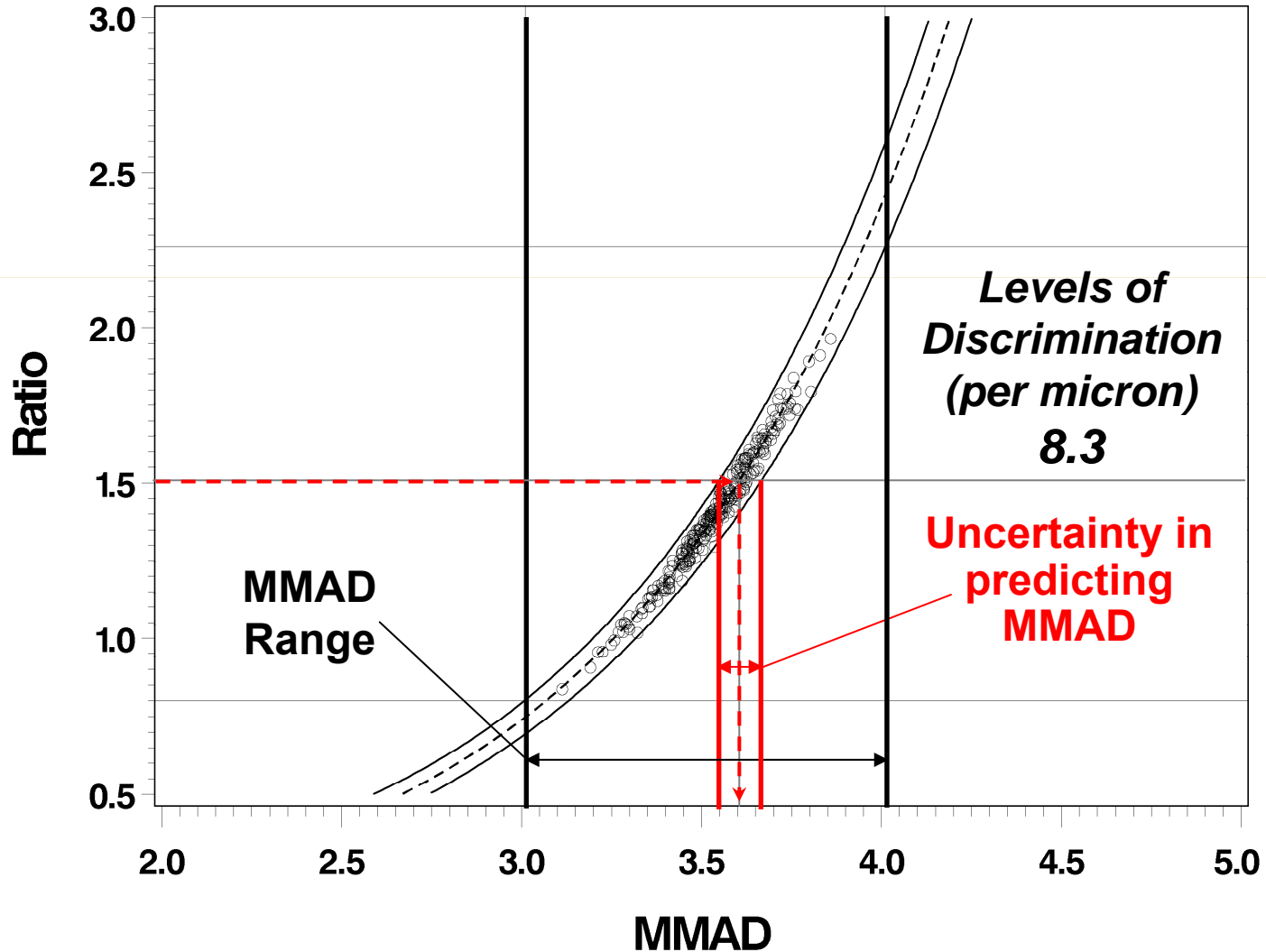
Levels of Quality – Grouped Stages

Measurement System Analysis (MSA)



Levels of Quality – EDA

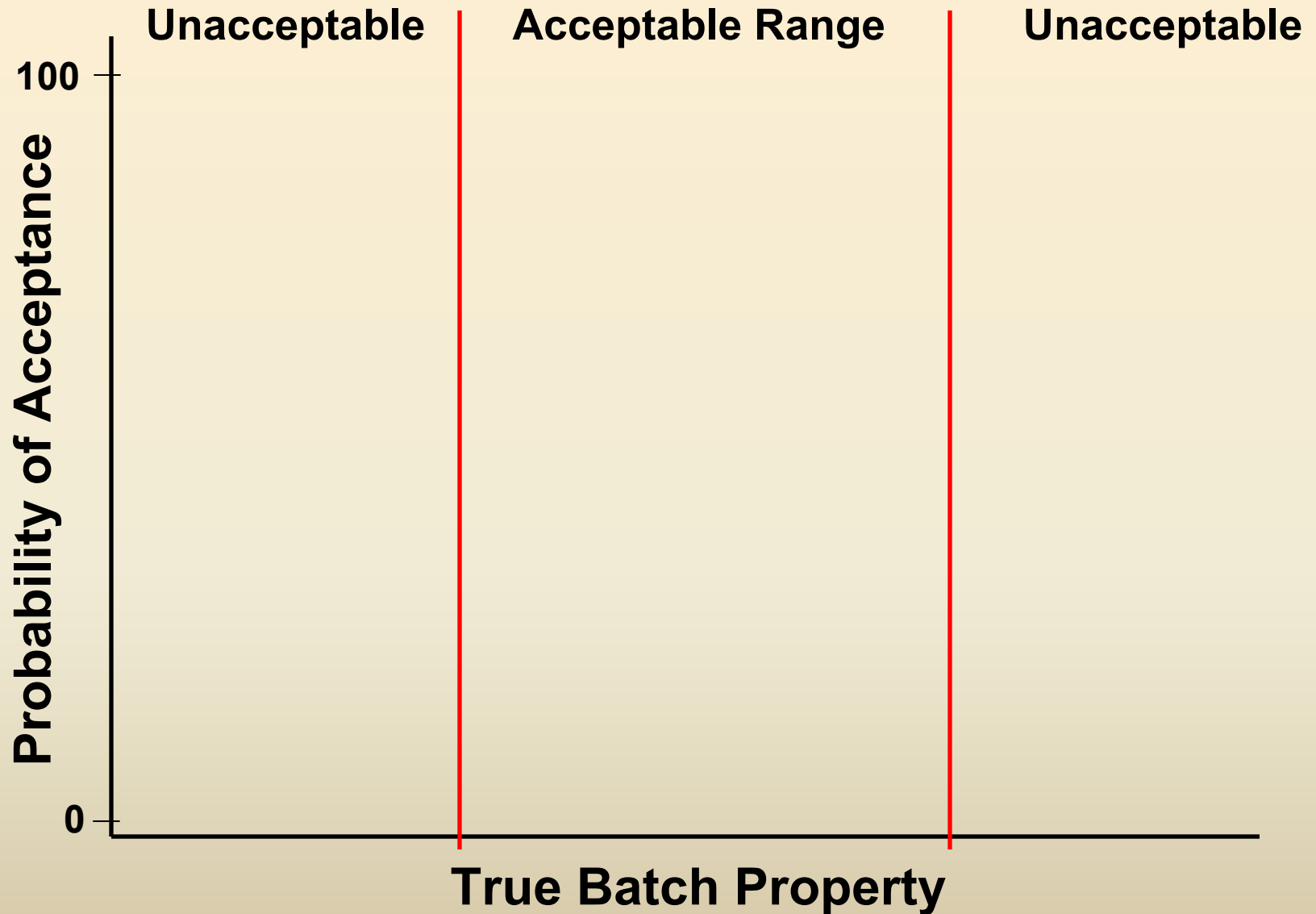
Measurement System Analysis (MSA)



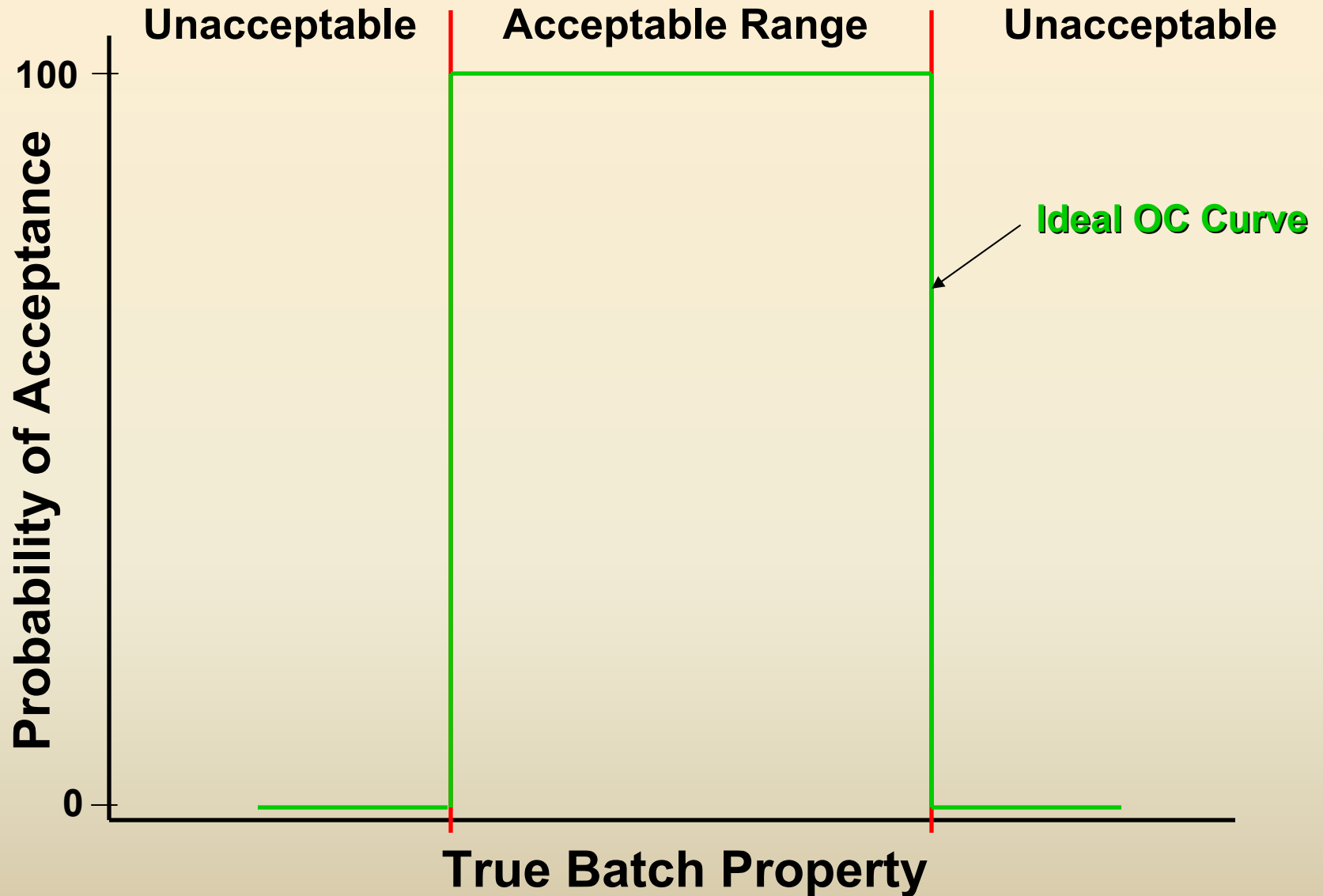
Using Operating Characteristic (OC) Curves to Compare Decision Making Capabilities

- OC curves can be used to compare the ability of these two approaches to make correct decision
- An OC curve is a plot of the probability of acceptance (or rejection) versus a true batch property (e.g. mean) using simulated data
- Simulated data created using SAS to model real data
 - Mean and variability of mass deposition on each stage
 - Also modeled inter-relationships among stages
 - Modeling does not require normal distribution of mass deposition on stages

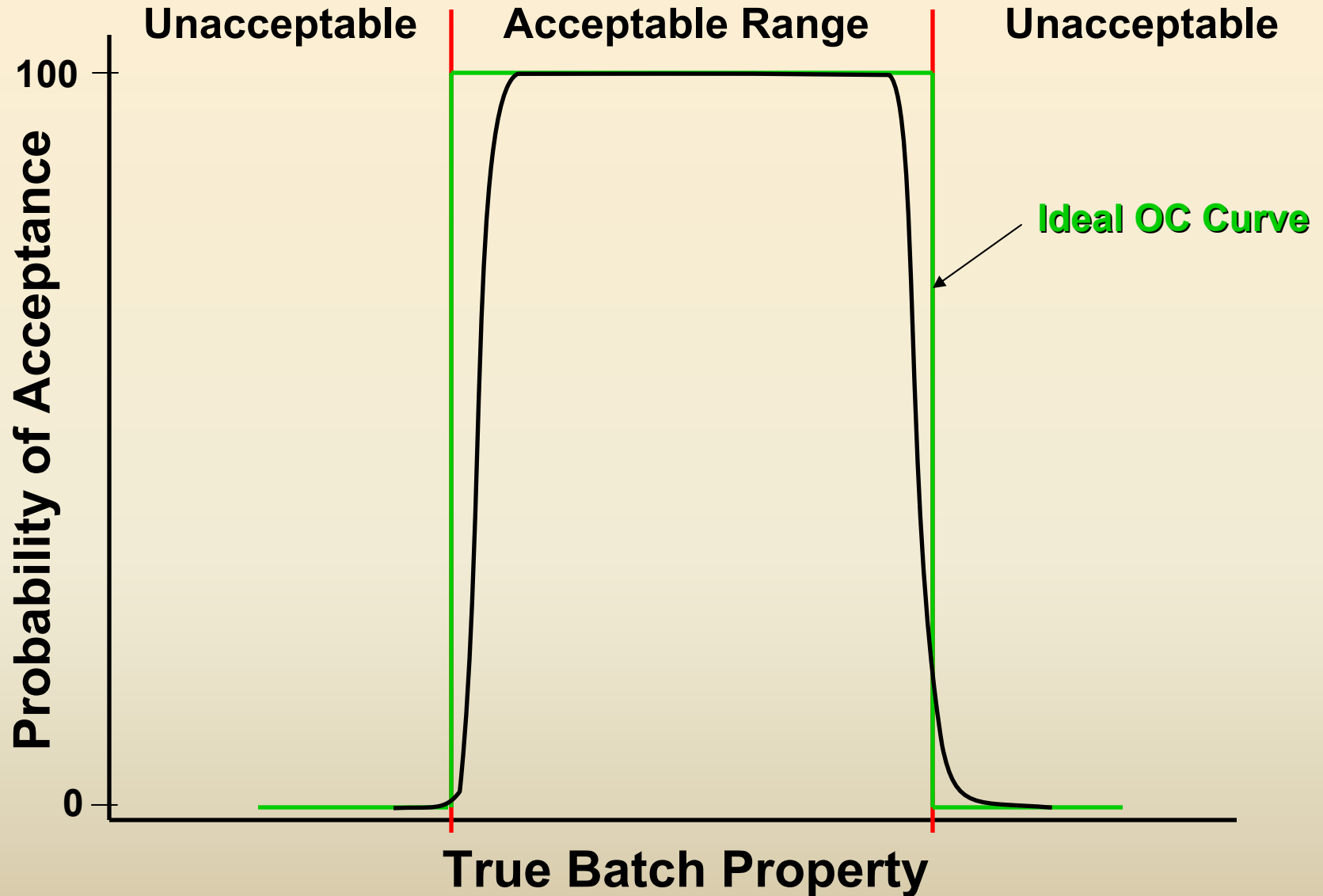
OC Curve Basic Principles



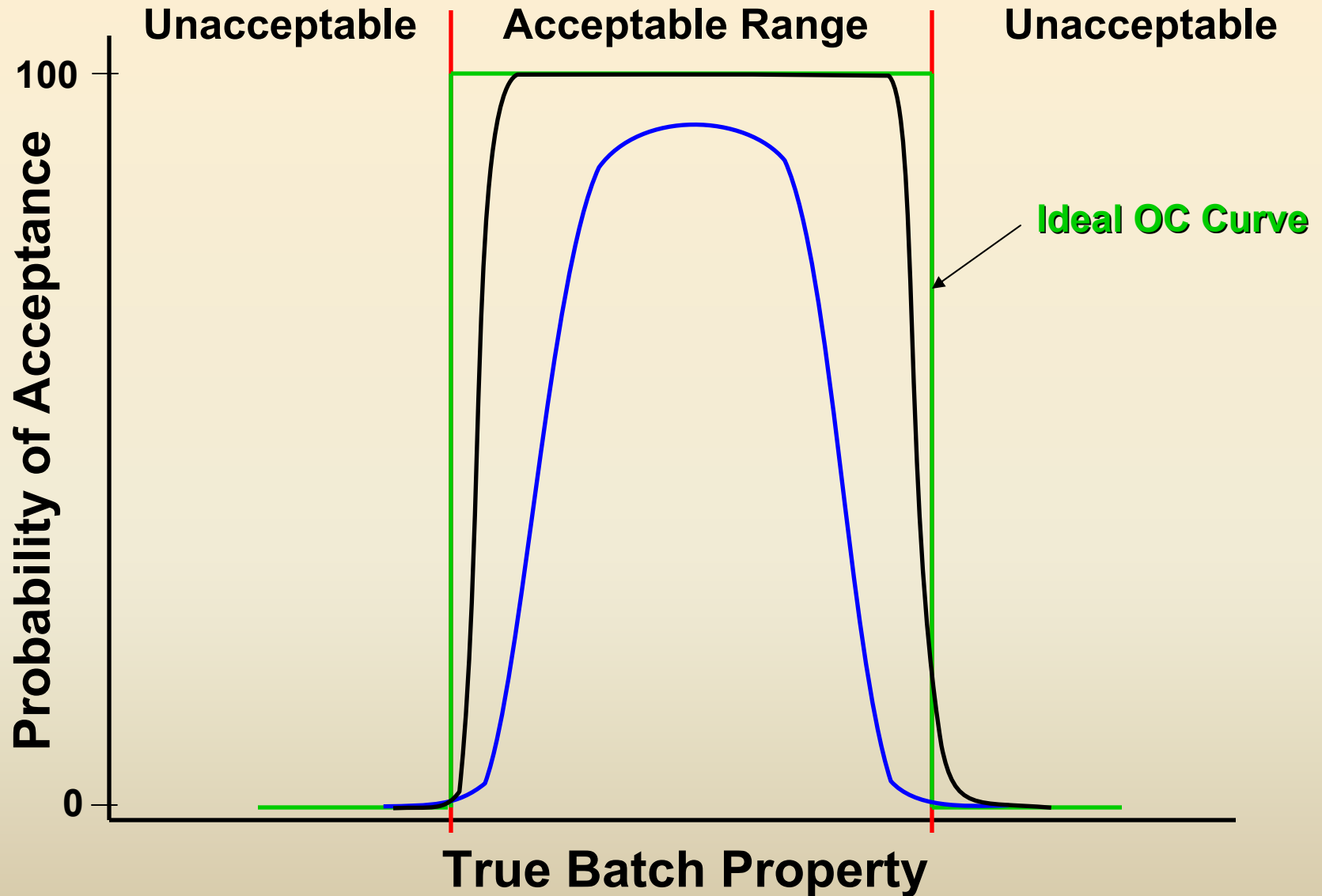
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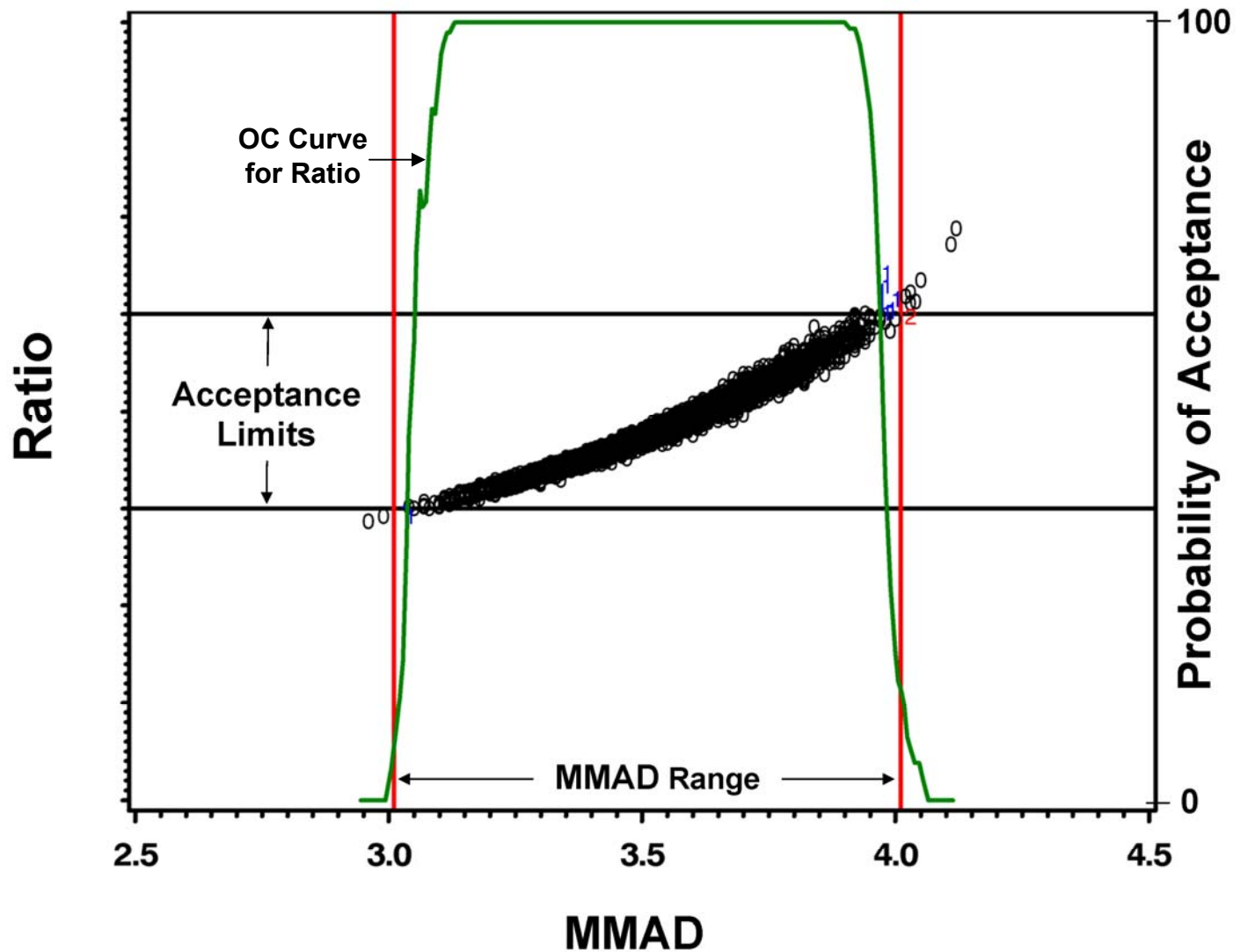


Error Rates – EDA vs. Grouped Stages

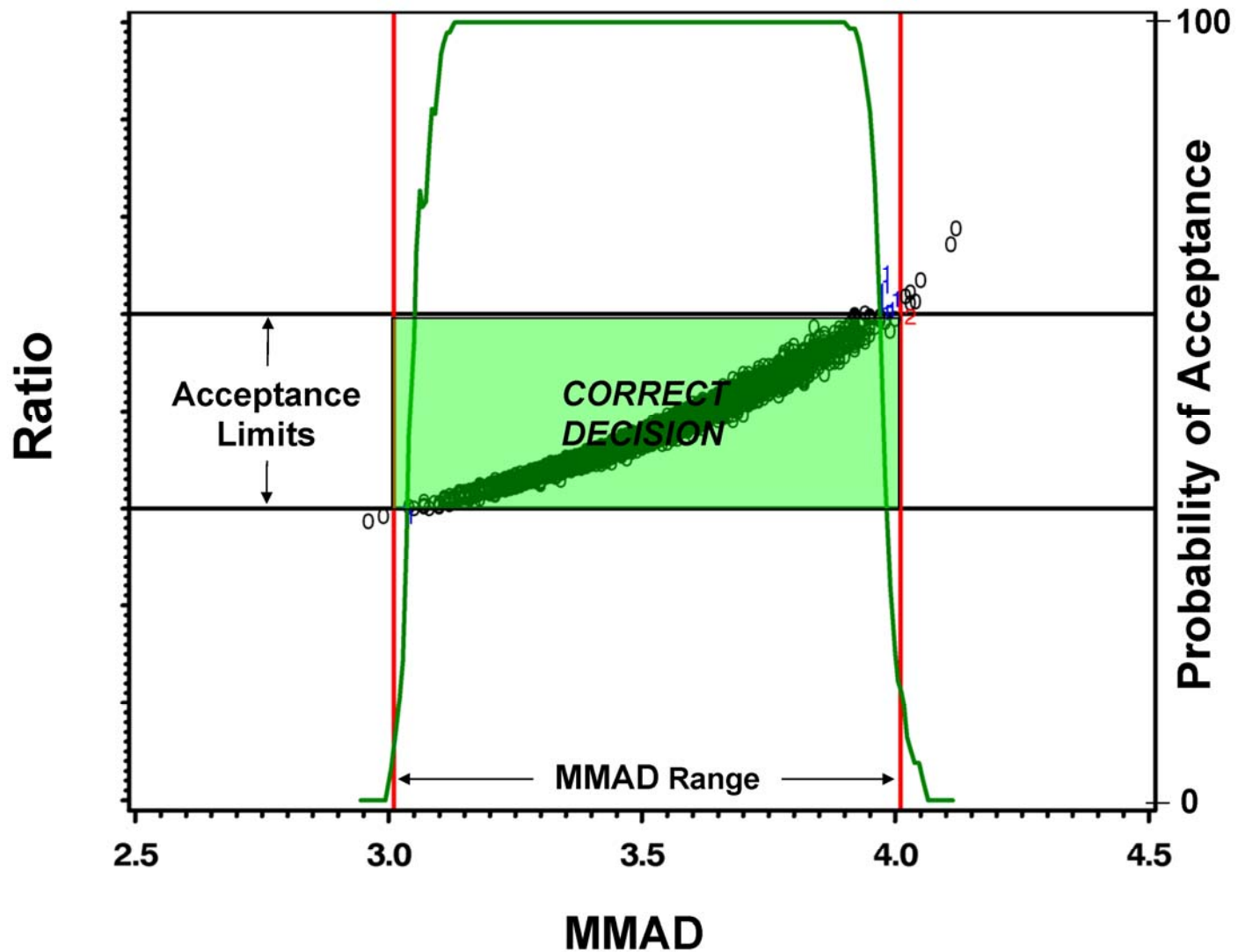
Test	% Correct Decisions	% Incorrect Rejection (Type I Error)	% Incorrect Acceptance (Type II Error)
EDA Ratio	99.72	0.27	0.00*
Grouped Stages	87.76	12.24	0.00

* 1 / 30,000

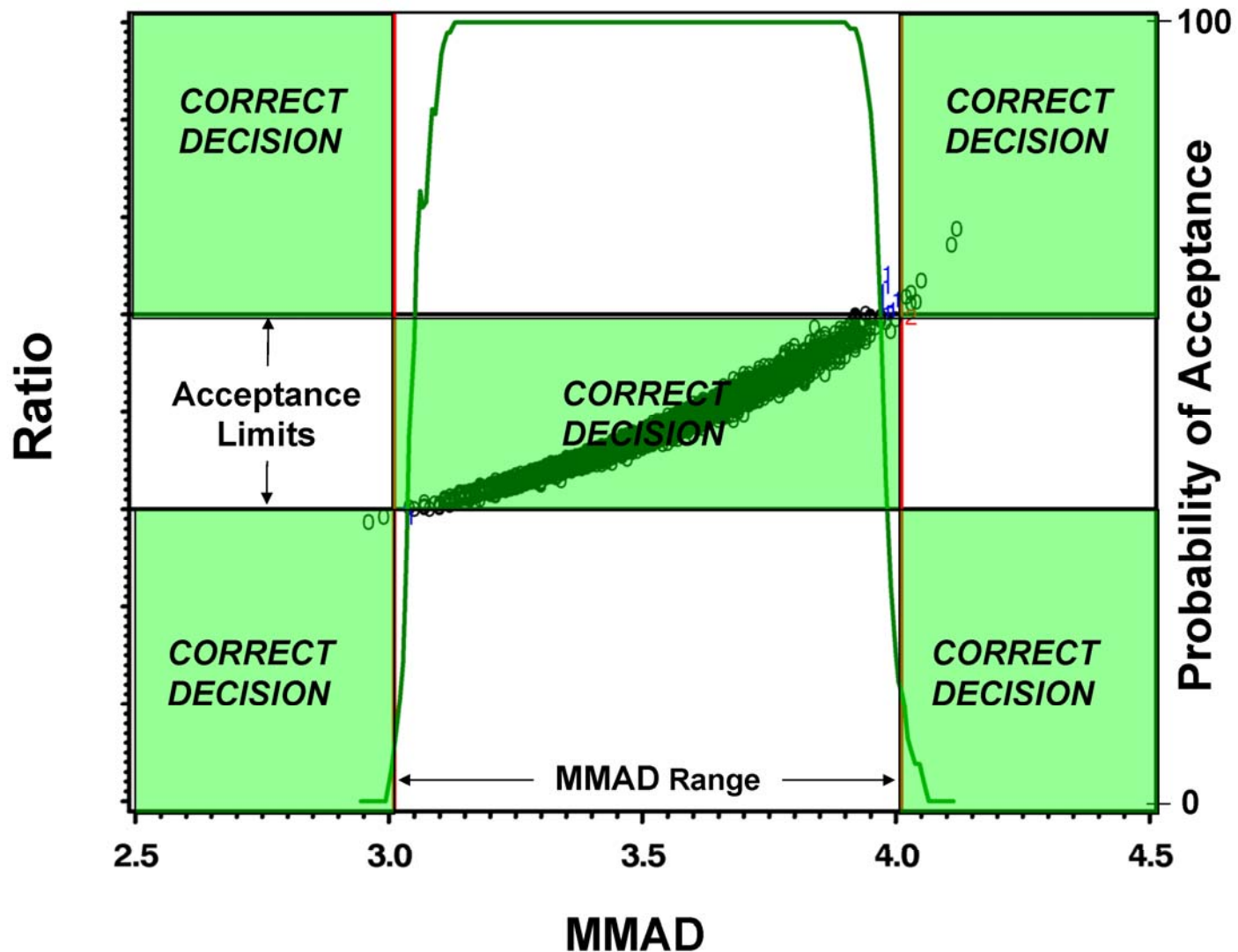
OC Curve and Error Rates - Ratio



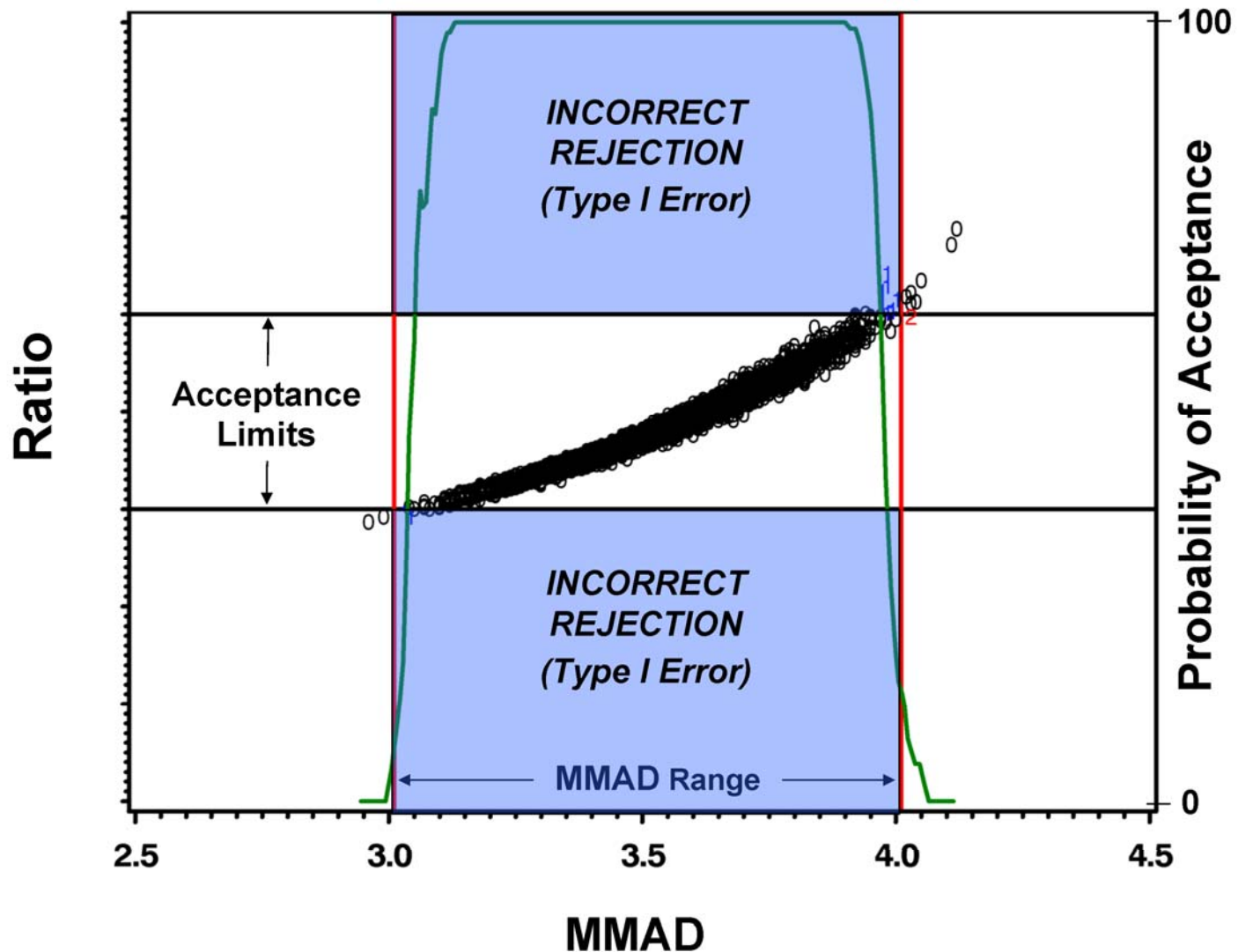
OC Curve and Error Rates - Ratio



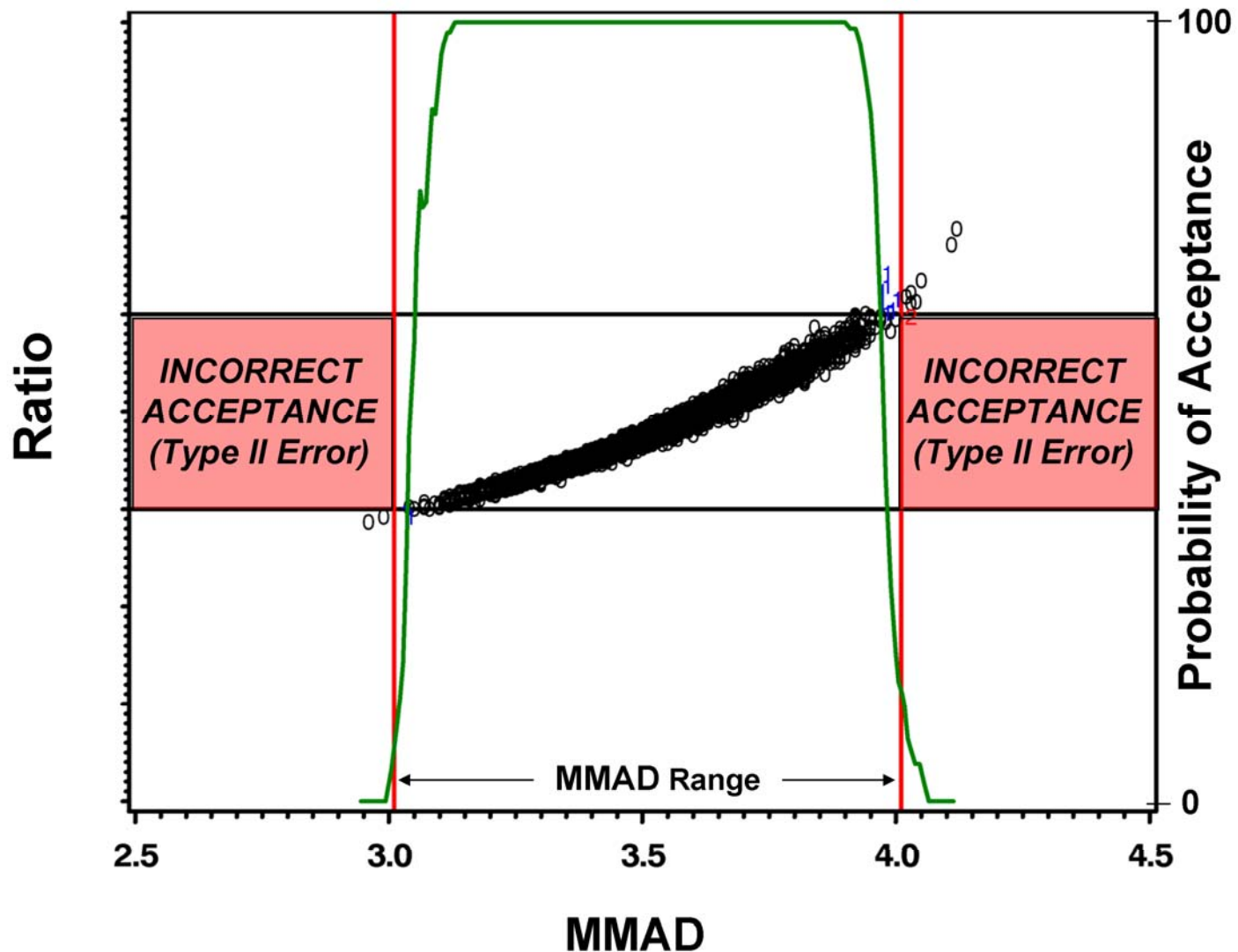
OC Curve and Error Rates - Ratio



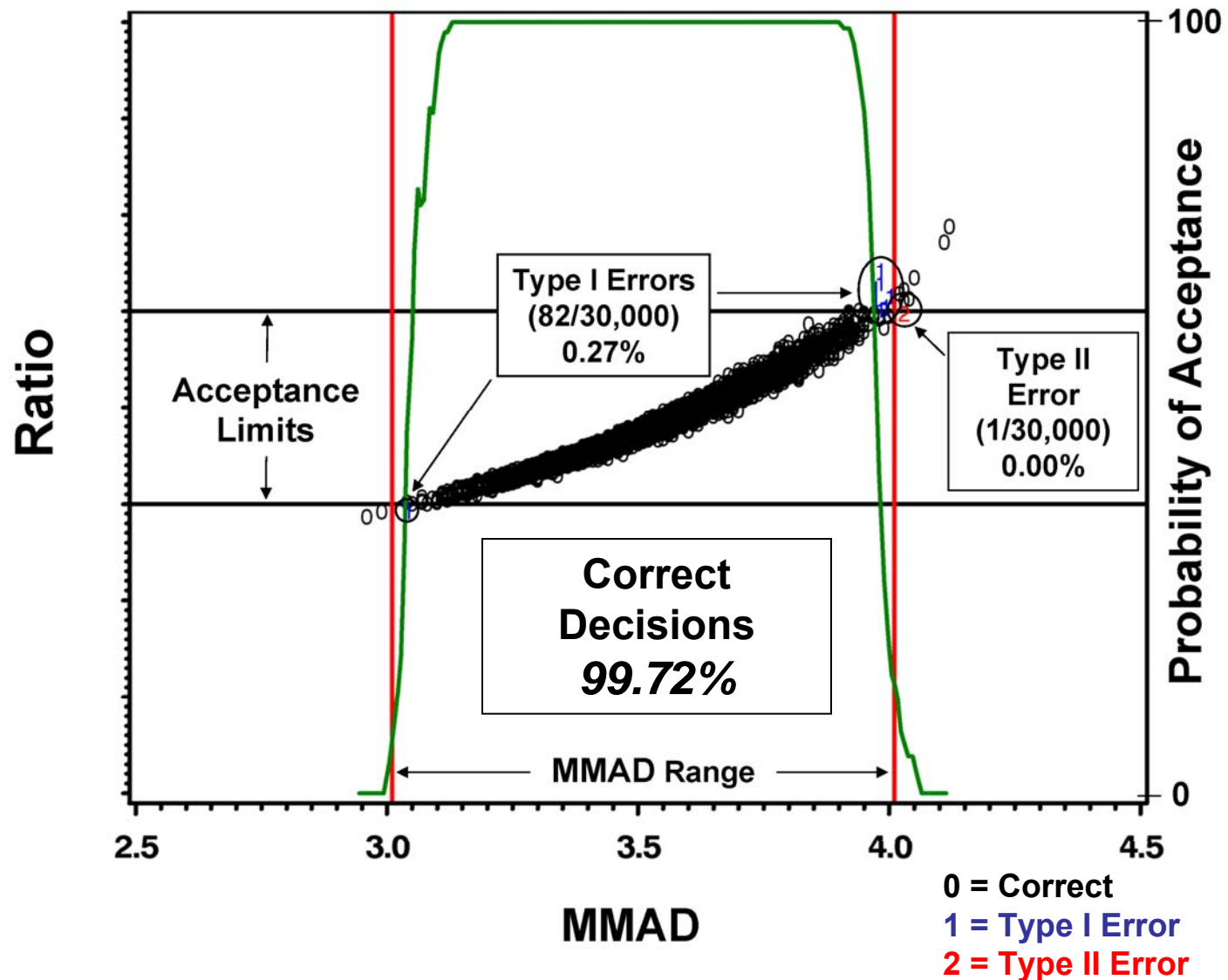
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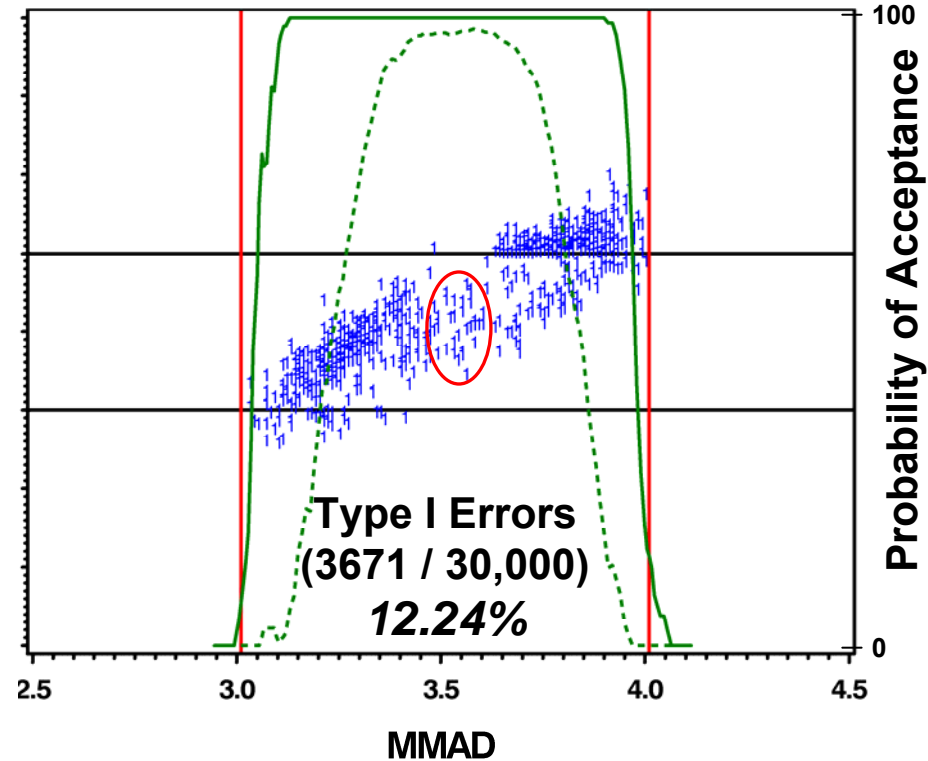
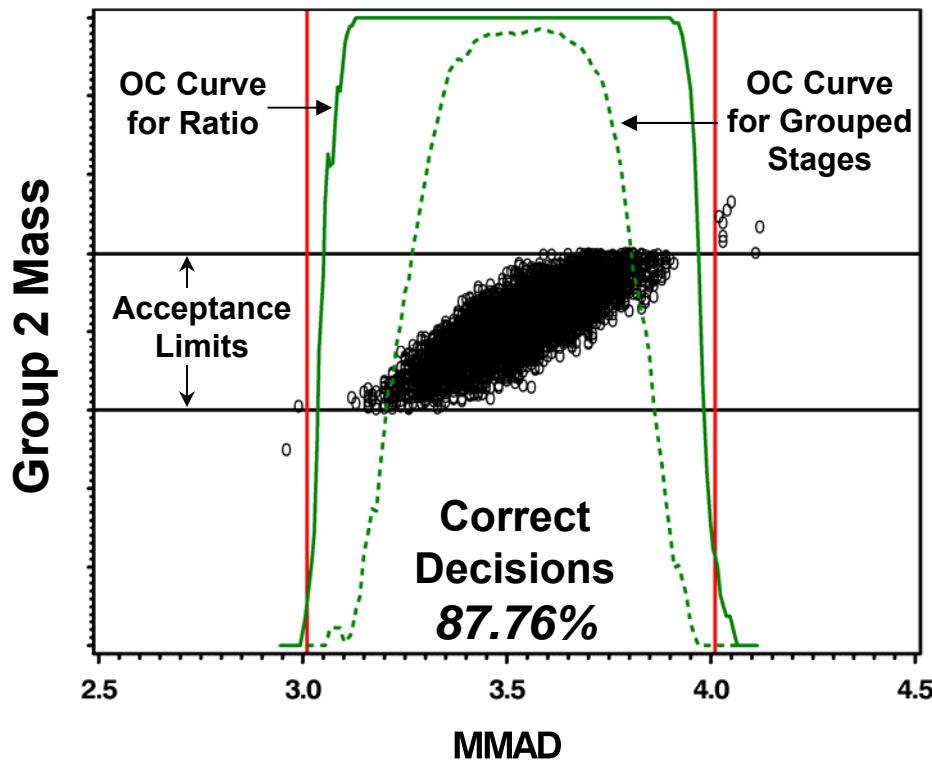
OC Curve and Error Rates - Ratio



OC Curves and Error Rates – Group 2

Correct Decisions

Incorrect Rejections



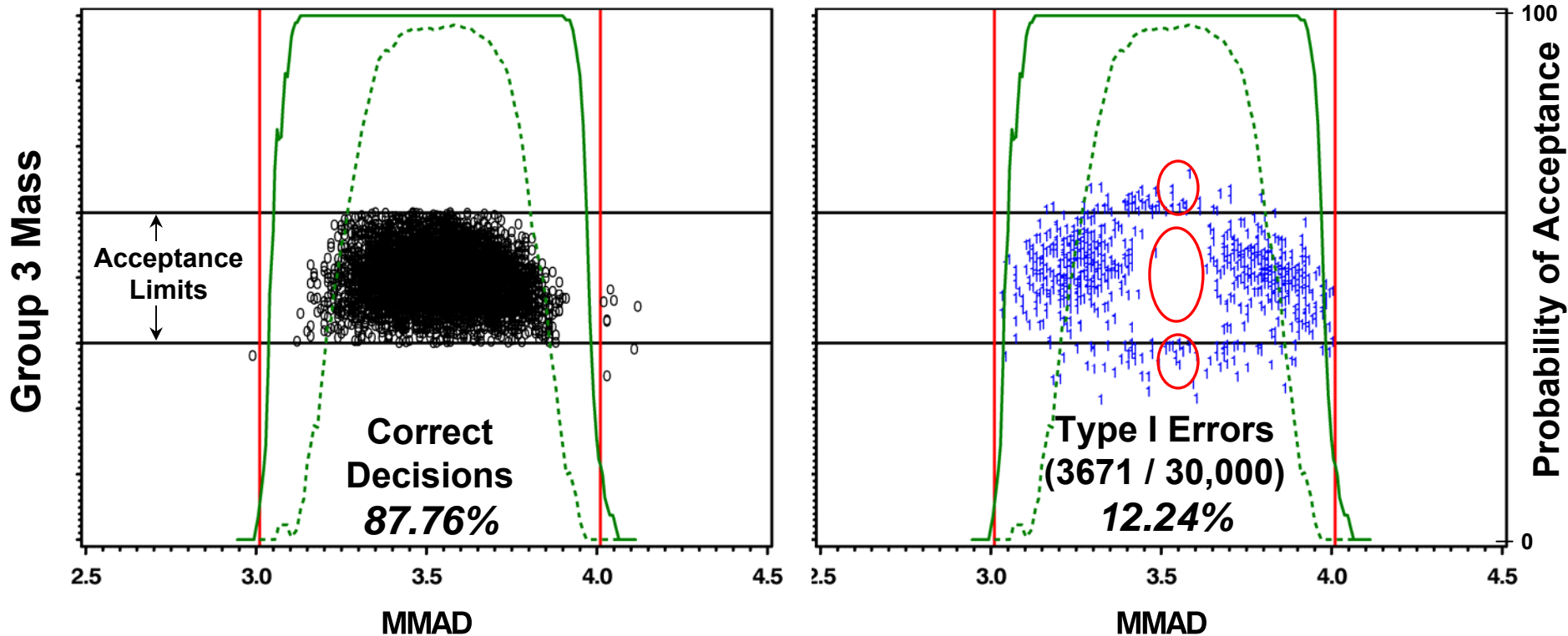
Because all three groups contribute to an outcome, the outcomes, OC curves and rates are the same for all three groups.

0 = Correct
1 = Type I Error

OC Curves and Error Rates – Group 3

Correct Decisions

Incorrect Rejections



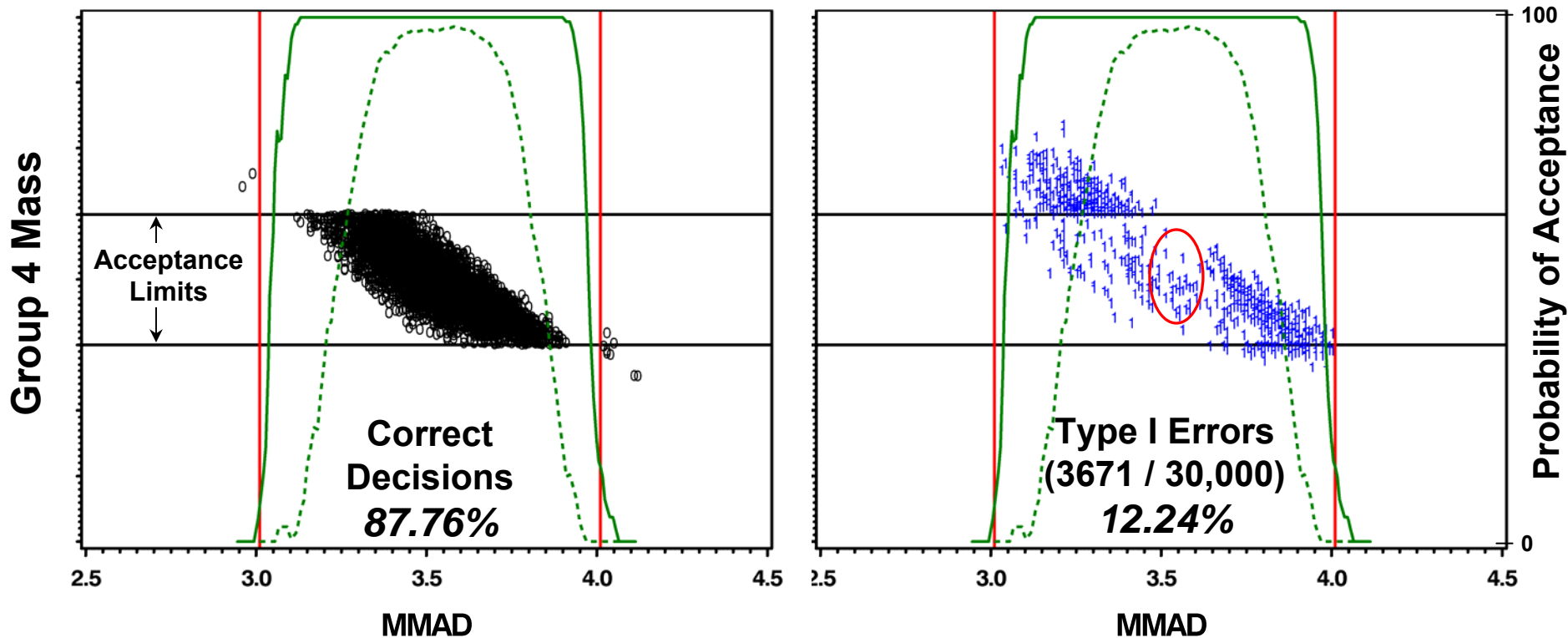
Because all three groups contribute to an outcome, the outcomes, OC curves and rates are the same for all three groups.

0 = Correct
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OC Curves and Error Rates – Group 4

Correct Decisions

Incorrect Rejections



Because all three groups contribute to an outcome, the outcomes, OC curves and rates are the same for all three groups.

0 = Correct
1 = Type I Error

Error Rates – EDA vs. Grouped Stages

Grouping Distribution Percentiles	Prediction Interval (%)	Error Rates (%)			
		Ratio		Grouped Stages	
		Type I	Type II	Type I	Type II
10, 90	95	3.04	0.24	55.32	0
	99	2.19	0.07	59.74	0
	99.9	1.6	0.01	62.21	0
5, 95	95	1.78	0.21	36.98	0
	99	1.51	0.05	39.61	0
	99.9	0.97	0.01	40.84	0
1, 99	90	0.8	0.18	10.37	0.17
	95	0.78	0.08	11.04	0.07
	99	0.39	0.02	11.94	0
	99.9*	0.27	0.00	12.24	0

* Parameters selected in this Summary.

Error Rates – EDA vs. Grouped Stages

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	99	0.39	0.02	11.94	0
	99.9*	0.27	0.00	12.24	0

* Parameters selected in this Summary.

Conclusions

- EDA approach is based on the relationship between Ratio and MMAD, plus uncertainty
- Ratio metric is more predictive of particle size changes in APSD than grouped stages
- EDA allows acceptance limits that minimize both incorrect rejection (Type I) errors and incorrect acceptance (Type II) errors
- Minimizing incorrect acceptance (Type II) errors for grouped stages comes only with increase of incorrect rejection (Type I) errors
- This work provides evidence that the EDA approach is more effective than grouped stages for decisions about changes in APSD that influence particle size

ACKNOWLEDGMENTS

CI WG Members

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5. Terry Tougas **BI (CHAIR)**
6. Tanya Church **Chiesi**
7. David Lewis **Chiesi**
8. Emilio Lutero **Chiesi**
9. Massimiliano Dagli Alberi **Chiesi**
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11. Geoff Daniels **GlaxoSmithKline**
12. Sue Holmes **GlaxoSmithKline**
13. Helen Strickland **GlaxoSmithKline**
14. Richard Bauer **MannKind Corporation**
15. Dave Christopher **Merck**
16. Monisha Dey **Merck**
17. Adrian Goodey **Merck**
18. Jorge Quiroz **Merck**
19. Nagaraja Rao **Novartis**
20. Dave Russell-Graham **Pfizer**
21. Hans Keegstra **Teva**
22. Zecai Wu **Teva**
23. Jolyon Mitchell **Trudell Medical International**
24. Bruce Wyka, **SpiraPharma Consulting**
25. Adam Watkins, **Vectura**

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Thank You

Questions?