From Q2 to QbD: The Influence of Formulation Changes on MDI Performance

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Outline

- QbD and Generic pMDI Product Development
- Reverse Engineering of a Commercial Albuterol Sulfate MDI and Model System Development
- Design of Experiments to Explore Impact of Formulation Changes
  - **Delivered dose (DD)**
  - **Aerodynamic particle size distribution (APSD)**
- Conclusions

MDI Generic Product Development

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Qualitative sameness (Q1): Test product uses the same inactive ingredient(s) as the Reference product.

Quantitative sameness (Q2): concentration of inactive ingredients within ± 5% of those used in Reference product.

- **FDA Draft Guidance (2013): Draft Guidance on Albuterol Sulfate**
- **But ± 5% range is arbitrary**

Under Quality by Design (QbD), one should understand how changes in critical quality attributes (CQAs) influence product performance.

- **ICH Guideline (2009): Q8(R2) pharmaceutical development.**

MDI Generic Product Development

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Premise: ***A QbD approach should define the design space within which a TEST product performs equivalently to the reference listed drug (RLD). This would provide a scientific basis for inactive ingredient levels.***

Goal: Evaluate effects of varying an MDI formulation using a multivariate statistical approach.

- **Use a range of inactive ingredients to explore the design space within and outside the Q2 acceptance range of ± 5%.**
- **Evaluate effect of primary particle size.**
- **Generate a target product profile around a commercial albuterol sulfate MDI, which will form the basis of a model system for evaluating the formulation effects.**

Reverse Engineering

3 lots of marketed product were reverse engineered to identify the following Q1 / Q2 equivalent formulation:

Reference Listed Drug (RLD) Formulation (% w/w)

Albuterol Sulfate	EtOH	Oleic Acid	HFA-134a
0.38	14.4	0.03	85.20

Estimated primary particle size via laser diffraction (µm)

X_{10}	X_{50}	X_{90}
0.7	1.5	3.4

Model System Development

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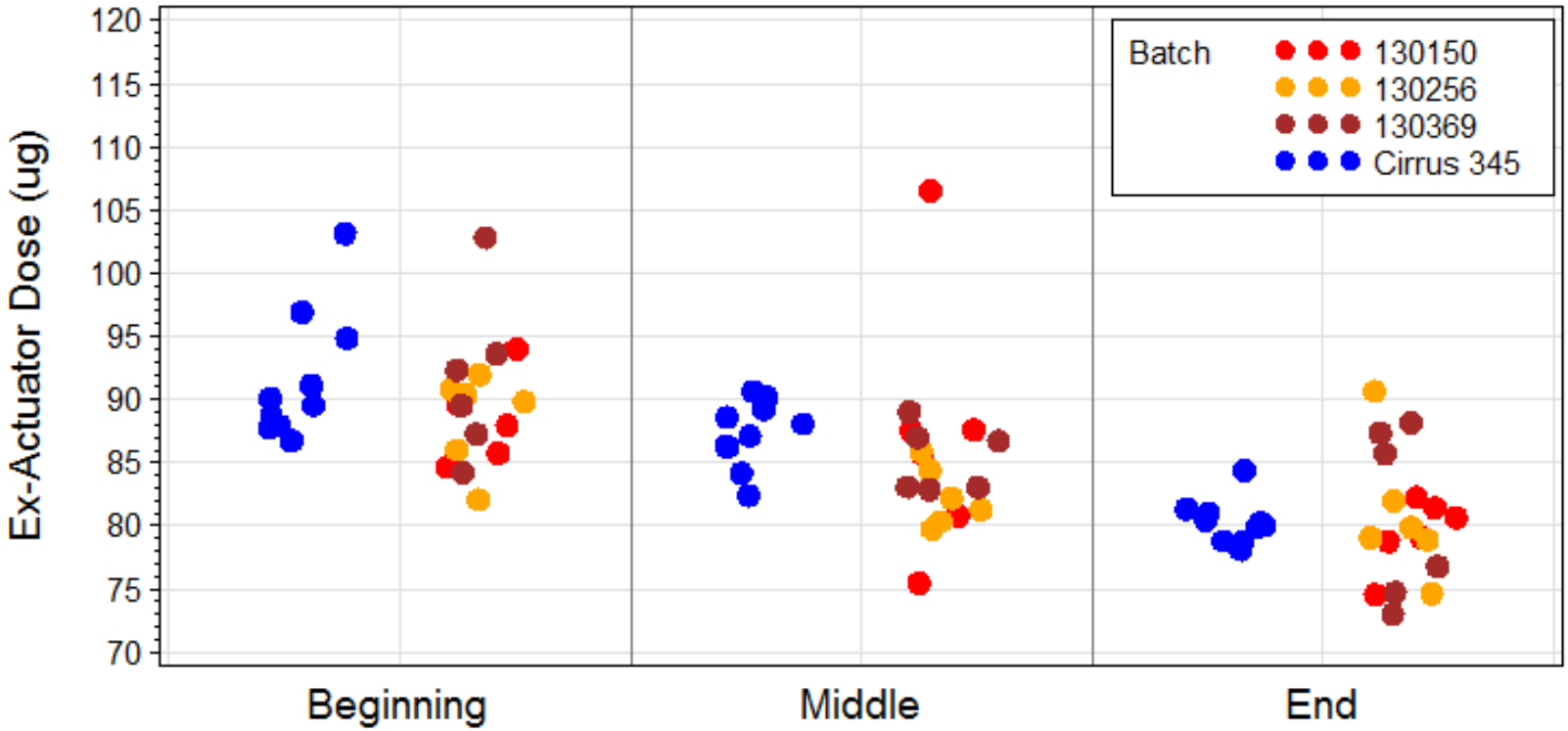
MDI Filling:

- **Albuterol sulfate milled to target size**
- **1-step pressure filling (Pamasol suspension filler) at 3 L**
- **17-mL uncoated cans (Presspart), 28-µL valves (Aptar), and actuators (RLD)**

Aerosol Testing:

- **USP methodologies for delivered dose uniformity through life & aerodynamic particle size distribution (APSD) via Next Generation Impactor (NGI)**

DD Uniformity:
RLD & Model System

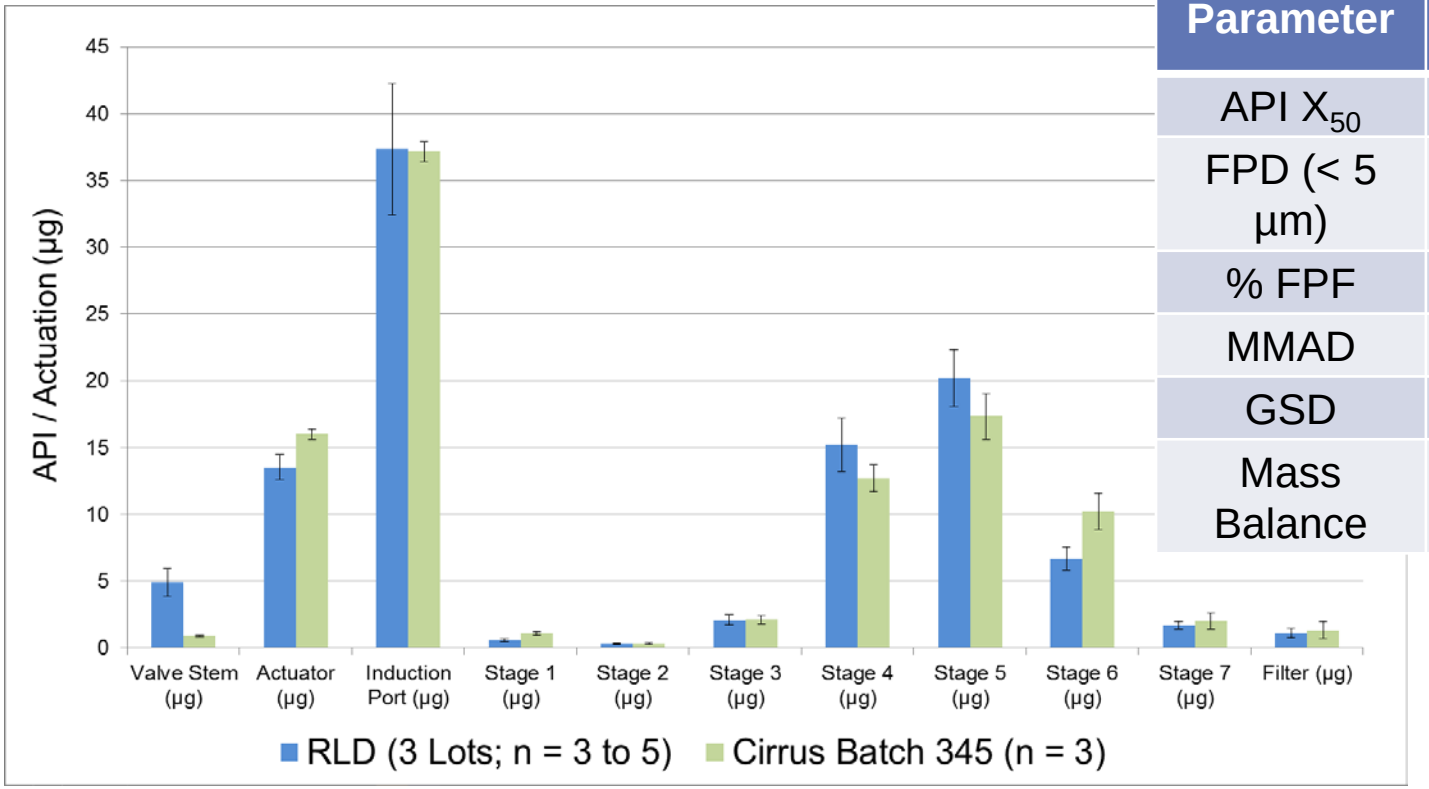


- RLD & model system show very similar performance.
- A downward through-life trend is observed in both systems.

APSD via NGI:

Comparison of RLD & Model System

Tested via USP Induction Port



Test Parameter	Cirrus Batch 345	RLD
API X_{50}	1.40 µm	n/a
FPD (< 5 µm)	45 µg	45 µg
% FPF	53%	53%
MMAD	1.9 µm	2.0 µm
GSD	1.7	1.6
Mass Balance	101%	104%

- RLD & model system show similar performance.

Experimental Design

- **Goal 1: Assess potential effects**
  - **API primary particle size (X_{50})**
  - **EtOH content**
  - **Oleic acid content**

	API X_{50} (µm)	EtOH (% w/w)	Oleic Acid (% w/w)
RLD	**1.5**	**14.4**	**0.03**
DoE (High)	2.5	20%	0.1% *
DoE (Med)	1.65	14%	0.02%
DoE (Low)	1.4	7%	0.005%

***OA level extended to 0.25%**

Experimental Design

- Goal 2: Establish models
  - How do different responses vary with changes in the three factors
  - Estimate effects of any change within experimental domain
- Consider potential conflicts in objectives
  - For the first objective above, it is optimal with two levels for each factor
  - For the second objective, one would like “many” levels of each
- Compromise approach
  - Three levels for each factor
  - Reduced factorial design: $3^3 = 27$ reduced to 18 batches
  - This allows estimation of main effects and all two-factor interactions

Experimental Design

X_{50} (µm)	EtOH (% w/w)	OA (% w/w)
*1.4	7	0.005
1.4	7	0.02
1.4	14	0.005
1.4	14	0.10
1.4	20	0.02
*1.4	20	0.10
1.65	7	0.005
1.65	7	0.10
1.65	14	0.02

X_{50} (µm)	EtOH (% w/w)	OA (% w/w)
1.65	14	0.10
1.65	20	0.005
1.65	20	0.02
2.5	7	0.02
*2.5	7	0.10
2.5	14	0.005
2.5	14	0.02
*2.5	20	0.005
2.5	20	0.10

Drug solubility at 20% ≈ drug solubility at 14%.

*** "Corner batches" = combination of high & low levels**

- **Tested first to confirm the experimental design**

Experimental Design

Additional batches added to evaluate OA up to 0.25%

X_{50} (µm)	EtOH (% w/w)	OA (% w/w)
2.5	2	0.005
2.5	2	0.25
2.5	5	0.005
2.5	5	0.25

Test Plan

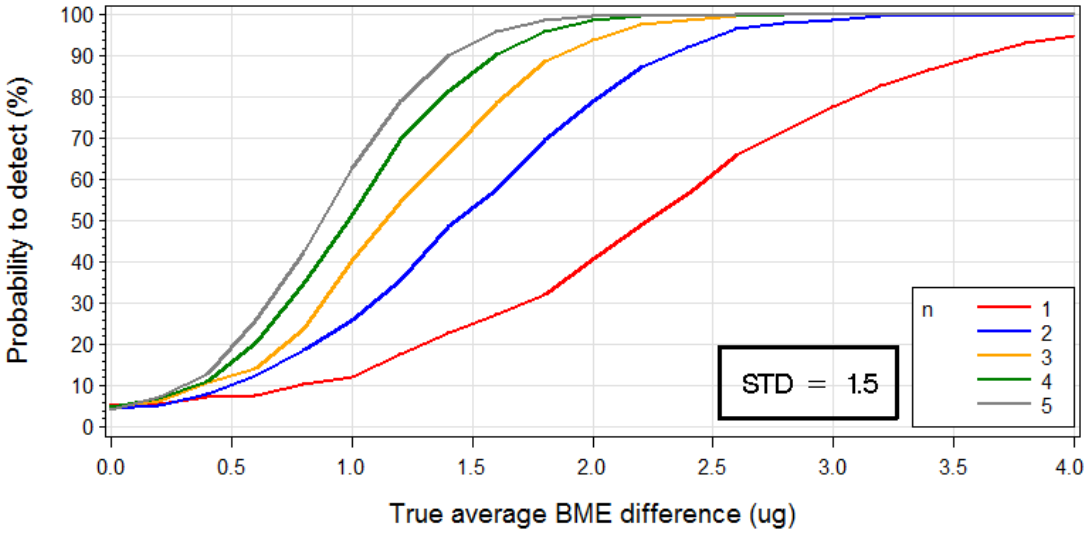
- Batch Testing (14 ± 2 days after filling)
  - EtOH & OA (to confirm successful manufacture & for modelling)
  - Total can content (to confirm manufacture)
  - Moisture content
  - Volumetric particle size distribution by laser diffraction
  - DDU & APSD (primary performance characteristics)
- Delivered Dose Uniformity
  - Two doses at each life-stages of Beg, Mid, & End (6 doses in total per can), for each of n cans/batch
  - End-points: DD average (BME), Trend (B-E as % of B) & RSD of DD
  - All testing by same analyst
- Aerodynamic Particle Size Distribution
  - Alberta Idealized Throat (beg & end doses) & USP throat (beg doses) for each of n cans/batch
  - End-point: FPD < 5 µm
  - All testing by same analyst

Delivered Dose Sample Size:

Probability to Detect Difference in BME

Estimates from Cirrus batch 345

End-point	Mean	STD	1.25 x STD	RSD
BME average	86.5	1.21	1.5	1.7
Trend	12.3	2.59	3.2	3.7
RSD	7.0	1.36	1.7	24



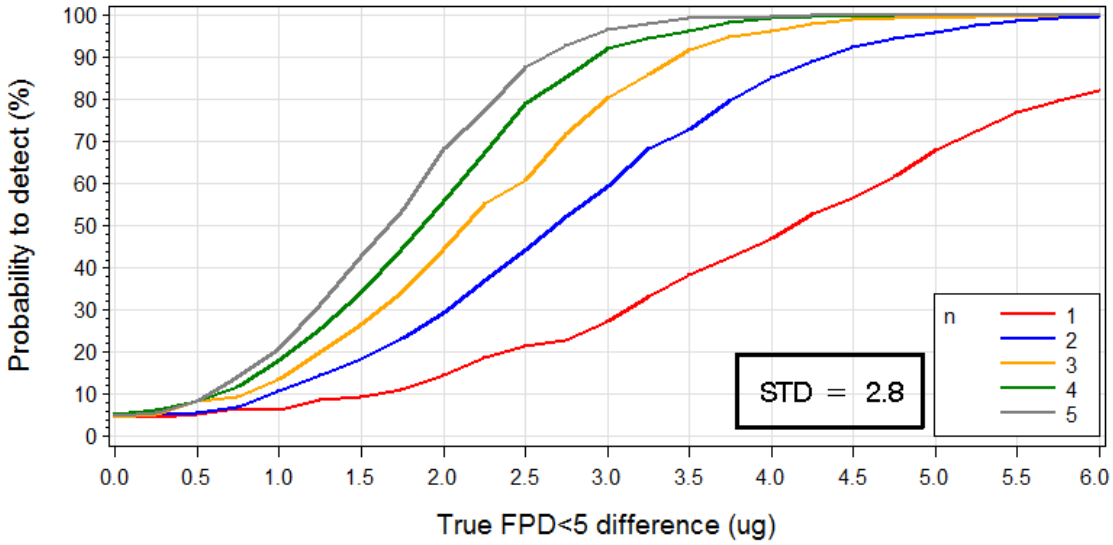
- With one can per batch (18 in total) a 4 µg difference (about 5% of 86.5 µg) is 96% sure to be detected
- One can is not enough for a good characterization of a batch, but the power is fully sufficient to assess effects and for modeling
- Sample size = 1 can/batch (plus 2 extra per batch for the 4 design corners)

APSD Sample Size

Probability to Detect Difference in FPDs

APSD/AIT: Estimates from Cirrus batch 345

End-point	Mean	STD	1.25 x STD	RSD
DD	83.8	2.06	2.6	2.5
FPD<5	52.5	2.24	2.8	4.3



- With one can per batch (18 in total) a 6 µg difference (about 11% of 52.5 µg) is 82% sure to be detected

- Initial testing with AIT throat B&E and USP throat B only for each can (54 NGIs in total)

Evaluation Plan

1. Visual assessment of data

2. ANOVA
   - Any statistically significant main effects or interactions?
   - Strongest factors?

3. Modeling
   - Will partly be guided by findings above
   - Both linear and non-linear models will be considered

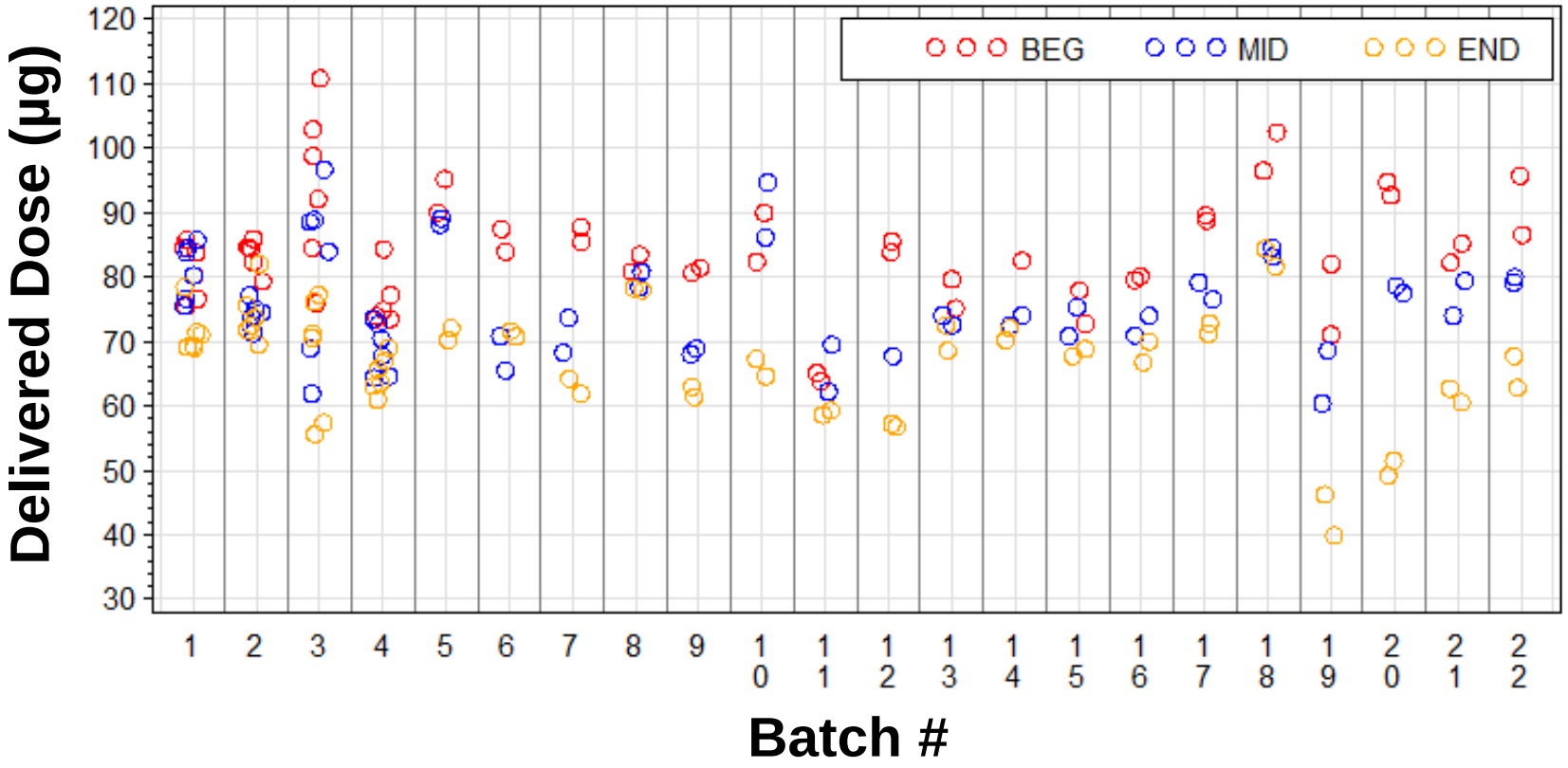
$$DD = \alpha_0 + \alpha_1 X50 + \alpha_2 EtOH + \alpha_3 OA$$

$$DD = (\alpha_0 + \alpha_1 X50)(\beta_0 + \beta_1 EtOH)(\delta_0 + \delta_1 OA)$$

$$DD = \alpha_0 + \alpha_1 X50^{\lambda_1} + \alpha_2 EtOH^{\lambda_2} + \alpha_3 OA^{\lambda_3}$$

$$DD = \lambda \cdot X50^{\lambda_1} \cdot EtOH^{\lambda_2} \cdot OA^{\lambda_3}$$

Delivered Dose Through Life



- Delivered dose ranges from 40 to 111 µg, with a mean of about 80 µg.
- A decreasing through-life trend is observed.

Delivered Dose

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ANOVA and Least Squared Means

ANOVA for batches 1-18 (p values)

Effect	Mean	Mean B	Mean M	Mean E	Trend %(B-E)/B	RSD
X_{50}	0.3823	0.4717	0.5253	0.2056	0.6172	0.4183
EtOH	0.1211	0.0193	0.1716	0.5612	0.0059	0.0004
OA	0.4188	0.2645	0.7131	0.5265	0.4701	0.1268
X_{50}*EtOH	0.6381	0.4597	0.5200	0.6819	0.3921	0.3771
X_{50}*OA	0.1863	0.2245	0.2273	0.1264	0.9686	0.9660
EtOH*OA	0.3459	0.4899	0.5339	0.1684	0.4589	0.0521

Least squared means for each level of EtOH (batches 1-18)

EtOH (%)	Mean (µg)	Mean B (µg)	Mean M (µg)	Mean E (µg)	Trend (%)	RSD (%)
7	80	90	81	68	24.1	14.3
14	77	86	76	71	17.3	9.5
20	71	75	70	68	10.1	5.8

- **Large effects are observed for Mean B DD, Trend, & RSD**

Delivered Dose

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ANOVA and Least Squared Means

ANOVA for batches 19-22 (p values)

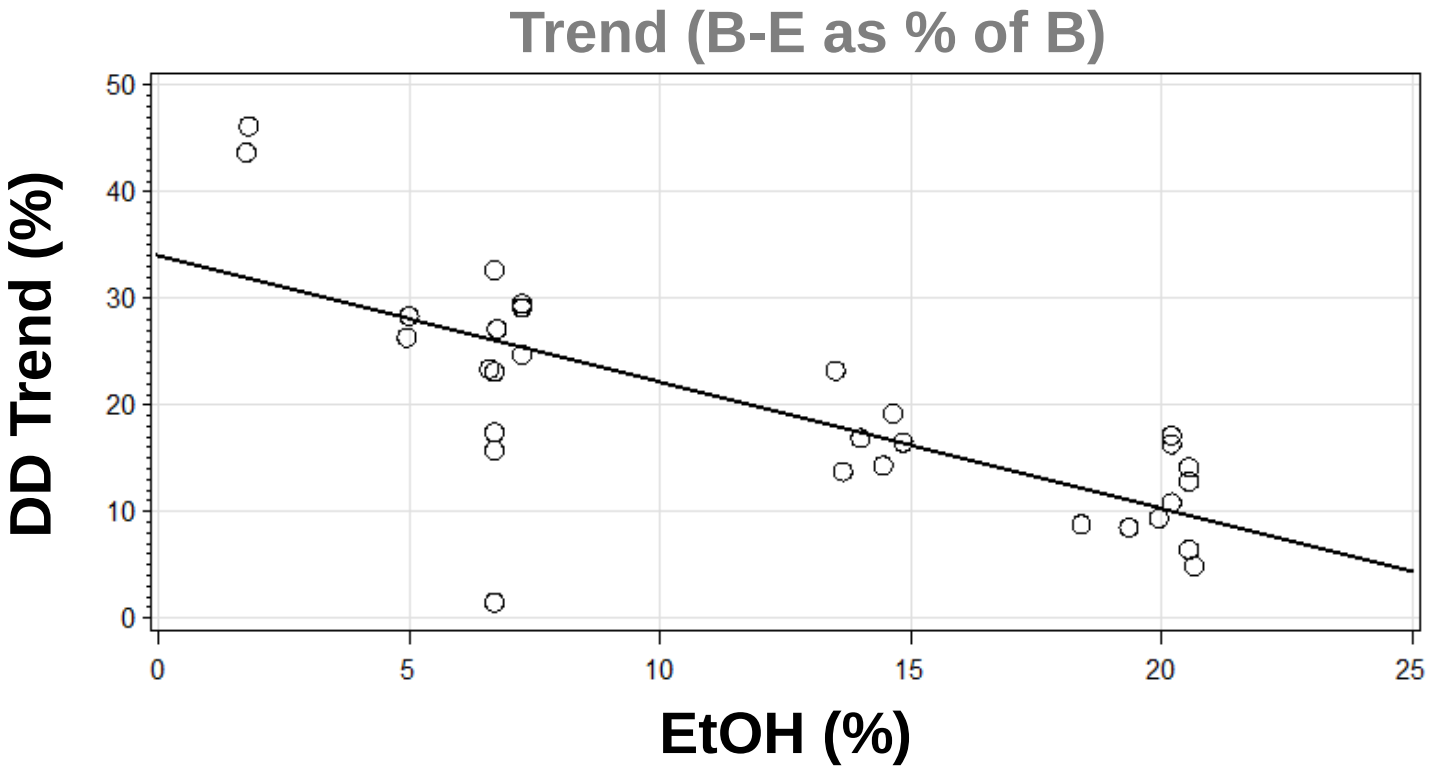
Effect	Mean	Mean B	Mean M	Mean E	Trend	RSD
EtOH	0.2762	0.7158	0.4203	0.0691	0.0092	0.0208
OA	0.2761	0.2399	0.3670	0.2050	0.0720	0.2289

Least squared means for each level of EtOH (batches 19-22)

EtOH (%)	Mean (µg)	Mean B (µg)	Mean M (µg)	Mean E (µg)	Trend (%)	RSD (%)
2	68	85	71	47	45.0	26.2
5	76	88	78	64	27.4	14.6

- **Still no effect by oleic acid (despite the wider range studied).**
- **EtOH has significant effects on trend and RSD.**

Delivered Dose Trend(%) vs EtOH Content



The delivered dose Trend(%) decreases as EtOH increases.

Delivered Dose Models

Multivariate models for mean delivered dose

- **All 3 factors used**
- **All 22 batches used in a pooled analysis**

Mean DD = a + b(X_{50}) + c(EtOH) + d(OA)

- **Explains only 12% of the total variation**

Based on residual plots for each factor, the following non-linear model was tested:

Mean DD =

a1 +a2(X_{50}) + a3(X_{50})^2 + a4(EtOH) + a5(EtOH)^2 + a6(X_{50})(EtOH) + a7(OA)

- **Explains 28% of total variation**

How Would a 5% Change in a Factor Affect Delivered Dose?

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1) Set 2 factors at their nominal values and change the third factor within 95% - 105% of target:

X_{50}	EtOH	OA	Mean DD (µg)
1.501 – 1.659	14.4	0.03	75.78 – 77.83
1.58	13.68 – 15.12	0.03	76.38 – 76.96
1.58	14.4	0.0285 – 0.0315	76.68 – 76.72

Result: at most approx 2 µg change in DD

2) Change all 3 factors 5% at once.

Result: approx 2.5 µg maximum change in DD

What Design Space Will the Delivered Dose Data Support?

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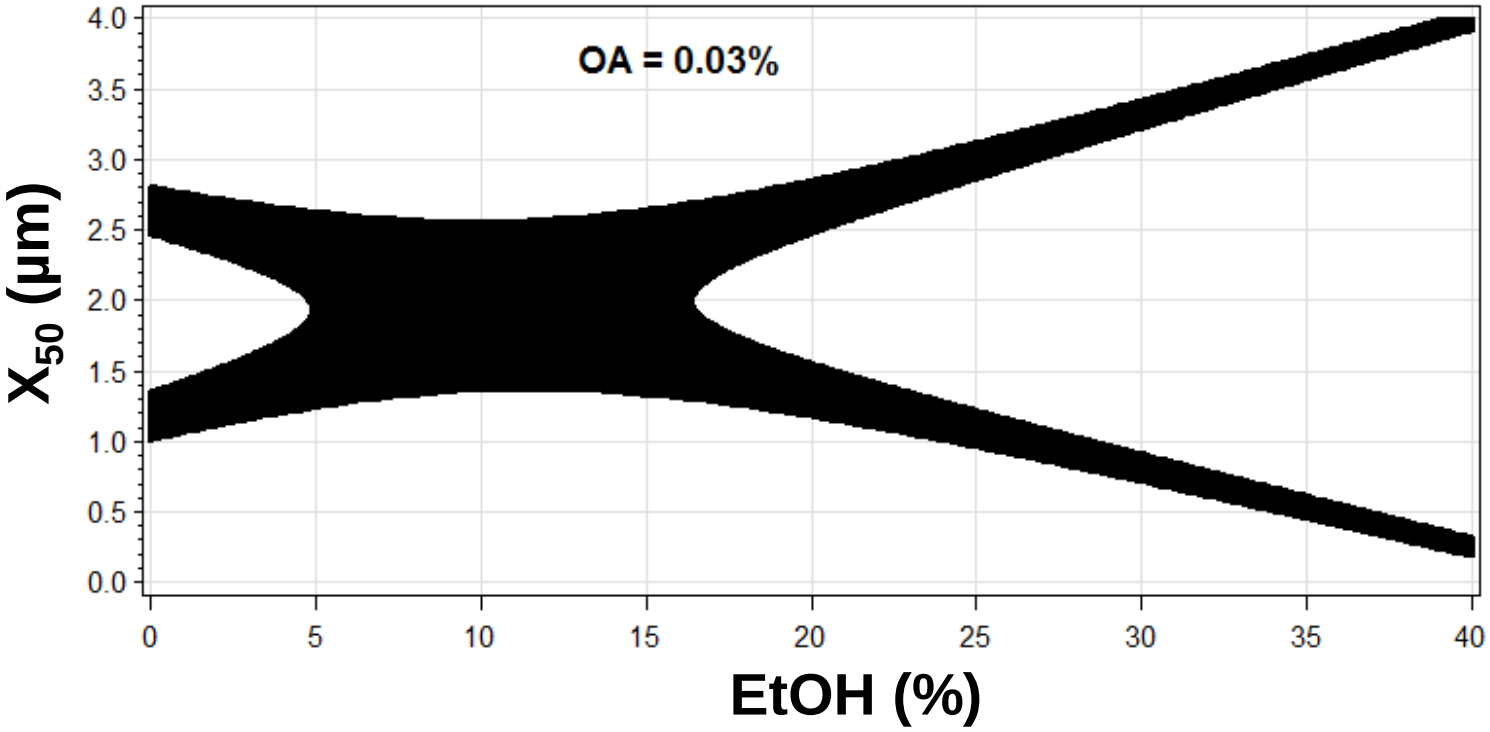
Assuming we want delivered dose to be 95% to 105% of target



Data do not rule out formulation changes outside of ±5% of EtOH target.

Multivariate Models for Delivered Dose RSD

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$RSD = a + b(\ln(X_{50})) + c(\ln(EtOH)) + d(\ln(OA))$

- Explains 85% of the total variation

How would a 5% change in a factor affect the DD RSD?

- If we set 2 factors at nominal values & vary the third factor, the largest effect is changing ethanol, where RSD increases by 0.7%
- Changing all 3 factors at once by 5% causes RSD to vary in range of 7.92 to 8.95%.

What Design Space Will the Delivered Dose Data Support?

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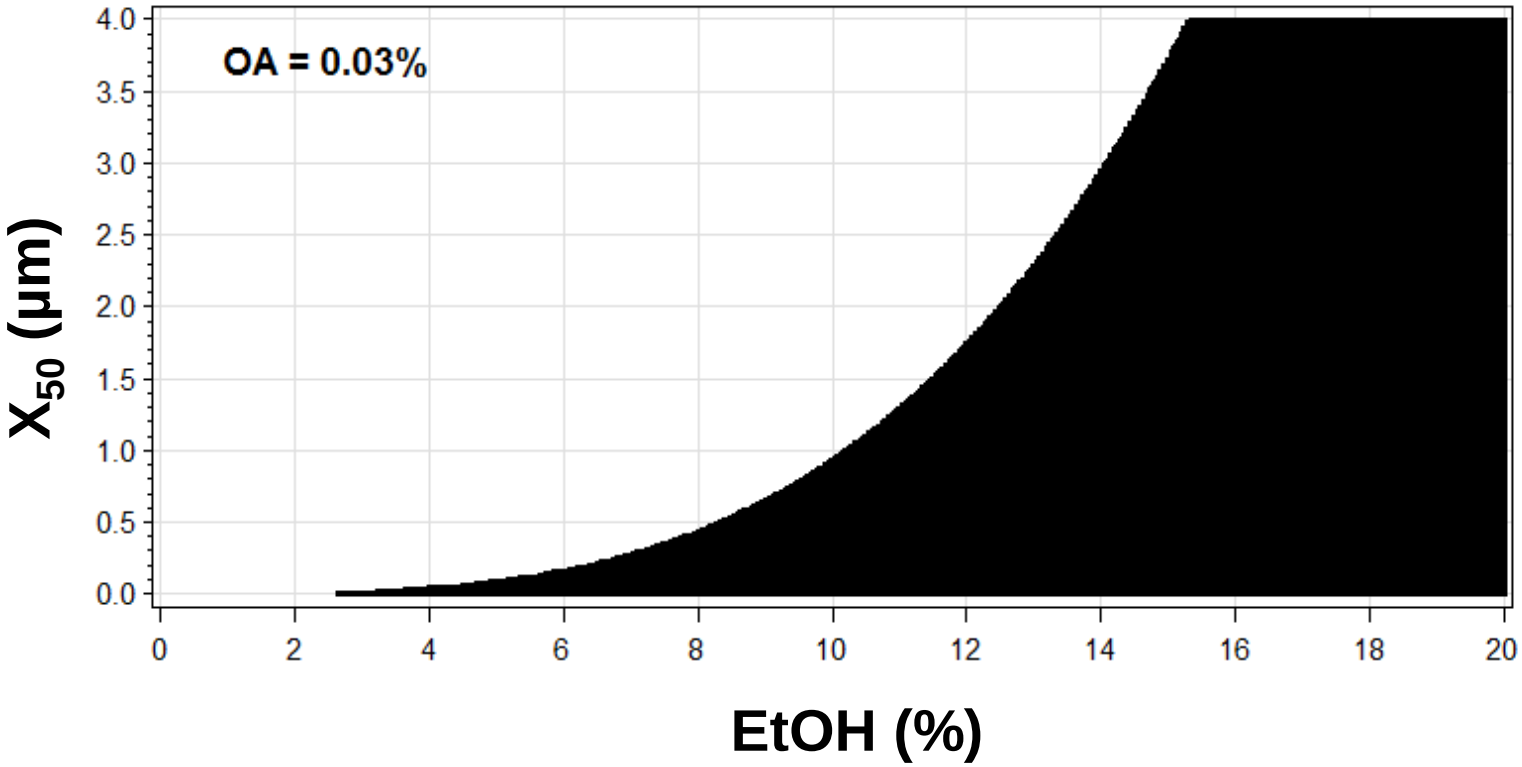
Assuming we want RSD < 10%

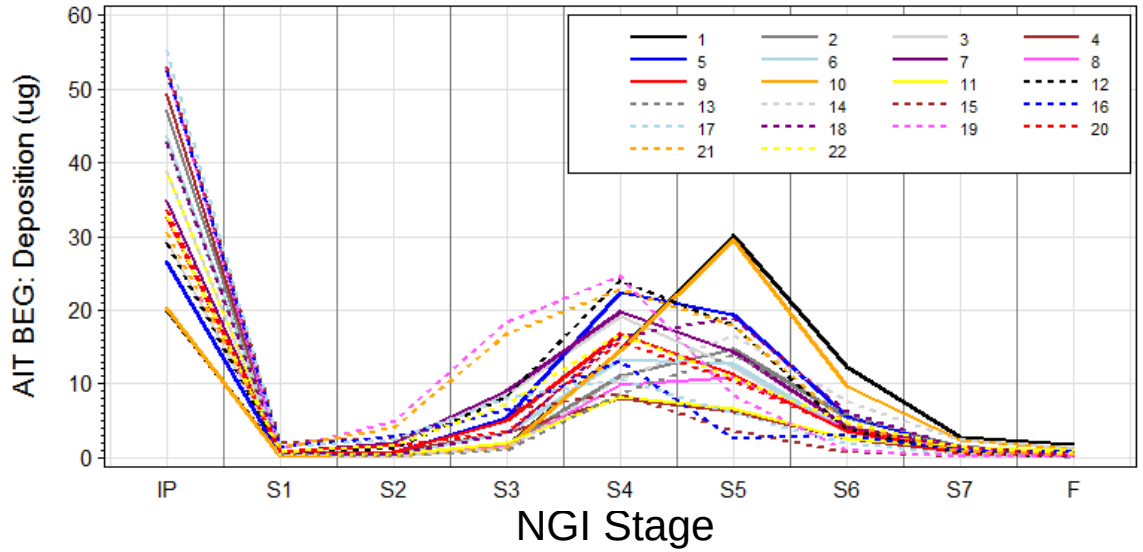


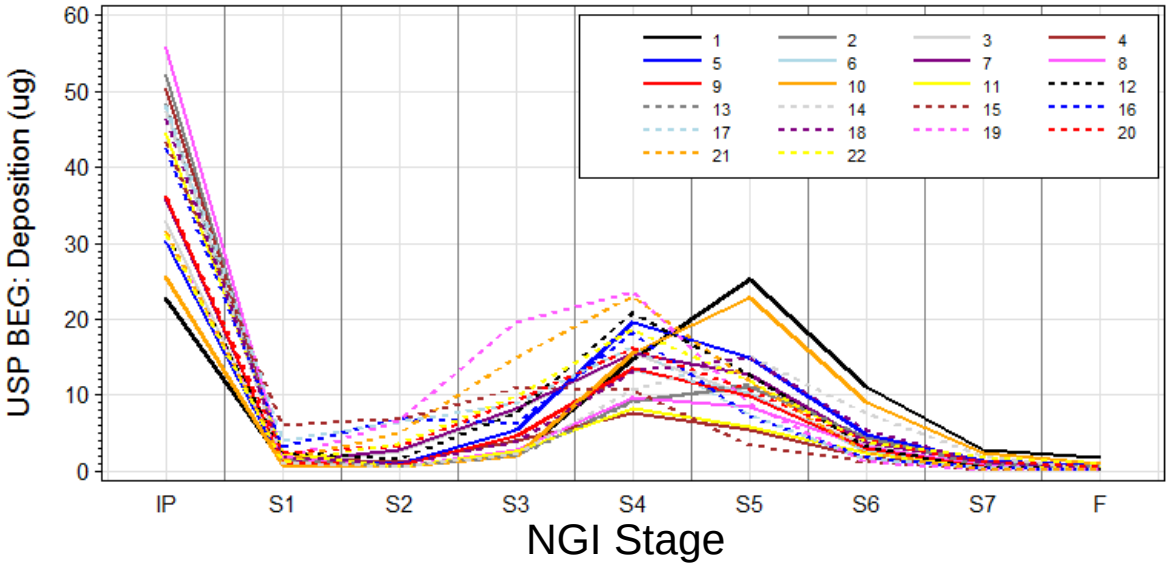
Data do not rule out formulation changes outside of ±5% of EtOH target.

Delivered Dose Summary

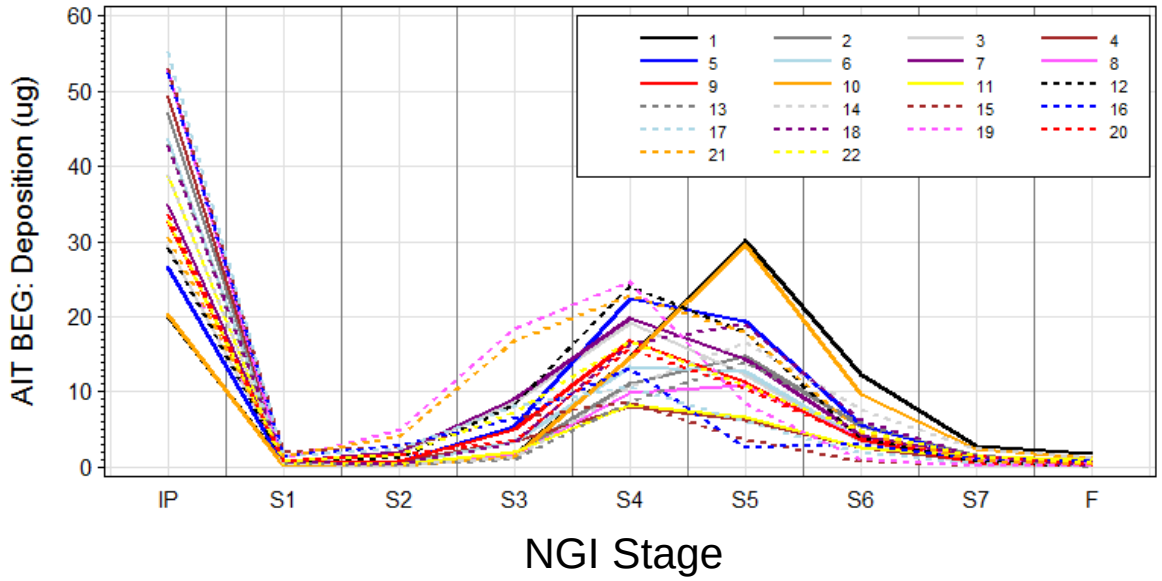
- Mean DD is not significantly affected by any of the three studied factors: X_{50}, EtOH, or OA
- EtOH does have statistically significant effects on beginning mean DD, through-life trend, & RSD.
  - All decrease with increasing EtOH
- Oleic acid has no effect.
- Using developed model, it was found that varying the factors up to 5% from target resulted in marginal effect on mean DD (2 µg), but the effect on RSD was much stronger (up to 1% absolute increase).

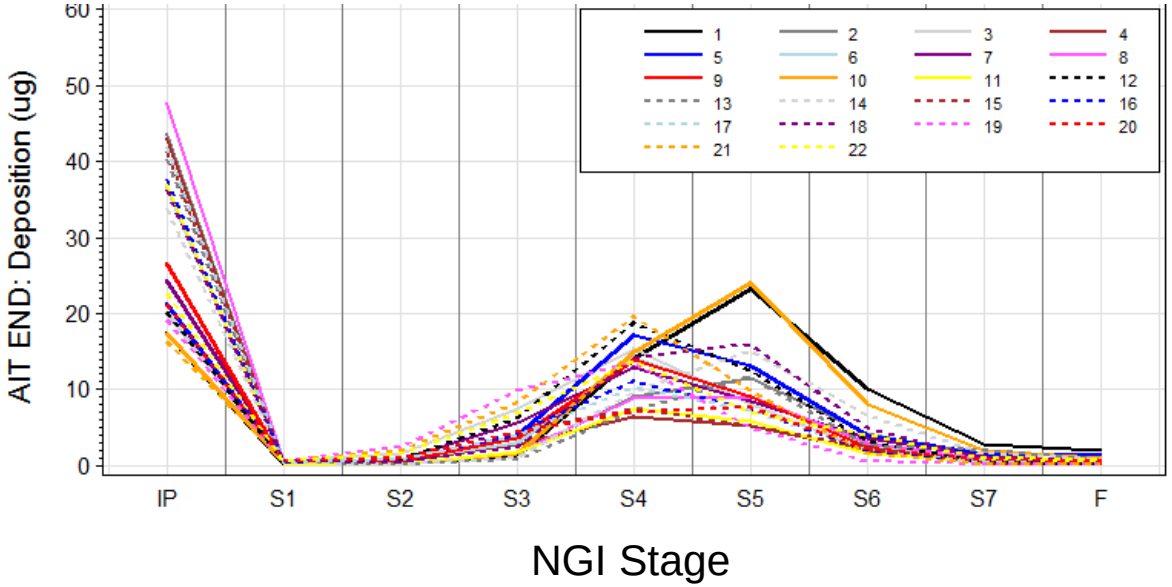
APSD at Beginning of Life for AIT & USP



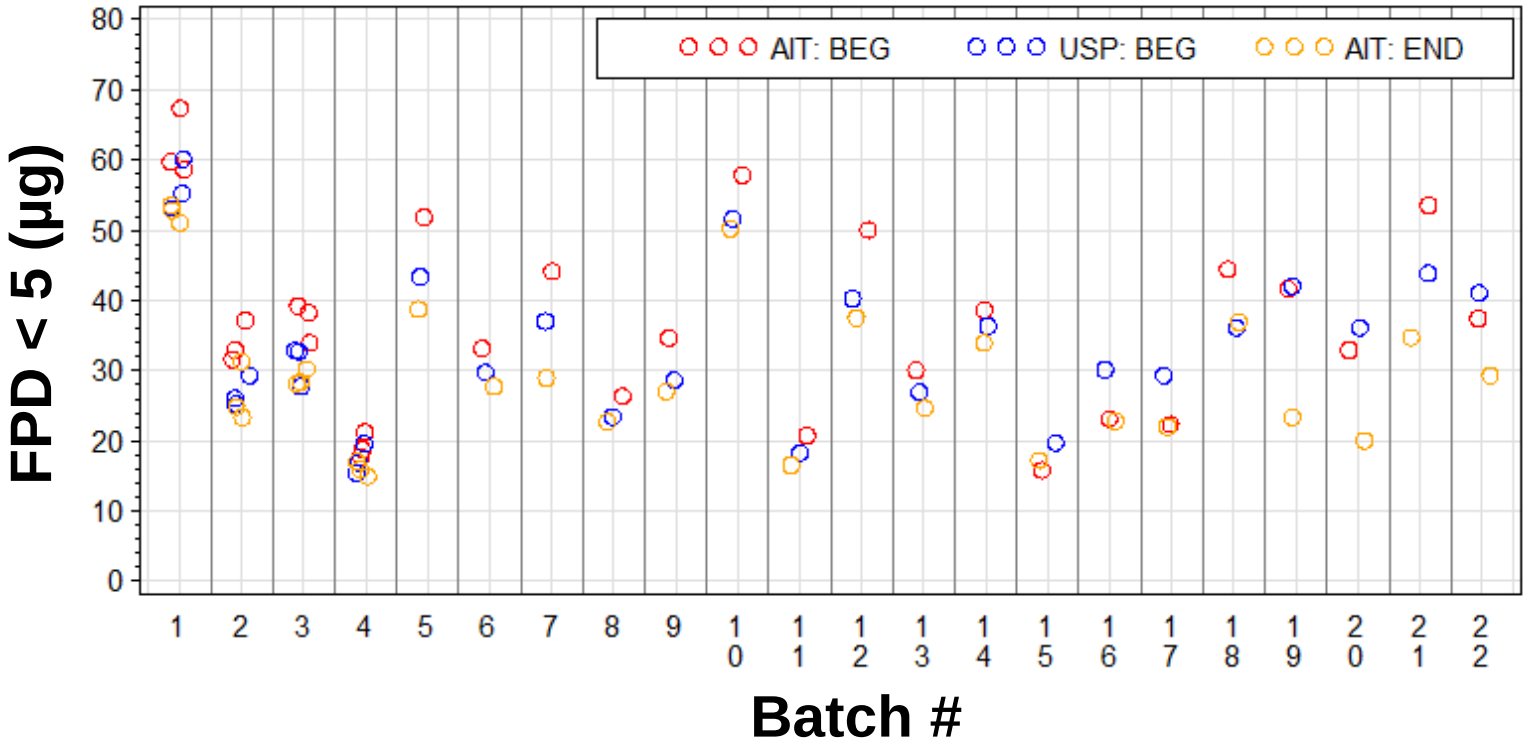


APSD at Beginning & End of Life for AIT





Individual FPDs by Batch & Throat / Life Stage



- Strong formulation effects are apparent
- No difference between AIT & USP

APSD ANOVA

For Batches 1 - 18

p-values

Effect	FPD<5 (µg)		
	AIT/B	USP/B	AIT/E
X_{50}	0.0001	0.0006	0.0000
EtOH	0.0000	0.0000	0.0000
OA	0.9688	0.5790	0.6903
X_{50}*EtOH	0.6679	0.0800	0.0310
X_{50}*OA	0.0938	0.4929	0.3051
EtOH*OA	0.3104	0.1980	0.3774

- For FPD
  - X_{50} and EtOH have strong effects
  - OA has no effect
  - One statistically significant interaction of X_{50}*EtOH

APSD: Least Squared Means for All Combinations of X_{50} & EtOH

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FPD < 5 microns

AIT/B

X_{50}	EtOH			
	7	14	20	Δ
1.4	61.0	41.6	33.0	85%
1.65	51.0	34.0	23.6	116%
2.5	39.0	22.8	18.4	112%
Δ	56%	82%	79%	232%

USP/B

X_{50}	EtOH			
	7	14	20	Δ
1.4	55.1	36.3	27.0	104%
1.65	41.8	29.2	21.0	99%
2.5	32.6	29.8	18.0	81%
Δ	69%	22%	50%	206%

AIT/E

X_{50}	EtOH			
	7	14	20	Δ
1.4	52.0	35.5	26.1	99%
1.65	38.2	27.4	19.7	94%
2.5	29.0	22.5	16.4	77%
Δ	79%	58%	59%	217%

FPD increased 3-fold when reducing factors from higher to lower levels.

APSD ANOVA

For Batches 19 – 22

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Oleic acid range = 0.005 to 0.25%

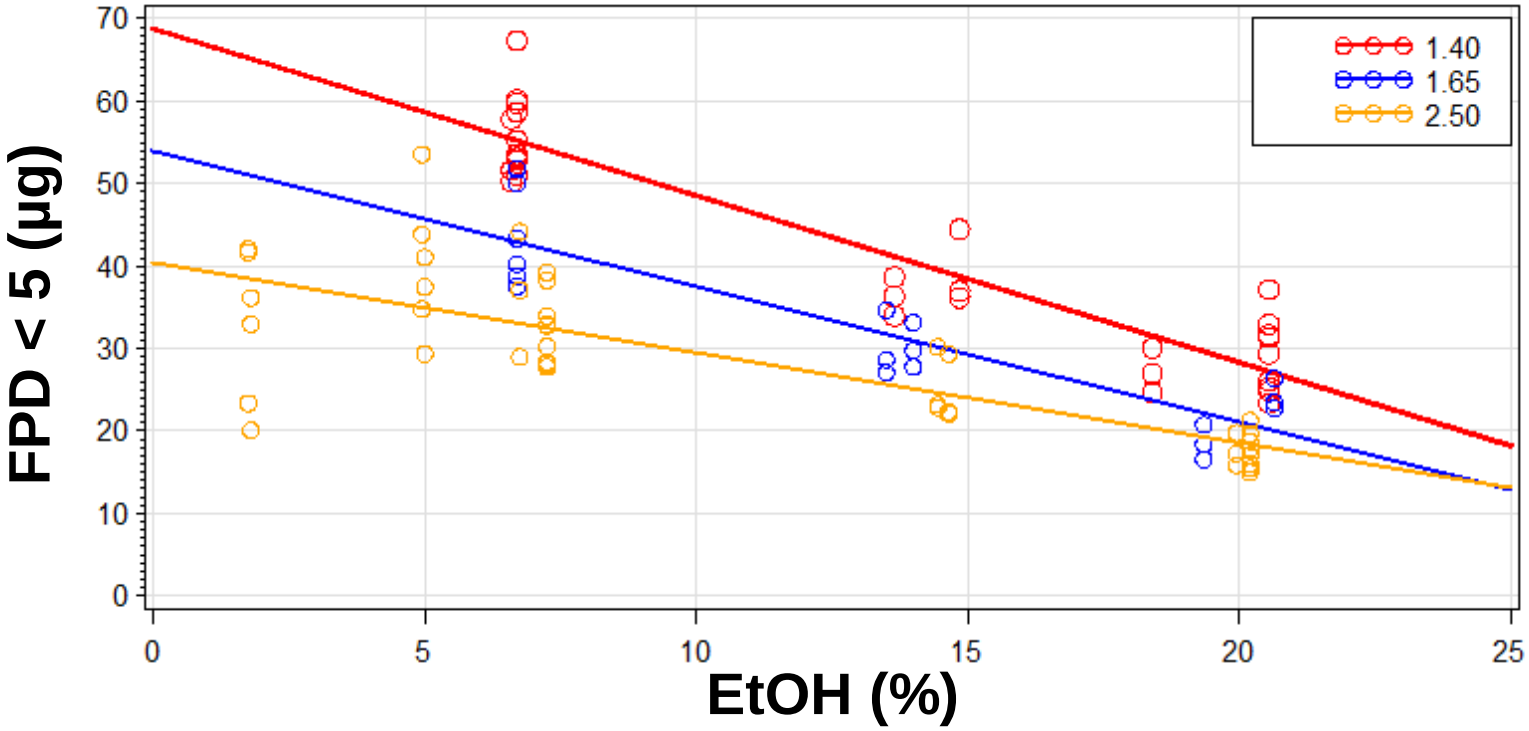
p-values:

Effect	FPD<5 (µg)		
	AIT/B	USP/B	AIT/E
EtOH	0.2698	0.2759	0.0644
OA	0.1846	0.2179	0.1508

- **Again, OA has no effect**
- **EtOH at 2 to 5%**
  - **No effect on total dose**
  - **No effect on FPD**

APSD

FPD vs Actual EtOH, by Target X_{50}



- The relation between FPD and EtOH depends on X_{50}
- Relationships are linear except for 2 batches at 2% EtOH

APSD Models

Model Fitted	Variability Explained
$FPD<5 = a1 + a2 \cdot X_{50} + a3 \cdot EtOH$	71.3%
$FPD<5 = b1 + b2 \cdot X_{50} + b3 \cdot EtOH + b4 \cdot X_{50} \cdot EtOH$	84.0%
$FPD<5 = c1 + c2 \cdot \ln(X_{50}) + c3 \cdot \ln(EtOH)$	82.9%
$FPD<5 = d1 + d2 \cdot \ln(X_{50}) + d3 \cdot \ln(EtOH) + d4 \cdot \ln(X_{50}) \cdot \ln(EtOH)$	**86.0%**
$\ln(FPD<5) = e1 + e2 \cdot \ln(X_{50}) + e3 \cdot \ln(EtOH) + e4 \cdot \ln(X_{50}) \cdot \ln(EtOH)$	85.9%

How Would a 5% Change in One Factor Affect FPD?

X_{50}	EtOH	FPD<5 (µg)
1.501 – 1.659	14.4	31.34 – 33.65
1.58	13.68 – 15.12	31.41 – 33.58

Both factors have a strong influence, but changes within 95% to 105% cause only a marginal change in FPD.

The combined effect of both factors being changed within 95% to 105% gave FPD of 30.32 – 34.81 µg (maximum change of about 14%).

What Design Space Will the APSD Data Support?

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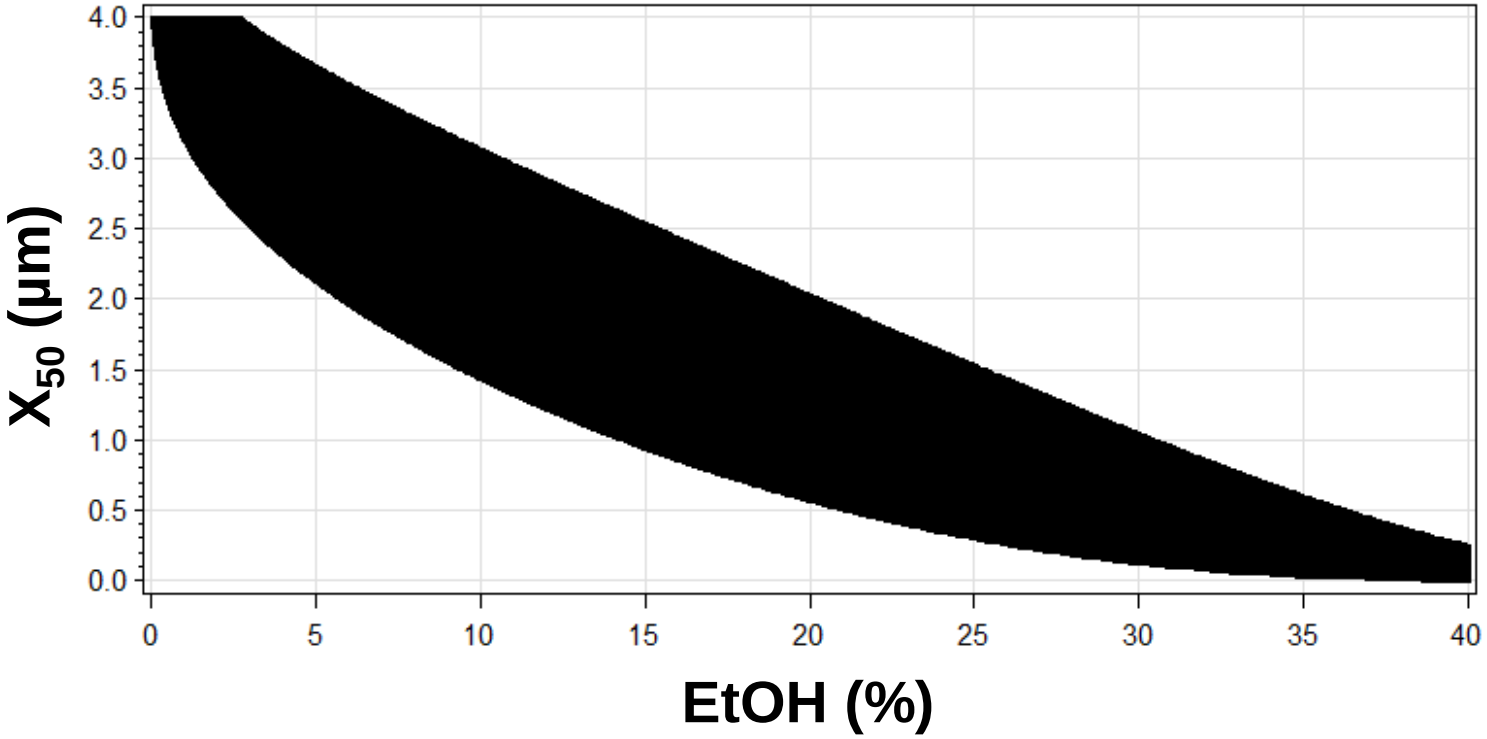
Assuming a specification of FPD of 21 – 43 µg:



Data do not rule out formulation changes outside of ±5% of EtOH target.

APSD Summary

- A strong effect by both X_{50} and EtOH on the FPD was observed.
  - FPD decreased with increasing X_{50} or EtOH
  - Results consistent between AIT and USP
  - Results consistent between beg & end of can
  - Size of effect is large (3x for low combination of factors compared to high combination)
  - Changes within ±5% of targets results in only about a 4.5 µg difference in FPD.
  - The design space for a “typical” specification for FPD has a fairly wide operating range.
- OA did not have a significant effect on FPD over range evaluated.

Conclusion

- An albuterol sulfate model system was developed based on a commercial product and used for statistically designed experiments to evaluate the impact of formulation changes.

- Varying the formulation parameters within the Q2 "limit" of ± 5% results in small changes to key responses of mean DD and FPD. The design spaces show that it may be feasible to accommodate formulation changes outside of ± 5% via a QbD approach.

- Would differences in formulation and *in vitro* performance translate into differences in clinical (e.g. PK) performance?

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