Demonstration of Blend & Content Uniformity in Process Validation of Oral Solid Dosage Forms

The Israel Chapter of PDA
העמותה לקידום המדע והטכנולוגיה הפרמצבטית בישראל

June 23, 2026

Dexcel pharma
דקסל. סיפור הצלחה

2021 Dexcel pharma

1971 עיריית נתניה

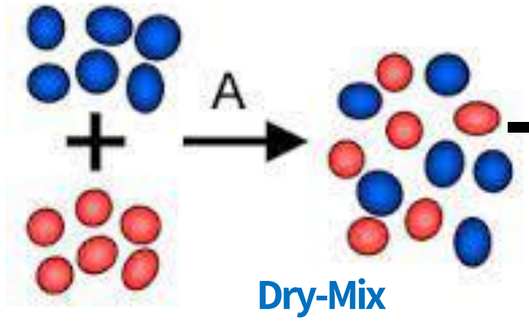
2003 teva

2017 CTS

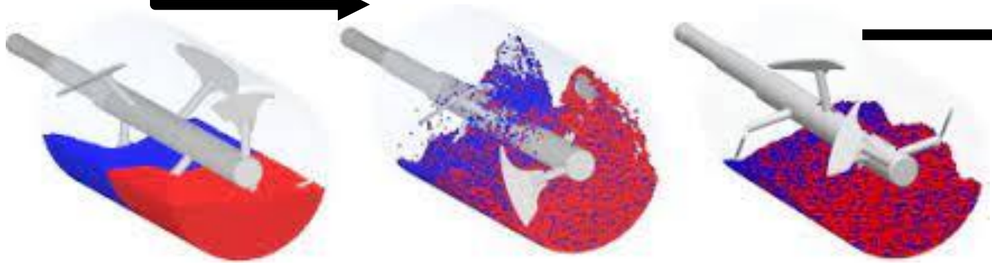
Dafna Arieli, Ph.D.
Head of MS&T
Dexcel Ltd., Israel

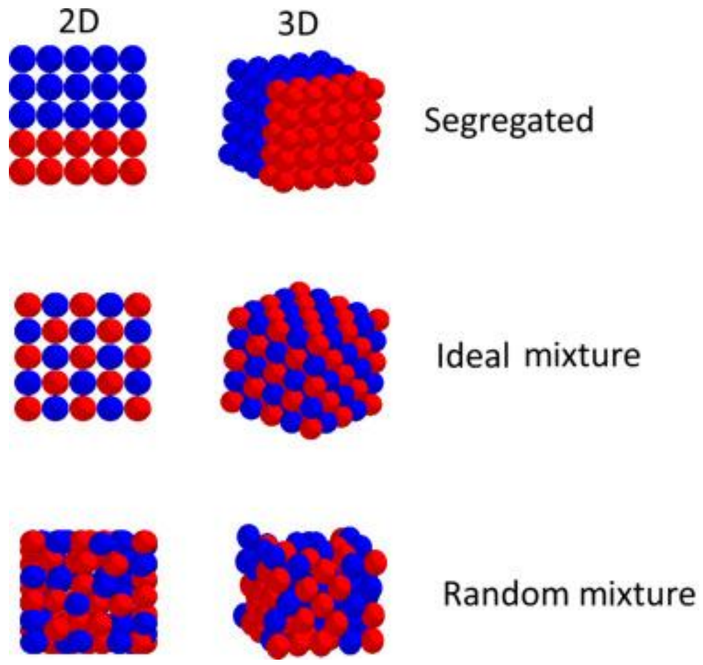
Uniformity is everywhere

Uniformity is a matter of Standardization

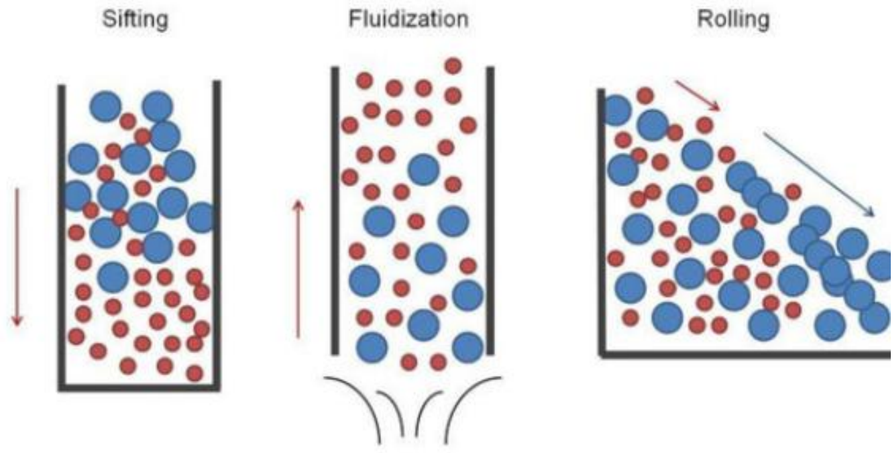


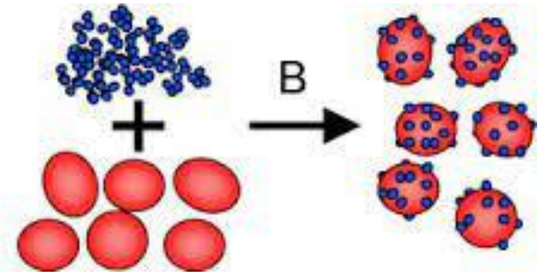
Dry-Mix





Mixing vs. Segregation





Granulation

Process Validation Regulation

1987	2004–2010	2011	2015	2016-2025	CURRENT
FDA	ICH	FDA	EMA EUROPEAN MEDICINES AGENCY		ICH
FDA Process Validation Guideline	ICH Q8/Q9/Q10	FDA Process Validation: General Principles and Practices	EU GMP Annex 15 Revision	Continued Process Verification maturity	ICH Q12 / digital validation trends
Qualification of three commercial batches	Quality by Design	Lifecycle approach	Lifecycle and risk-based validation adopted in EU	Emphasis on CPV, Statistical monitoring	*"How can we improve the validated process efficiently?"*
"Can the process make acceptable product?"	Risk Management	Process Design → PPQ → CPV			

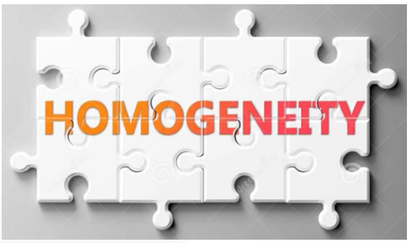
Blend Uniformity Specifications Evolution

Period	FDA	
<2007	n=10+20	Each Ind. 90.0-110.0% RSD≤5.0%
2007-2014	n=10+20	Each Ind. 90.0-110.0% from AVG. RSD<5.0%
2014-Today	n=10 n=30	SD≤3.0% SD≤5.0%

Period	EMA	
<2004	n=10	AVG: 90-110% of LC Each Ind.: 85-115% of LC
2004-2017	n=10	≤1 Ind. outside 85-115% from AVG. All Ind. 75-125% from AVG.
	n=30	≤3 Ind. outside 85-115% from AVG. All Ind. 75-125% from AVG.
2017-Today	n=10 n=30	SD<3.0% SD<5.0%

- No limits on the actual Average or Individual content of the blend
- Monitoring the variability of Individual Content results *wrt.* the Average Content

CFR Mixing Adequacy Requirement



§ 211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

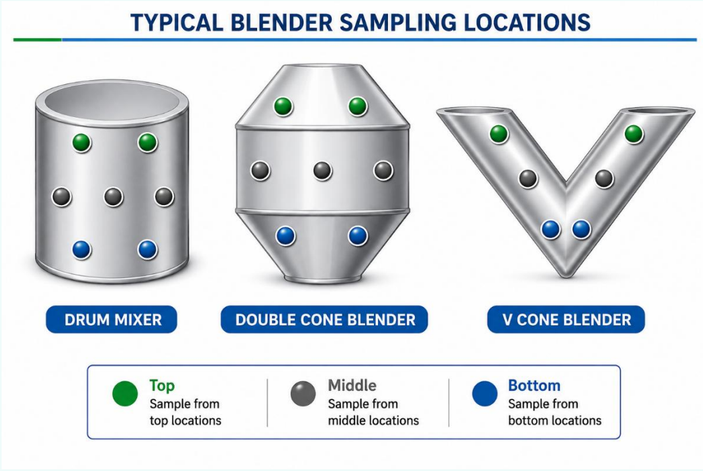
(2) Disintegration time;

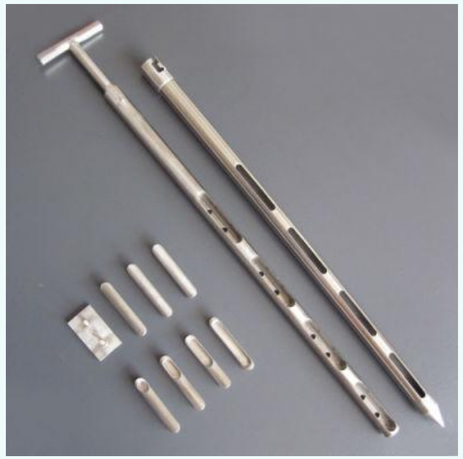
(3) Adequacy of mixing to assure uniformity and homogeneity;

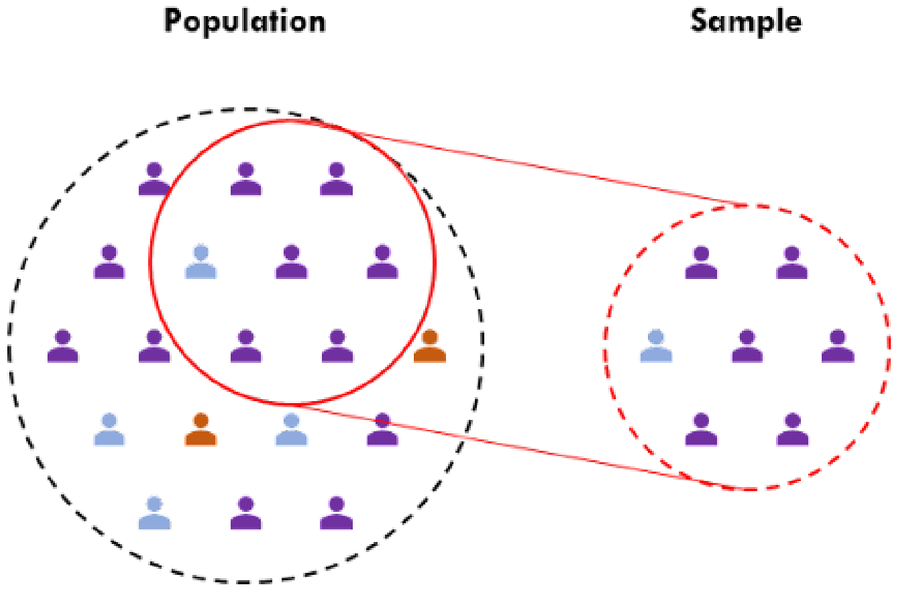
(4) Dissolution time and rate;

However, the CFR does not prescribe HOW to demonstrate mixing adequacy

Thief Sampling; The Classical Approach







2003

Guidance for Industry

Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

DRAFT GUIDANCE

Powder sample
(1X-3X)

Compressed core
Label Claim

Compressed core
Weight Correction

250 mg per Recipe

LC= 99.1%
WC=103.2%

LC= 99.1%
WC=95.3%

Assay , % of Target	Assay , % LC	Assay , % WC
Lab Result, 95.0%	Lab Result, 99.1%	$Assay\ (WC) = Assay\ (LC) \times \frac{Theoretical\ core\ weight}{Ind.\ core\ weight}$

Draft Guidance 2003

From blend, sample at least 10 locations, with at least 3 replicates from each location

Assay 1 per location

Blend Sample Criteria: RSD≥5.0% and all individuals are within +/- 10% of mean (absolute)[1]

No

Yes

Assay 2nd and 3rd blend samples from each location

Investigate original criteria "failure"

No

Is mixing problem identified?

Yes

Blend is not uniform

Investigate to blend sampling error or some other attributable ca

Assay at least 7 dosage units per each location, weight correct each result

Assay remaining dosage units from each location (7 per location altogether), weight correct each result

Dosage Units
During Filling or compression take 7 dosage unit samples from each of at least 20 locations

Assay at least 3 dosage units per each location, weight correct each result

Unit Readily Pass Criteria: all individuals ≤4.0%. Each location within 90.0% - 110.0% of target potency, and all individuals are within 75.0% and 125.0% of target potency[2]

No

Meet criteria?

Yes

Adequate Powder Mix

Assay remaining dosage units from each location (7 per location altogether), weight correct each result

Dosage Unit Marginally Pass Criteria: RSD of all individuals ≤5.0%. Each location mean is within 90.0% - 110.0% of target potency, and all individuals are within 75.0% and 125.0% of target potency[2]

No

Meet criteria?

Yes

Blend Is not uniform or post blending practices are causing segregation

Go back to development

Withdrawn in 2013 due to limited stat. sampling

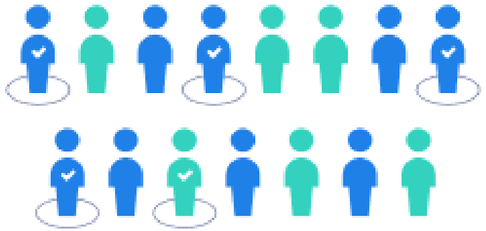
1*10 locations-→3*10

*20 locations

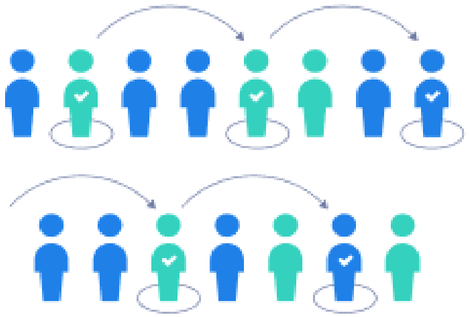
Sampling Approaches

Gives each unit an app. equal probability of being chosen (e.g. QC sample)

Simple random sample



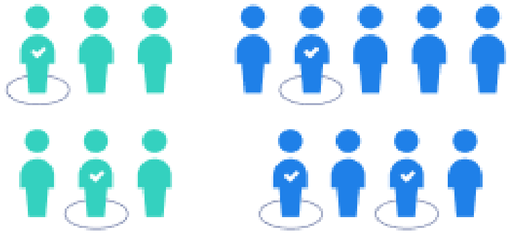
Systematic sample



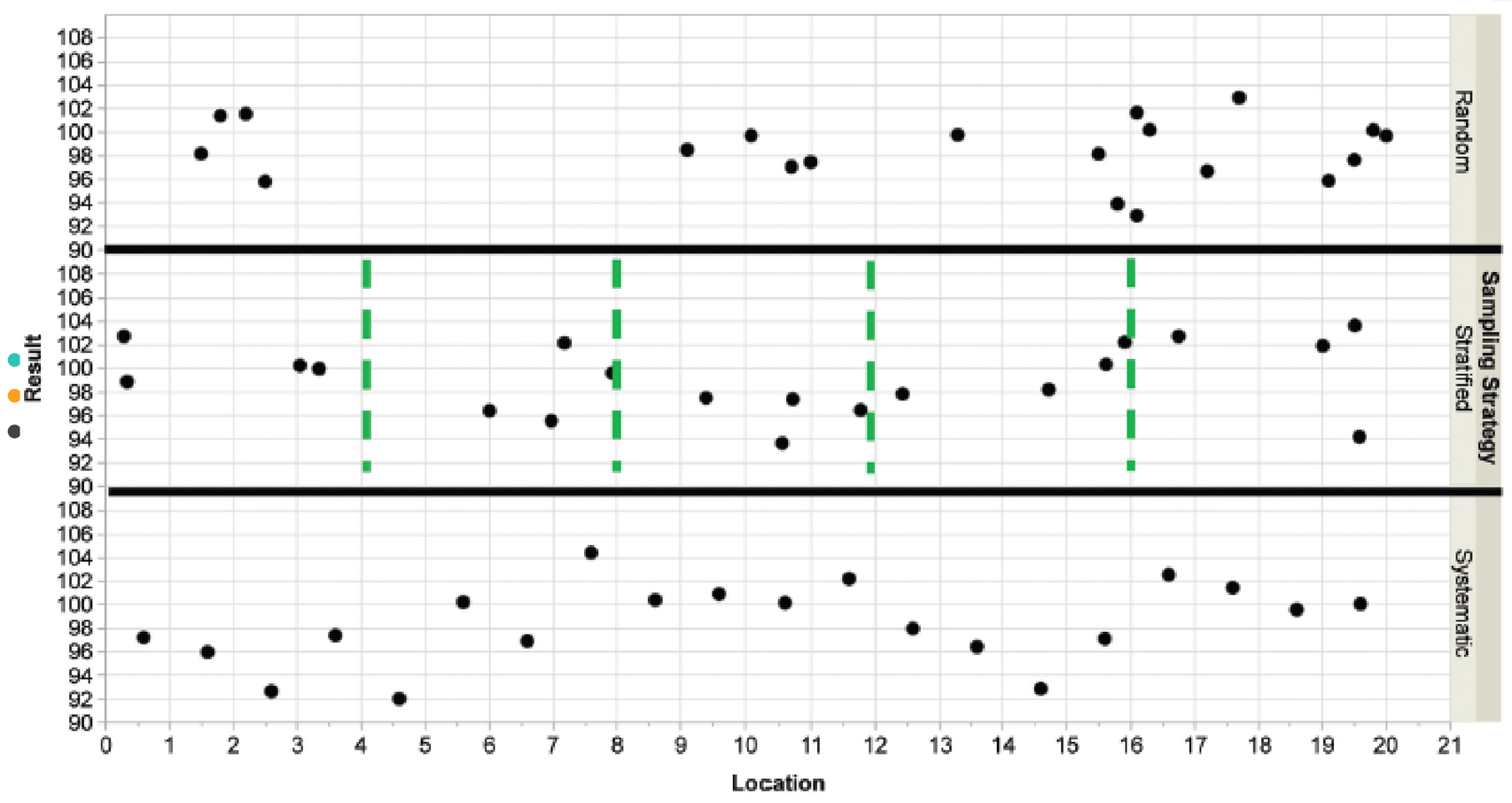
Taking a sample(s) at equal intervals throughout the batch typically by total number of dosage units or manufacturing time

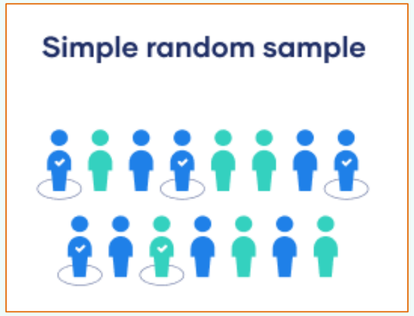
Partition the batch into “strata” (e.g., 1/20). The combination of all strata must cover the entire batch. Random sampling is performed within each stratum

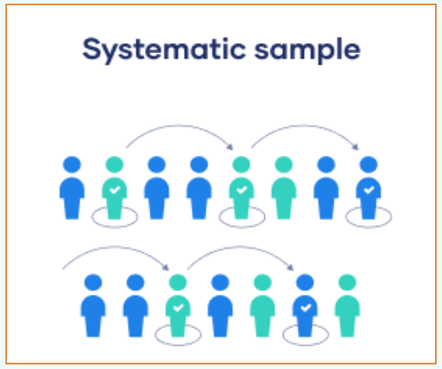
Stratified sample



Sampling Approaches- Cont'd







So, let's implement systematic sampling in practice..

ISPE Recommendation for BU and CU Evaluation in Validation Batches

2015

ISPE

GOOD PRACTICE GUIDE:

Practical Implementation of the Lifecycle Approach to Process Validation

J Pharm Innov (2015) 10:76–83
DOI 10.1007/s12247-014-9207-0

RESEARCH ARTICLE

Recommendations for the Assessment of Blend and Content Uniformity: Modifications to Withdrawn FDA Draft Stratified Sampling Guidance

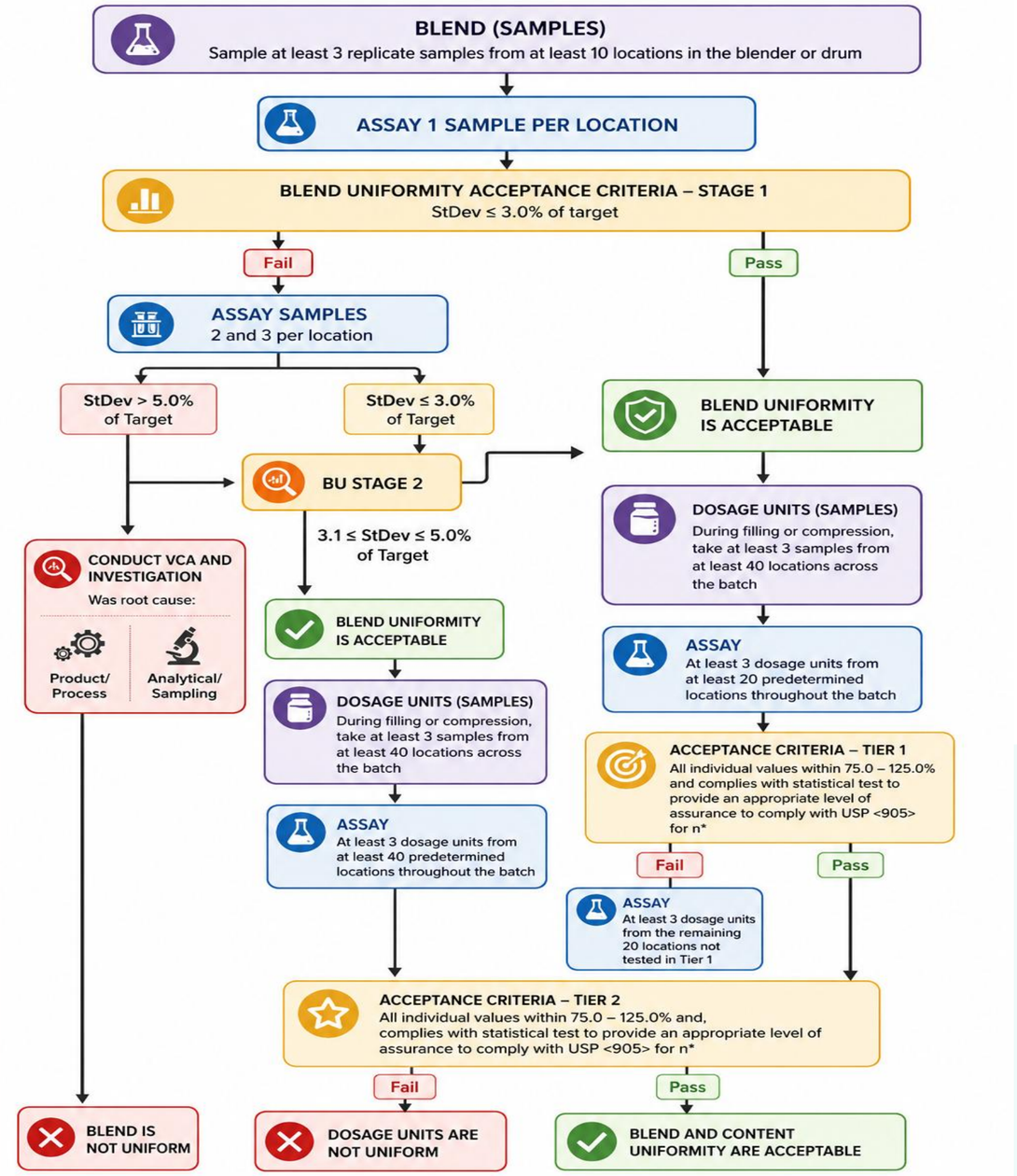
Thomas Garcia · James Bergum · James Prescott · Ravindra Tejwani · Thomas Parks · Jon Clark · William Brown · Fernando Muzzio · Samir Patel · Charles Hoiberg

J Pharm Innov (2015) 10:84–97
DOI 10.1007/s12247-014-9208-z

RESEARCH ARTICLE

Assessment of Blend and Content Uniformity. Technical Discussion of Sampling Plans and Application of ASTM E2709/E2810

James Bergum · Thomas Parks · James Prescott · Ravindra Tejwani · Jon Clark · William Brown · Fernando Muzzio · Samir Patel · Charles Hoiberg



Blend Uniformity Evaluation

Powder sample
(1X-3X)

Content Uniformity Assessment

Compressed core
Label Claim

Blend Uniformity Assessment

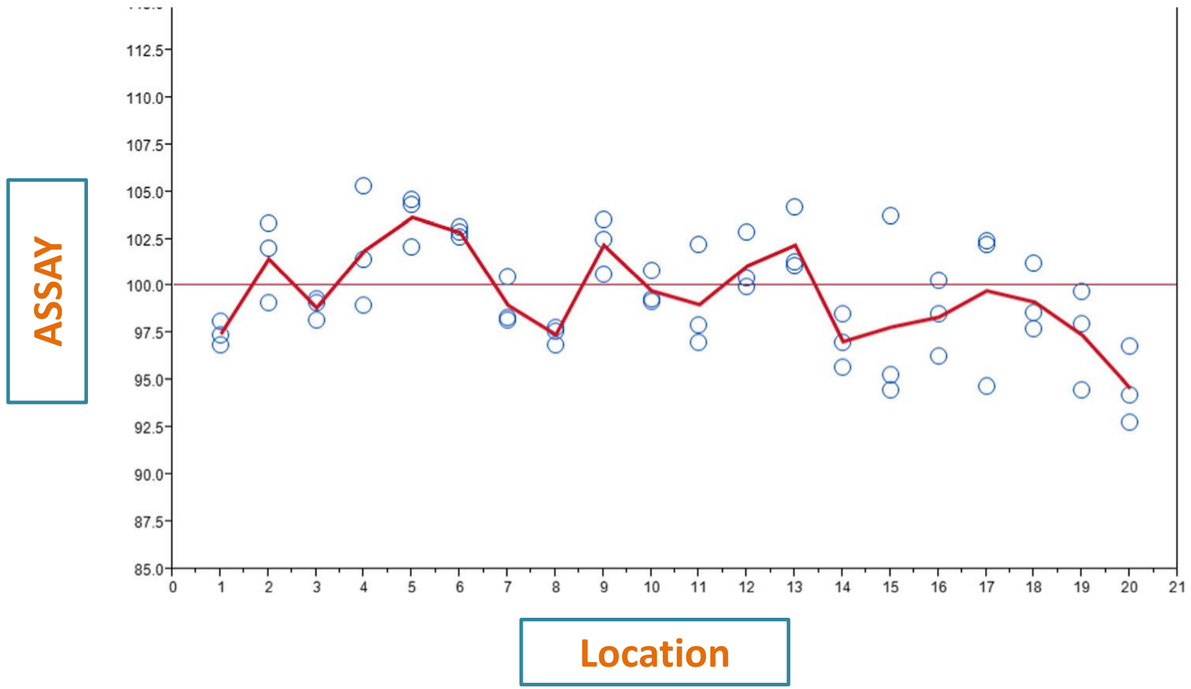
Compressed core
Weight Correction

Proving Mixing Adequacy	Prediction for passing USP 905	Proving Mixing Adequacy
SD≤ 3.0% for 10/15 units SD ≤5.0% for 30/45 units	90% Confidence level for 95% Coverage based on ASTM E2709/E2870	90% Confidence level for 95% Coverage based on ASTM E2709/E2870

ISPE SP 1 Vs. SP 2

Sampling Plan 1 : 1 unit per location

Sampling Plan 2 : >1 unit per location



Within and Between Location Variances

	Sample Potency(%)			Each Location (n = 3)	
Sample Location	A	B	C	Mean ($\bar{x}$)	Variance(s\(_{i}^{2}\))
1	97.8	97.2	95.2	96.73	1.80
2	97.9	99.1	98.9	98.65	0.39
3	98.1	101.8	103.3	101.07	7.01
4	99.8	103.0	101.7	101.49	2.47
5	99.7	100.9	100.3	100.31	0.32
6	98.6	100.8	99.2	99.54	1.25
7	99.8	98.8	98.8	99.12	0.31
8	102.7	100.4	105.9	102.98	7.61
9	101.2	102.0	103.6	102.26	1.42
10	97.4	99.2	101.0	99.20	3.23

$$\sigma^2 = \frac{\sum_{i=1}^{N} (x_i - \overline{x})^2}{N}$$

$\overline{x}$ - ממוצע האוכלוסייה.

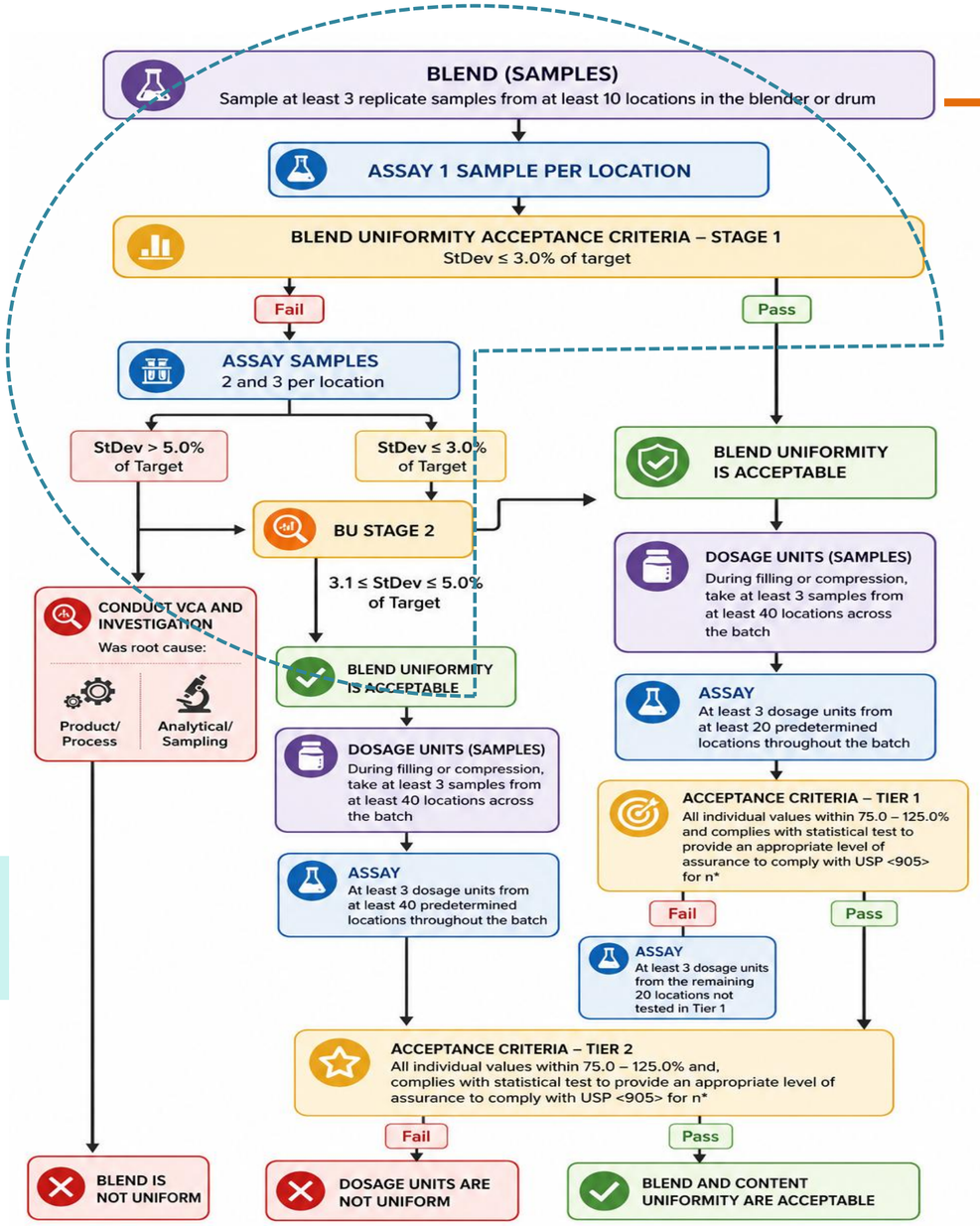
N - מספר האיברים באוכלוסייה.

Variance per subgroup

$$SD(\text{within location}) = \sqrt{(\overline{variance})}$$

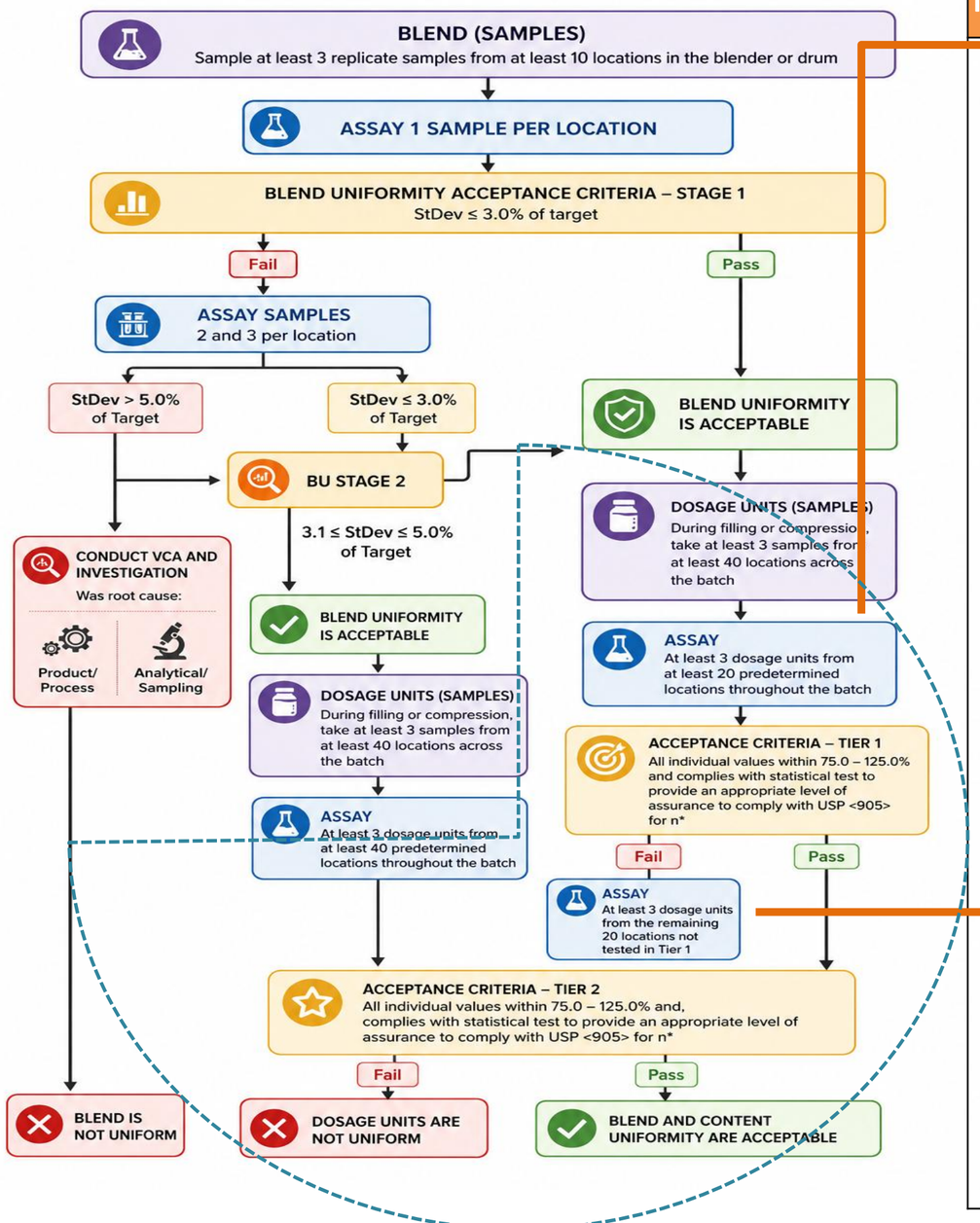
$$SD(\text{between location}) = SD(\bar{x}_i)$$

ISPE Rec. for BU and CU Evaluation in Validation Batches- Blend Stage



Sample No.	Sampling Size	Acceptance Criteria
1B-10B	10x3 sets 1X-3X mg	**Stage 1** $SD_{10} \leq 3.0\%$ ⇨ if met go to *Tier 1* if failed go to Stage 2.1 **Stage 2.1** $SD_{30} \leq 3.0\%$ ⇨ if met go to *Tier 1* if failed go to Stage 2.2 **Stage 2.2** $3.1\% \leq SD_{30} \leq 5.0\%$ of target ⇨If met go to *Tier 2* If failed – Investigate applying VCA

ISPE Rec. for BU and CU Evaluation in Validation Batches- DU Stage



Samp No.	Parameter	Sample Size & Intervals	Acceptance criteria
1C-20C	Blend and Content Uniformity Assessment on Assay, % Label Claim (LC), & Weight Corrected (WC)	**Tier 1 (30 units)**	
		3 DUs (tablets) from the following location: <u>1C (Start),</u> 3C, 5C, 7C, 9C, 10C, 12C, 16C, 18C, 20C <u>(End).</u> Assay, %LC, %WC	<u>Sampling Plan 2 10x3</u> Assay, %LC and %WC for 3 DUs - Sample Overall Mean - Between locations SD. - Within location SD. Acceptance criteria: ❖ All individual values of Assay, %LC within 75.0-125.0%. ❖ ASTM E2709/2810 statistical criteria for passing Ph. Eur. 2.9.40 with 90% confidence for 95% coverage on Sampling Plan 2 (10x3). ⇨ if failed, go to Tier 2
		Tier 2 (60 units)	
		3 DUs from remaining locations: 2C, 4C, 6C, 8C, 11C, 13C, 14C, 15C, 17C, 19C. Assay, %LC, %WC Total: 10x3 (Tier 1) + 10x3=20x3=60 DUs	<u>Sampling Plan 2 20x3</u> See above

ASTM E2709/E2810 Acceptance Limit Tables

Sampling Plan 1; 90%CL/95% Coverage

90% Confidence Level and 95% Coverage (i.e., Probability of Passing USP UDU)

Sampling Plan 1: (1 dosage unit tested from n locations (nx1)), where n=10 – 500

[Sample Mean found in either Column 1 or 2]

Upper Bound on the Standard Deviation																
		Sample Size														
Sample Mean		10	20	30	40	50	60	70	80	90	100	125	150	175	200	500
100.0	100.0	3.211	4.079	4.479	4.719	4.883	5.002	5.095	5.168	5.229	5.279	5.377	5.448	5.502	5.545	5.767
100.1	99.9	3.192	4.055	4.454	4.695	4.859	4.979	5.073	5.147	5.208	5.260	5.359	5.431	5.486	5.530	5.756
100.2	99.8	3.172	4.031	4.429	4.670	4.834	4.955	5.049	5.125	5.186	5.238	5.339	5.412	5.468	5.513	5.744
100.3	99.7	3.153	4.007	4.403	4.644	4.809	4.931	5.025	5.101	5.163	5.216	5.318	5.392	5.449	5.495	5.730
100.4	99.6	3.134	3.983	4.377	4.617	4.783	4.905	5.000	5.076	5.139	5.192	5.295	5.370	5.428	5.474	5.714
100.5	99.5	3.115	3.958	4.351	4.591	4.756	4.878	4.973	5.050	5.114	5.167	5.271	5.347	5.406	5.453	5.697
100.6	99.4	3.095	3.934	4.325	4.564	4.729	4.851	4.946	5.023	5.087	5.141	5.246	5.322	5.382	5.429	5.678
100.7	99.3	3.076	3.910	4.299	4.536	4.701	4.823	4.919	4.996	5.060	5.114	5.219	5.297	5.357	5.405	5.656
100.8	99.2	3.057	3.885	4.272	4.509	4.673	4.795	4.890	4.968	5.032	5.086	5.192	5.270	5.330	5.379	5.634
100.9	99.1	3.037	3.861	4.245	4.481	4.644	4.766	4.862	4.939	5.003	5.057	5.163	5.242	5.303	5.352	5.610
101.0	99.0	3.018	3.836	4.219	4.453	4.616	4.737	4.832	4.909	4.974	5.028	5.134	5.213	5.274	5.323	5.584
101.1	98.9	2.999	3.812	4.192	4.425	4.587	4.708	4.803	4.880	4.944	4.998	5.104	5.183	5.245	5.294	5.556
101.2	98.8	2.979	3.787	4.165	4.397	4.558	4.678	4.773	4.850	4.913	4.968	5.074	5.153	5.214	5.264	5.528
101.3	98.7	2.960	3.763	4.138	4.369	4.529	4.649	4.743	4.819	4.883	4.937	5.043	5.122	5.183	5.233	5.498
101.4	98.6	2.941	3.738	4.111	4.340	4.500	4.619	4.712	4.788	4.852	4.906	5.012	5.090	5.152	5.201	5.467
101.5	98.5	2.921	3.714	4.084	4.312	4.470	4.589	4.682	4.758	4.821	4.874	4.980	5.058	5.120	5.169	5.435
101.6	98.4	2.902	3.689	4.057	4.284	4.441	4.559	4.651	4.727	4.790	4.843	4.948	5.026	5.087	5.137	5.403
101.7	98.3	2.883	3.665	4.030	4.255	4.411	4.529	4.621	4.696	4.758	4.811	4.916	4.994	5.055	5.104	5.370
101.8	98.2	2.863	3.640	4.004	4.227	4.382	4.498	4.590	4.664	4.727	4.779	4.883	4.961	5.022	5.071	5.336
101.9	98.1	2.844	3.616	3.977	4.198	4.353	4.468	4.559	4.633	4.695	4.747	4.851	4.928	4.988	5.037	5.302
102.0	98.0	2.824	3.591	3.949	4.170	4.323	4.438	4.528	4.602	4.663	4.715	4.818	4.895	4.955	5.004	5.267
102.1	97.9	2.805	3.567	3.923	4.141	4.294	4.408	4.498	4.571	4.632	4.683	4.786	4.862	4.921	4.970	5.232
102.2	97.8	2.786	3.542	3.896	4.113	4.264	4.377	4.467	4.539	4.600	4.651	4.753	4.829	4.888	4.936	5.197
102.3	97.7	2.766	3.517	3.869	4.084	4.235	4.347	4.436	4.508	4.568	4.619	4.720	4.795	4.854	4.902	5.161

n	30
SD	4.40%
Average	99.7 - 100.3%

n	60
SD	4.40%
Average	97.9 - 102.1%

ASTM E2709/E2810 Acceptance Limit Tables

Sampling Plan 2; 10*3; 90%CL/95% Coverage

n	**10*3=30**
SD between	**0.6%**
SD within	**1.1%**
Average	**87.8 - 112.2%**

TARGET=100, LOWER BOUND = 95, CONFIDENCE LEVEL = 90
TABLE ENTRIES ARE LOWER(LL) AND UPPER(UL) LIMITS ON THE MEAN
OF 30 ASSAYS-3 ASSAYS AT EACH OF 10 DIFFERENT LOCATIONS
SE IS THE POOLED WITHIN LOCATION STANDARD DEVIATION
STANDARD DEVIATIONS AND MEANS ARE EXPRESSED IN % CLAIM

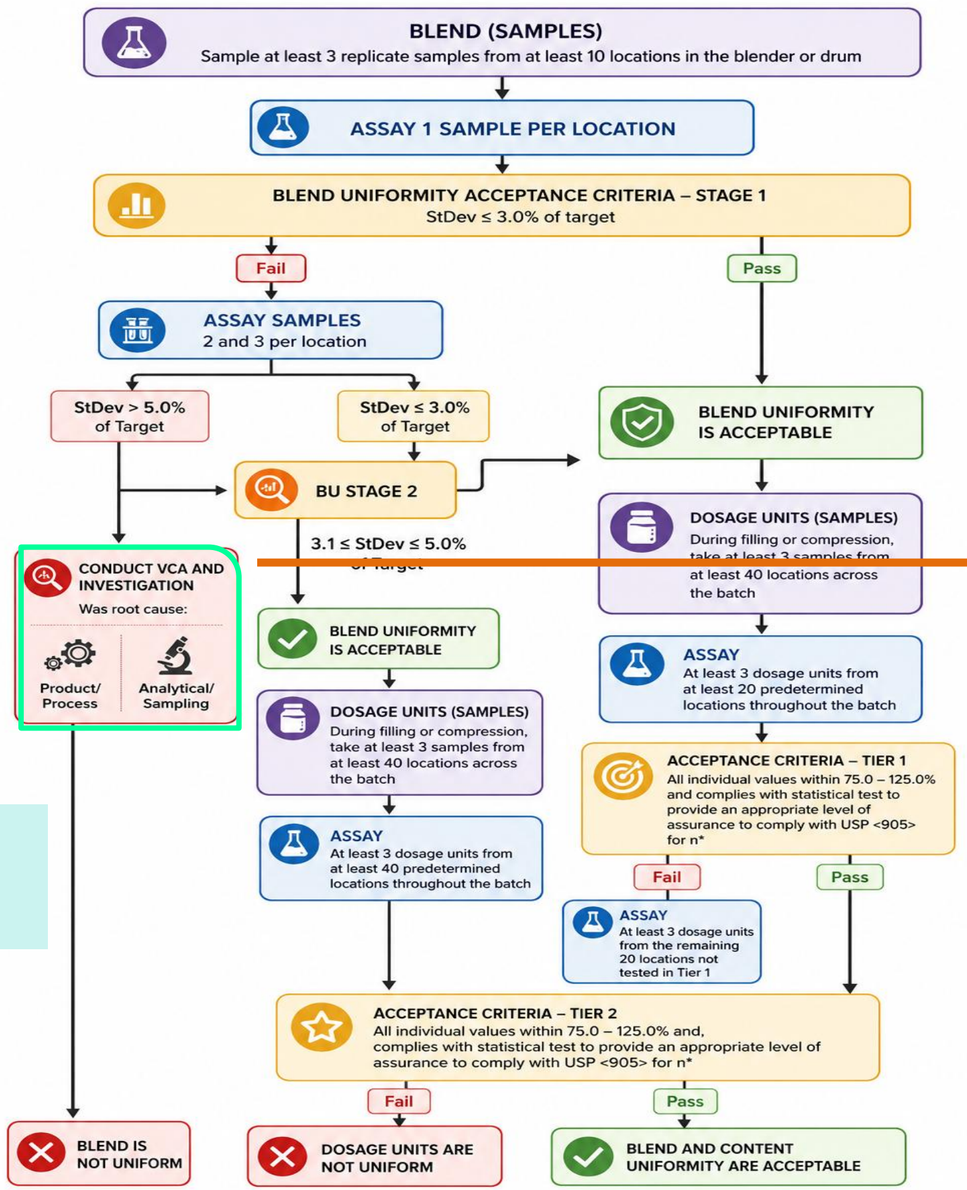
STANDARD DEVIATION OF LOCATION MEANS

Between Location

Within Location

SE	0.1 LL	0.1 UL	0.2 LL	0.2 UL	0.3 LL	0.3 UL	0.4 LL	0.4 UL	0.5 LL	0.5 UL	0.6 LL	0.6 UL	0.7 LL	0.7 UL	0.8 LL	0.8 UL	0.9 LL	0.9 UL
0.1	84.1	115.9	84.6	115.4	85.1	114.9	85.6	114.4	86.1	113.9	86.6	113.4	87.1	112.9	87.7	112.3	88.2	111.8
0.2	84.3	115.7	84.7	115.3	85.2	114.8	85.7	114.3	86.2	113.8	86.7	113.3	87.2	112.8	87.7	112.3	88.2	111.8
0.3	84.5	115.5	84.8	115.2	85.3	114.7	85.7	114.3	86.2	113.8	86.7	113.3	87.2	112.8	87.7	112.3	88.2	111.8
0.4	84.8	115.2	85.0	115.0	85.4	114.6	85.8	114.2	86.3	113.7	86.8	113.2	87.3	112.7	87.8	112.2	88.3	111.7
0.5	85.1	114.9	85.3	114.7	85.6	114.4	86.0	114.0	86.4	113.6	86.9	113.1	87.3	112.7	87.8	112.2	88.3	111.7
0.6	85.3	114.7	85.5	114.5	85.8	114.2	86.1	113.9	86.5	113.5	87.0	113.0	87.4	112.6	87.9	112.1	88.4	111.6
0.7	85.6	114.4	85.8	114.2	86.0	114.0	86.3	113.7	86.7	113.3	87.1	112.9	87.5	112.5	88.0	112.0	88.5	111.5
0.8	85.9	114.1	86.0	114.0	86.2	113.8	86.5	113.5	86.8	113.2	87.2	112.8	87.6	112.4	88.1	111.9	88.5	111.5
0.9	86.2	113.8	86.3	113.7	86.5	113.5	86.7	113.3	87.0	113.0	87.4	112.6	87.8	112.2	88.2	111.8	88.7	111.3
1.0	86.4	113.6	86.6	113.4	86.8	113.2	87.0	113.0	87.2	112.8	87.6	112.4	87.9	112.1	88.3	111.7	88.8	111.2
1.1	86.7	113.3	86.9	113.1	87.0	113.0	87.2	112.8	87.5	112.5	87.8	112.2	88.1	111.9	88.5	111.5	88.9	111.1
1.2	87.0	113.0	87.1	112.9	87.3	112.7	87.5	112.5	87.7	112.3	88.0	112.0	88.3	111.7	88.7	111.3	89.1	110.9
1.3	87.3	112.7	87.4	112.6	87.6	112.4	87.7	112.3	88.0	112.0	88.2	111.8	88.5	111.5	88.9	111.1	89.2	110.8
1.4	87.6	112.4	87.7	112.3	87.8	112.2	88.0	112.0	88.2	111.8	88.4	111.6	88.7	111.3	89.0	111.0	89.4	110.6
1.5	87.8	112.2	88.0	112.0	88.1	111.9	88.3	111.7	88.5	111.5	88.7	111.3	89.0	111.0	89.3	110.7	89.6	110.4
1.6	88.1	111.9	88.2	111.8	88.4	111.6	88.5	111.5	88.7	111.3	88.9	111.1	89.2	110.8	89.5	110.5	89.8	110.2
1.7	88.4	111.6	88.5	111.5	88.6	111.4	88.8	111.2	89.0	111.0	89.2	110.8	89.4	110.6	89.7	110.3	90.0	110.0
1.8	88.7	111.3	88.8	111.2	88.9	111.1	89.1	110.9	89.2	110.8	89.4	110.6	89.7	110.3	89.9	110.1	90.2	109.8

ISPE Rec. for BU and CU Evaluation in Validation Batches- VCA



Sample No.	Sampling Size	Acceptance Criteria
1B-10B	10x3 sets 1X=3X mg	<u>Stage 1</u> $SD_{10} \leq 3.0\%$ ⇨ if met go to *Tier 1* if failed go to Stage 2.1 <u>Stage 2.1</u> $SD_{30} \leq 3.0\%$ ⇨ if met go to *Tier 1* if failed go to Stage 2.2 <u>Stage 2.2</u> $3.1\% \leq SD_{30} \leq 5.0\%$ of target ⇨If met go to *Tier 2* If failed – Investigate applying VCA

1995

Variance Component Analysis (VCA)

Drug Development and Industrial Pharmacy ›
Volume 21, 1995 - Issue 18
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39
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CrossRef citations to date
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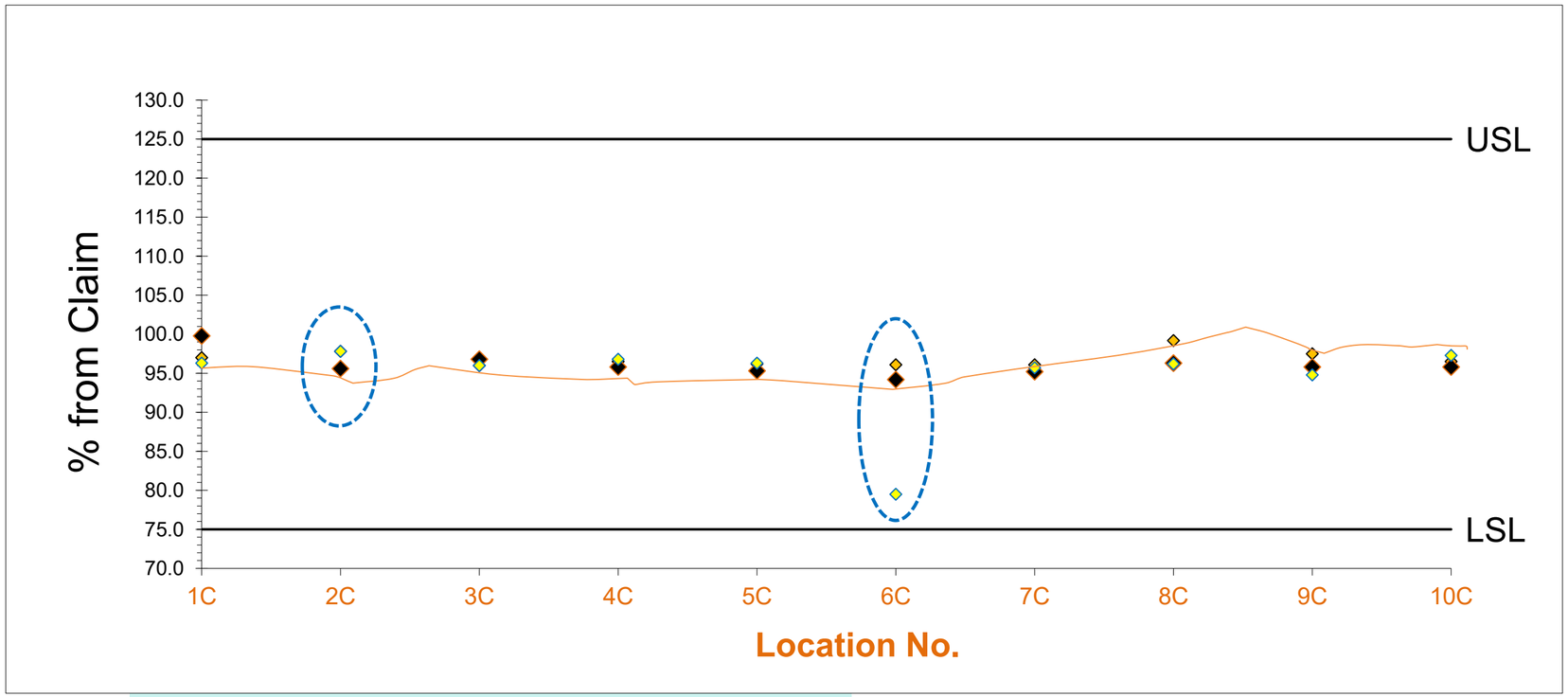
Research Article

Examination of Components of Variance for A Production Scale, Low Dose Powder Blend and Resulting Tablets

Thomas Garcia, Bruce Elsheimer & Frank Tarczynski

Pages 2035-2045 | Published online: 20 Oct 2008



- **Within location -**Variability across replicate samples within a single location
- **Between location**- Variability across sampling locations

Variance Component Analysis (VCA)- Cont'd

Blend SD		Dosage Unit SD		Interpretation
Within Location	Between Location	Within Location	Between Location	
Low	Low	Low	Low	**Uniform**
Low	Low	Low	High	**Segregation during compression**
Low	Low	High	Low	**Agglomeration. Poor flow**
Low	Low	High	High	**Significant Segregation and/or Agglomeration**

Vs.

Blend SD		Dosage Unit SD		Interpretation
Within Location	Between Location	Within Location	Between Location	
High	Low	Low	High	**Sampling Bias/Agglomeration**
High	High	Low	Low	**<u>Sampling Bias</u>/blend not uniform and downstream process results in uniformity**

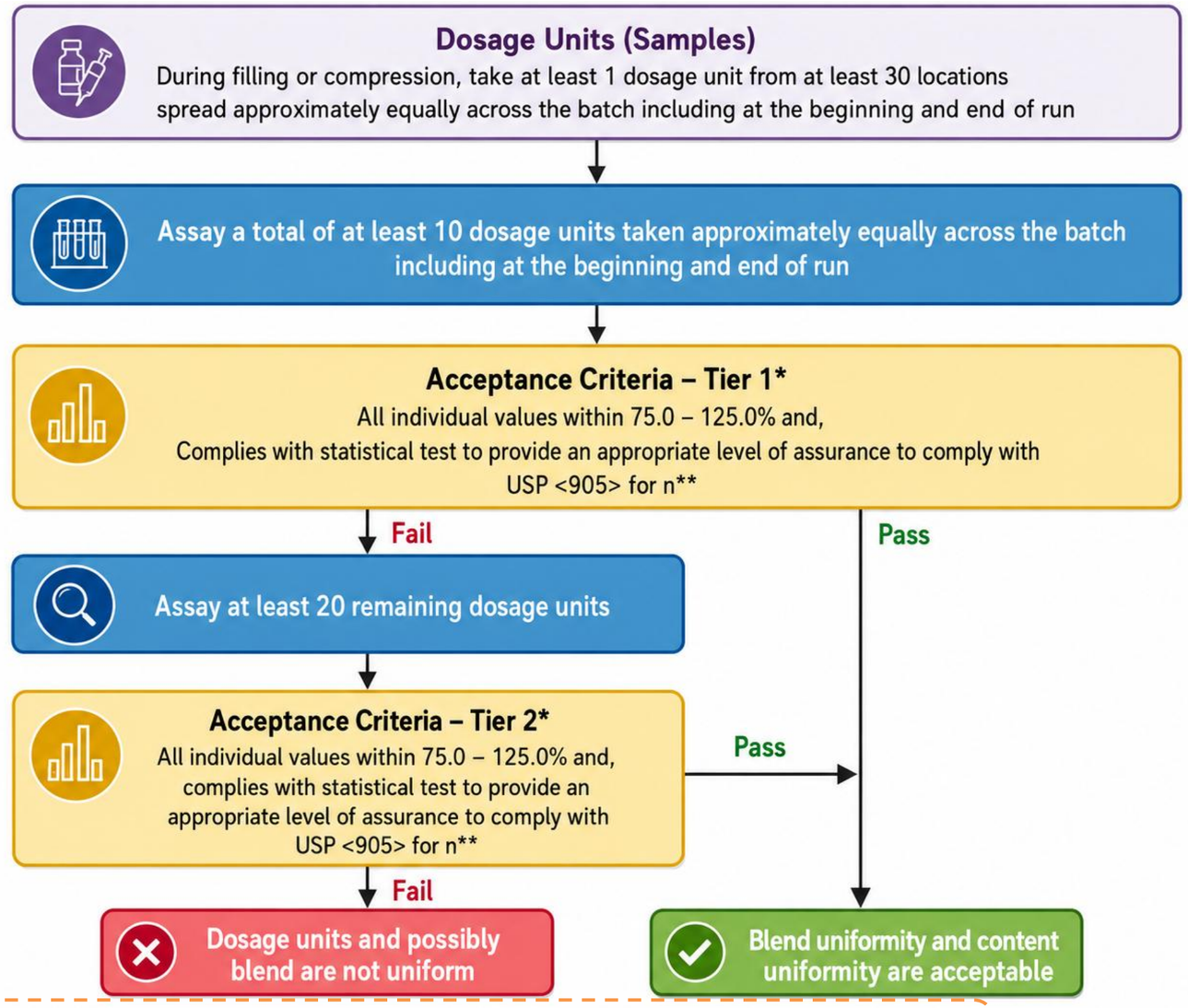
Example: Dry-Mix VCA- Cont'd

BY081023 VCA Outcome				
Blend		**Dosage Unit**		**Interpretation**
Within Location	Between Location	Within Location	Between Location	Either the blend is not uniform and downstream processing (e.g., milling) results in uniformity, or the blend data are biased due to sampling technique/ error
4.0	3.5	1.1	0.9	
High	High	Low	Low	

Sampling Bias!

Vs.

ISPE Rec. for BU and CU Evaluation in Routine Batches

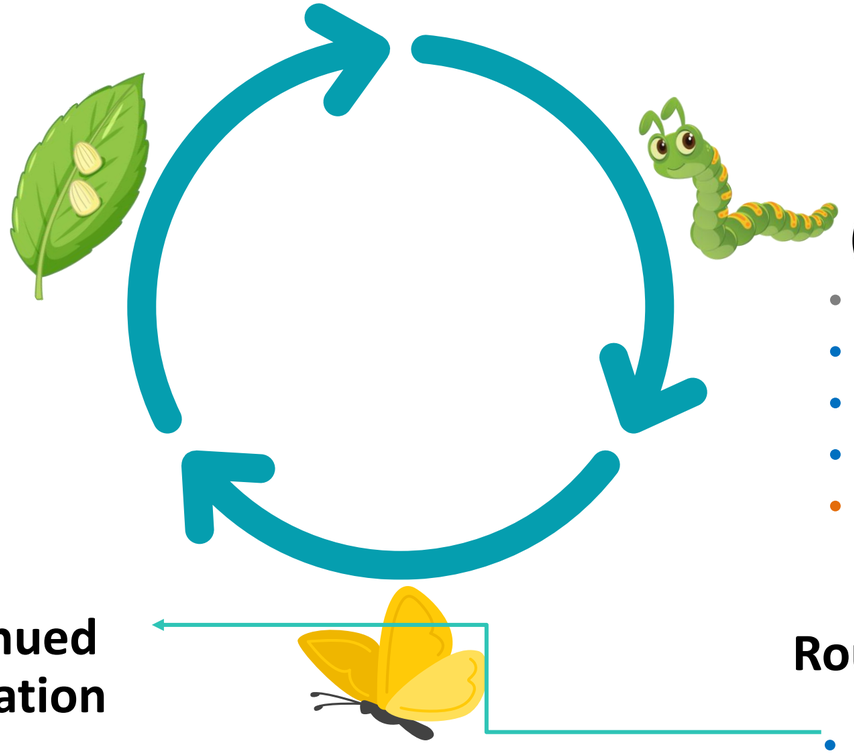


Change from **90%** confidence for 95% coverage to **50% confidence** for 95% coverage

Uniformity is involved in all Process Validation Stages

Stage 1- Process Design

- Blend Uniformity
- Blend Uniformity Assessment
- Content Uniformity
- Content Uniformity Assessment
- 90% CI/95% Coverage



Stage 2- Process Qualification (Initial/Changes)

- Blend Uniformity
- Blend Uniformity Assessment
- Content Uniformity
- Content Uniformity Assessment
- 90% CI/95% Coverage

Stage 3- Continued Process Verification

- Blend Uniformity Assessment
- Content Uniformity Assessment
- 90% CI/95% Coverage

Routine Production

- Blend Uniformity Assessment
- 50% CI/95% Coverage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Thanks!
Grazie
THANK YOU!