Solid Oral Dosage Forms
Powder Blending

İKEV Meeting

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Mechanisms of Powder Blending

- **Diffusion**- redistribution of particles by random motion
  - Vertical or axial motion
  - Seen in rotational blenders
- **Convection**- transfer from one location to another
  - Motion imparted by impeller as in Ribbon Blender
- **Shear-** formation of slip planes
  - Motion imparted by high intensity mixers

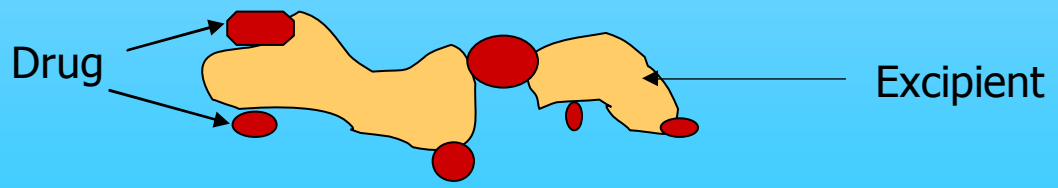
Classification of Mixing Equipment

Mechanism	Equipment
Diffusion (Tumble)	V-Blender (Twin Shell) Double Cone Blender Bin Blender Horizontal/Vertical Drum
Convection (Paddle or Plow)	Ribbon Planetary Horizontal High Intensity Vertical High Intensity Diffusion (with I-Bar)
Pneumatic (Expansion with Gas)	Fluid Bed Reimelt

Reference: FDA Draft Guidance- SUPAC IR/MR-Scale-Up Post Approval Changes - Immediate and Modified Release - Equipment Addendum, April 1998; http://www.fda.gov/cder/guidance/index.htm

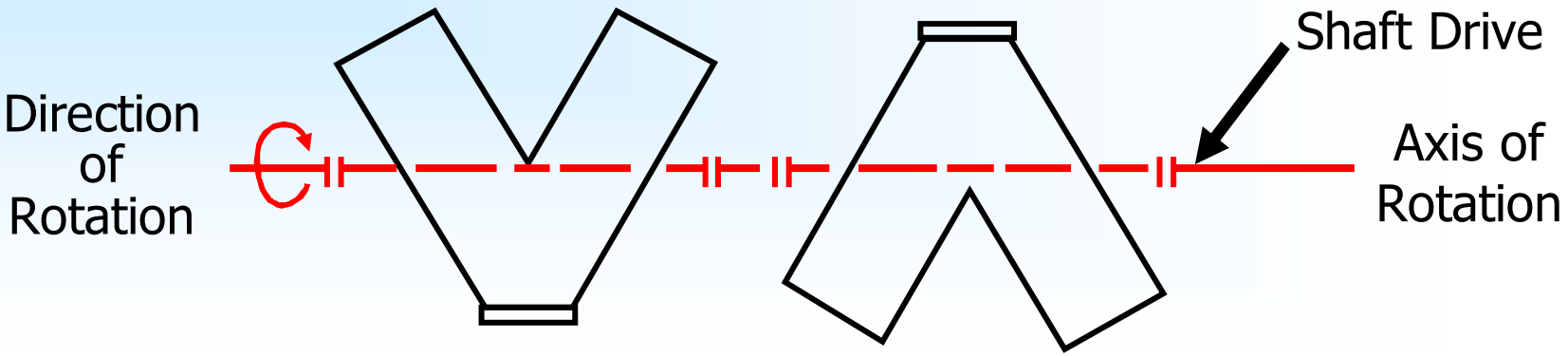
Blender Selection vs. Material Type

- Non-cohesive blend (flows & mixes easily)
  - Bin Blender
  - Twin Shell
  - Other precision, rotational blender
- Cohesive blend (lumpy, not free-flowing)
  - High Shear (e.g. Twin Shell w/ I-Bar, Colette, Lodige)
- Ordered Mix (drug << excipient)
  - Tumbling mixers, cone mixer, high energy many types are allowable.
  - Drug is glued to larger excipient particles
  - Drug may 'coat' larger excipient particles



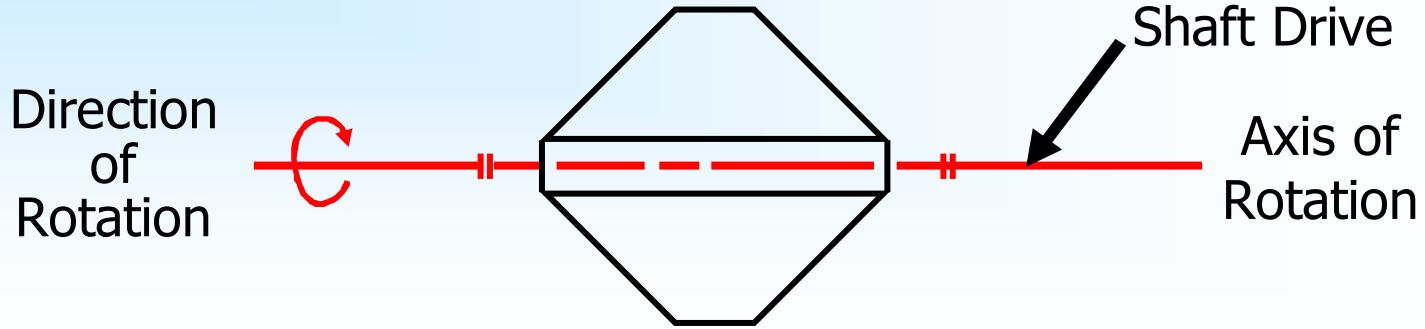
Rotating Shell Blenders

V-shaped Blender



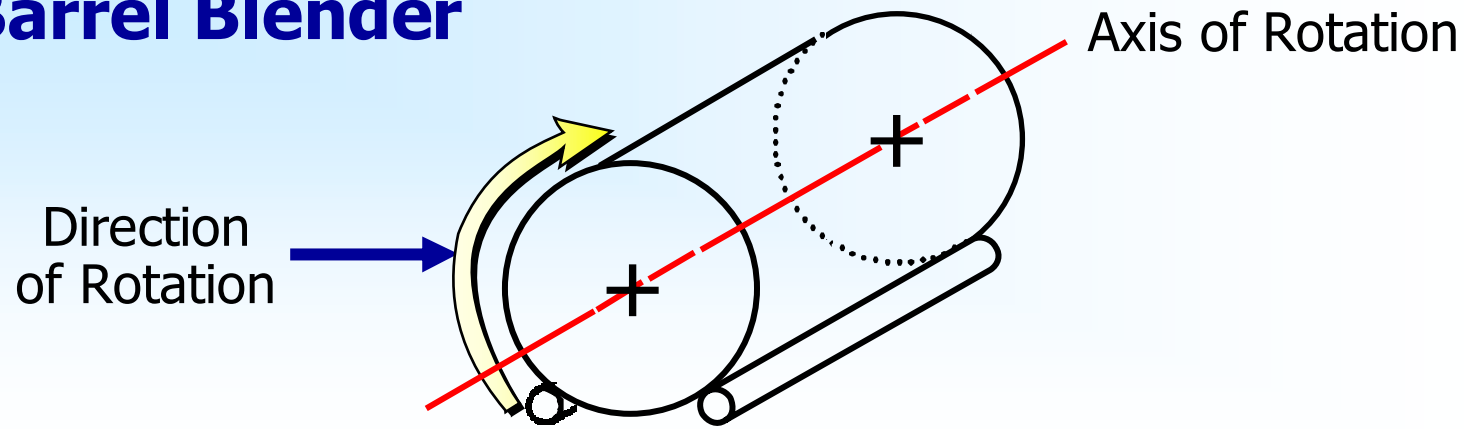
Keep shell tip speed constant at approximately 100 m/min (300 ft/min)

Double-cone Blender

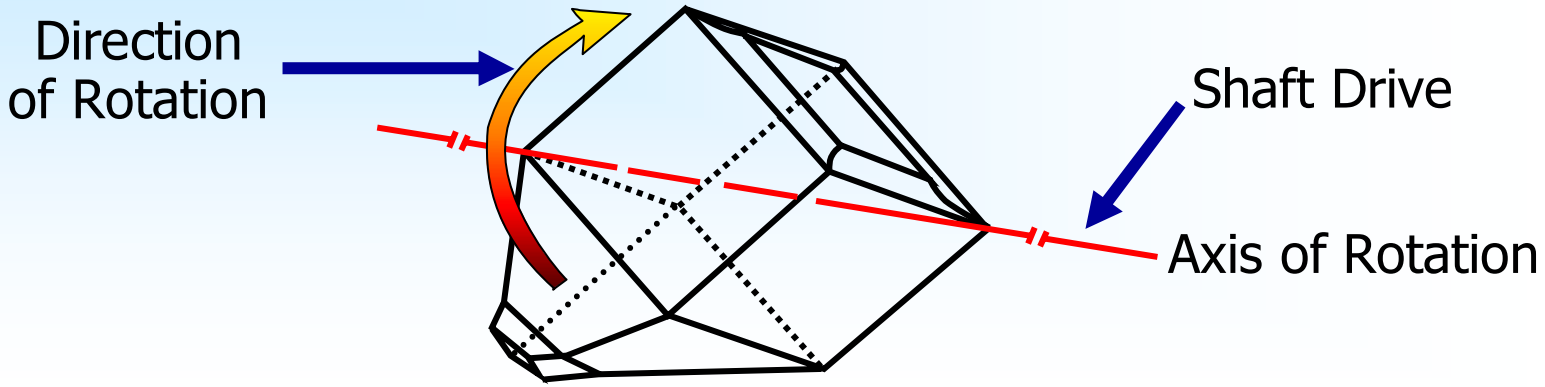


Rotating Shell Blenders

Barrel Blender



Bin Blender



Physical Properties of Blend Components

Materials

- Active Ingredients
- Excipients
- Dried Milled Granulations
- Final Blends

Tests

- Particle size Distribution
  (coarse, medium, fine)
- Density
  (loose or bulk, tapped)

If possible, match particle size/densities, especially for dry blends. For example,

- Break-up lumpy excipients with delumping agents (e.g.fumed SiO_2)
- Screen/ delump actives with excipients
- Coarse particle sizes could create content uniformity issues.

Factors in Blending

- Blender Volume
  - Usually 60% (±10%) of total air volume is working volume (40% air to mix and flow). Example: total air volume: 3000L, working vol: 2000 L (66%); Density - 0.48-0.52 g/mL; Batch size is 1,000 Kg.
  - Sliding (cascading) fall vs drop.
- Blend times for pharmaceuticals: typically 10-20 minutes.
- Obtain accurate powder density from trials
- Constant batch size
- Visual and calculated observations (before/ after blending)
- Nature of material
- Raw Material physical properties are in control

Need for Preblending

Direct Blending	Preblending (Nongeometric)	Preblending (Geometric)	Solvent Addition
>5-10% Active	1-5% Active	< 1%	< 0.1% active
Straight mixing	Use (drug fraction)$^{1/2}$ {e.g. $(0.04)^{1/2}$ = 20%; 4 Kg drug + 16 Kg Excipient}- Preblend	1:1 (Drug:Exc), 1:1 (Mix: Exc), 1:1 (Mix: Exc), and so on.	Dissolve in liquid and spray/coat/ granulate
Adequate	Good method	Cumbersome	For low dose products (e.g. hormones)

Scale-Up of Blending

Working Capacity (L)	Typical RPM	Typical Amount (Kg)
20-50	25–30	8-30
250	22–28	80-150
500	12–18	200-300
2000	8–12	800-1200

Rotational velocity is key blending parameter
Rotational Tip speed (100 m/min) and momentum (mass x velocity) stay same during scale-up; as mass increases blender RPM decreases.

Scale-up of Blending

- Pilot Plant development
  - Evaluate and determine blending times
    - Start at 10 min, sample every minute thereafter
    - Select three times and bracket with acceptable results
  - Sampling methods, sizes, and locations are developed
  - Determine if blending is critical (i.e. sensitive, problematic)
- Qualify Production Blender
  - Verify blending time and rotational speed
- Production blending instructions
  - Specific, precise blending speed and blending time.
  - Ranges are not usually in batch directions
  - No variation from batch to batch

Segregation (Demixing of components)

- Occurs during blending, transport, storage or discharge.
  - Seen mostly during transport and discharge.
- Greater with free-flowing powders since they can separate easily (based on size, shape, and density)
- Overcome by
  - Minimizing physical differences
  - Increasing cohesiveness of formulation
  - Optimizing blending conditions

Types of Segregation

- Sifting - smaller particles slipping between larger ones.
  - Particle size differences > 3:1
  - Mean Particle size > 300 µm
  - Free flowing pile formed through funnel
  - Major component is > 3 times minor one.

Example - Granules on top of powder bed in tablet press hopper or coarse particles at the end of a container. Related to Vibration effects that may accelerate the sifting phenomenon.

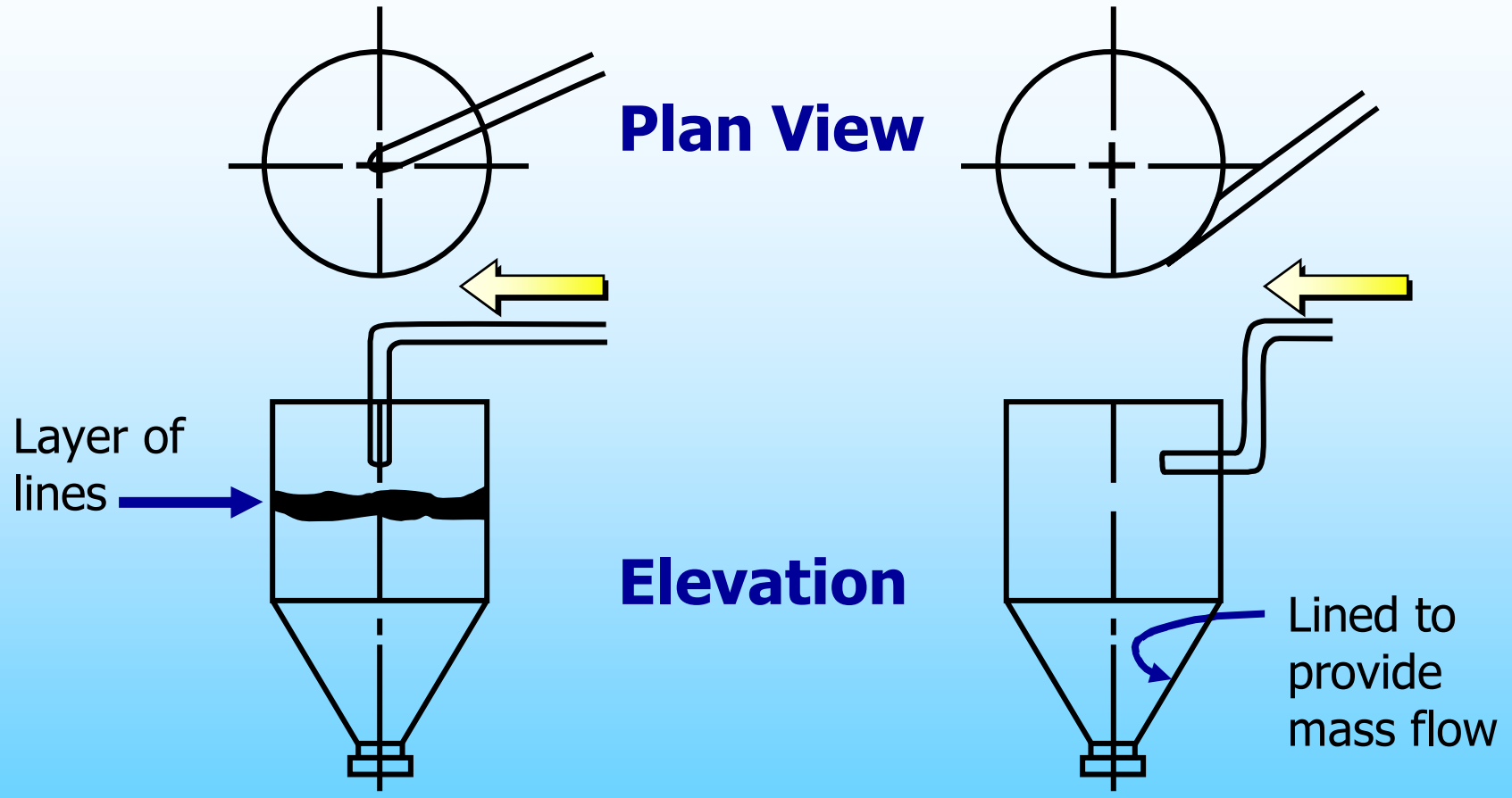
Correction:

- Narrower particle size distribution
- More cohesiveness
- Reduce material handling (discharge, scooping, transport)
- Change equipment design (angles, vents, cone-in-bin)
- Use equal portions if possible (50/50 mix)

Types of Segregation, Contd..

- Aeration (percolation) or Fluidization causes fines to travel to the top with air.
  - Particle size differences
  - Excessive high shear mixing (air introduced during blending)
  - Settling effects
- Dusting or particles in the air - fines accumulating at side or perimeter of drum/bin.
- Arching or 'rat holing' - different angle of repose and cohesiveness of mix components leads to differences in sliding, mixing, and discharge pattern of mix components.

Segregation by Fluidization

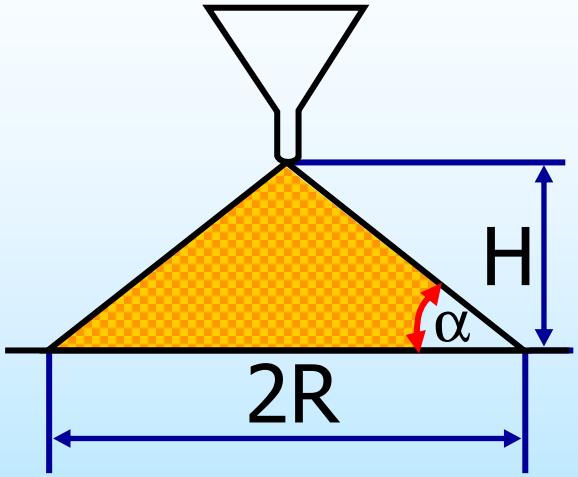


Original configuration- too much air during filling

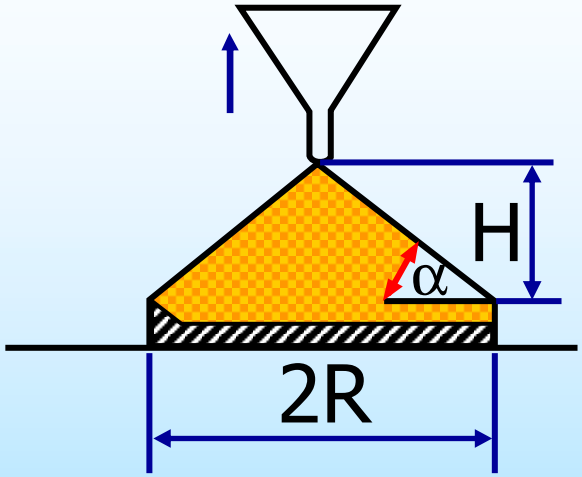
Revised Configuration- less air effect as it enters tangentially

Reference: Pharm Tech, June 1994.

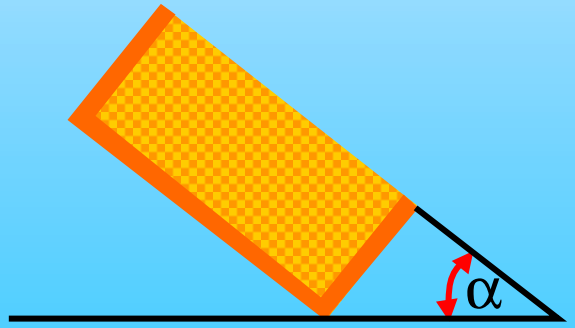
Measuring Angle of Repose



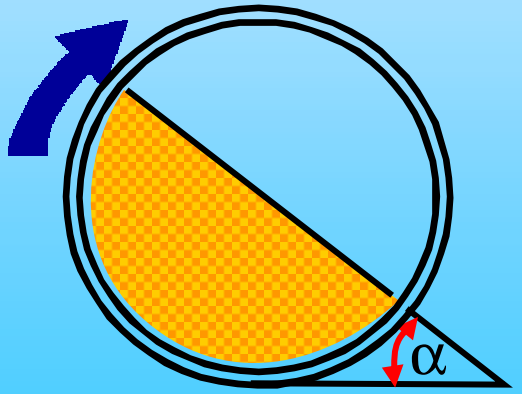
Fixed-Funnel



Fixed-Bed Cone

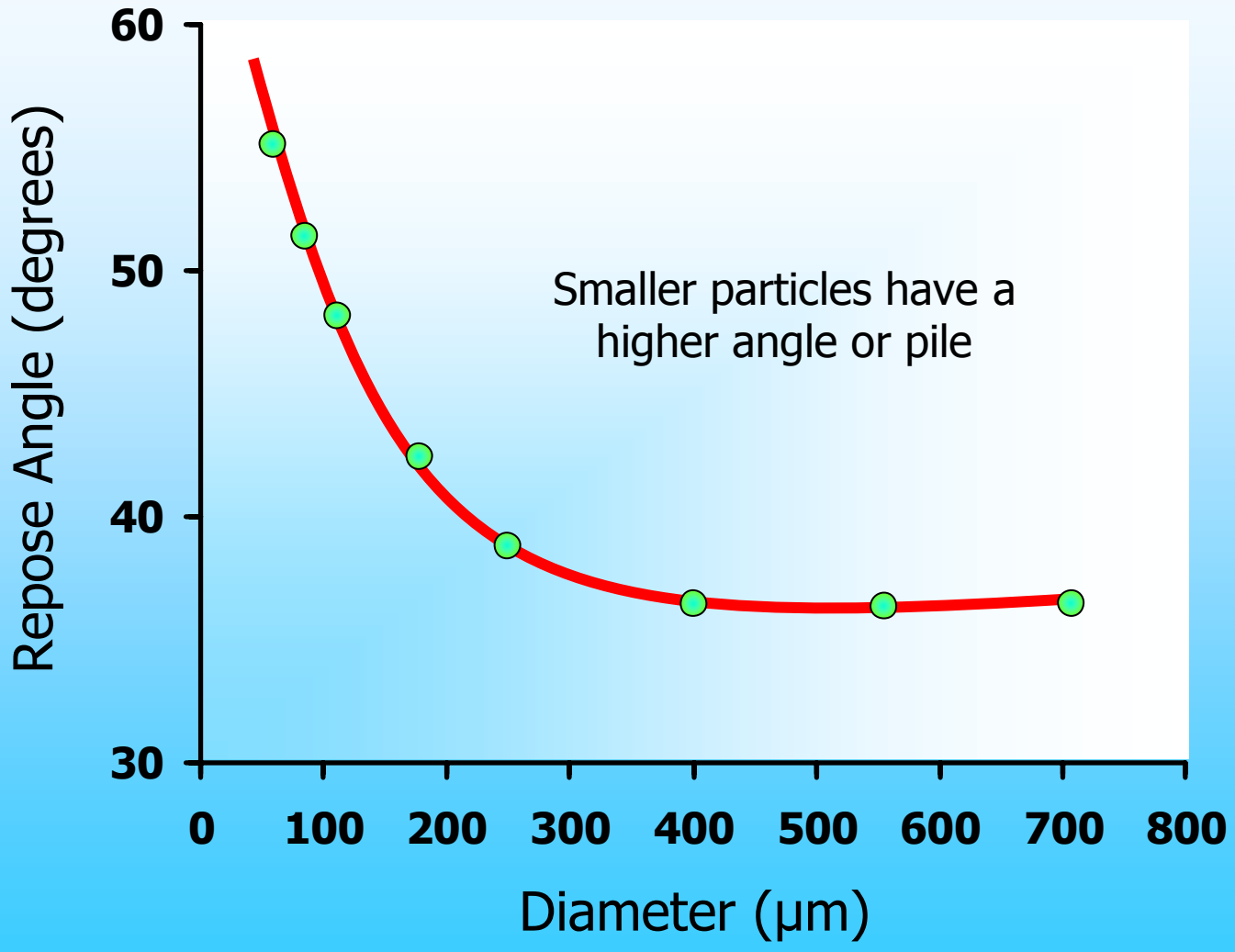


Tilting Box



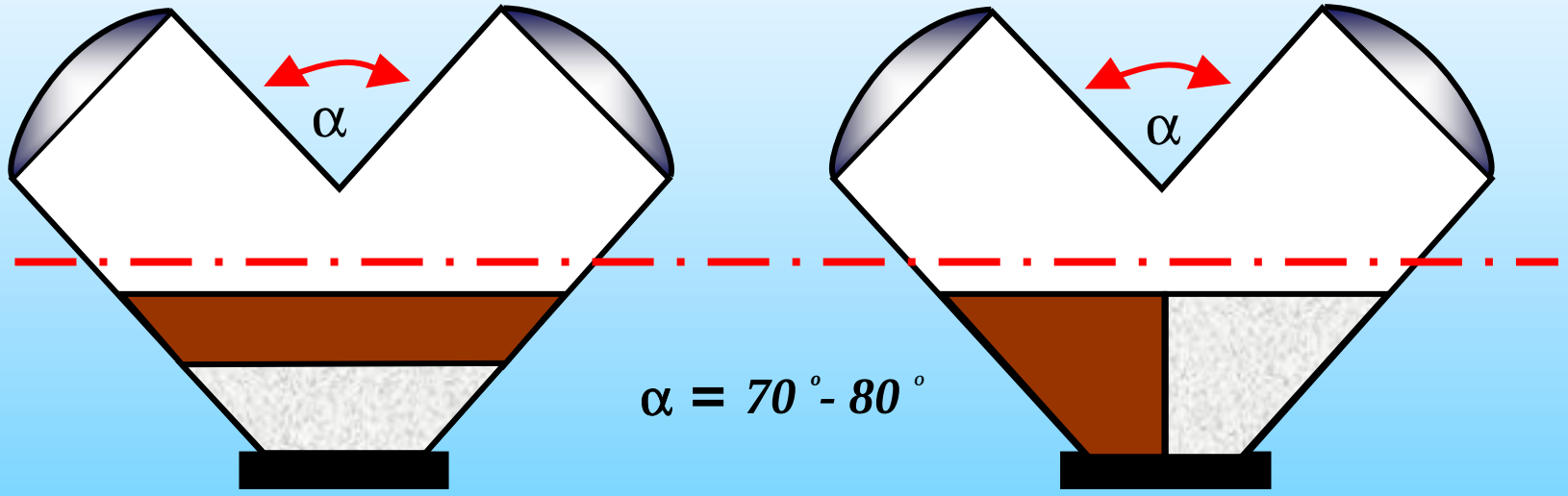
Revolving Cylinder

Angle of Repose for Different Sieve Cuts of MgO



V-type Blenders: Effect of loading

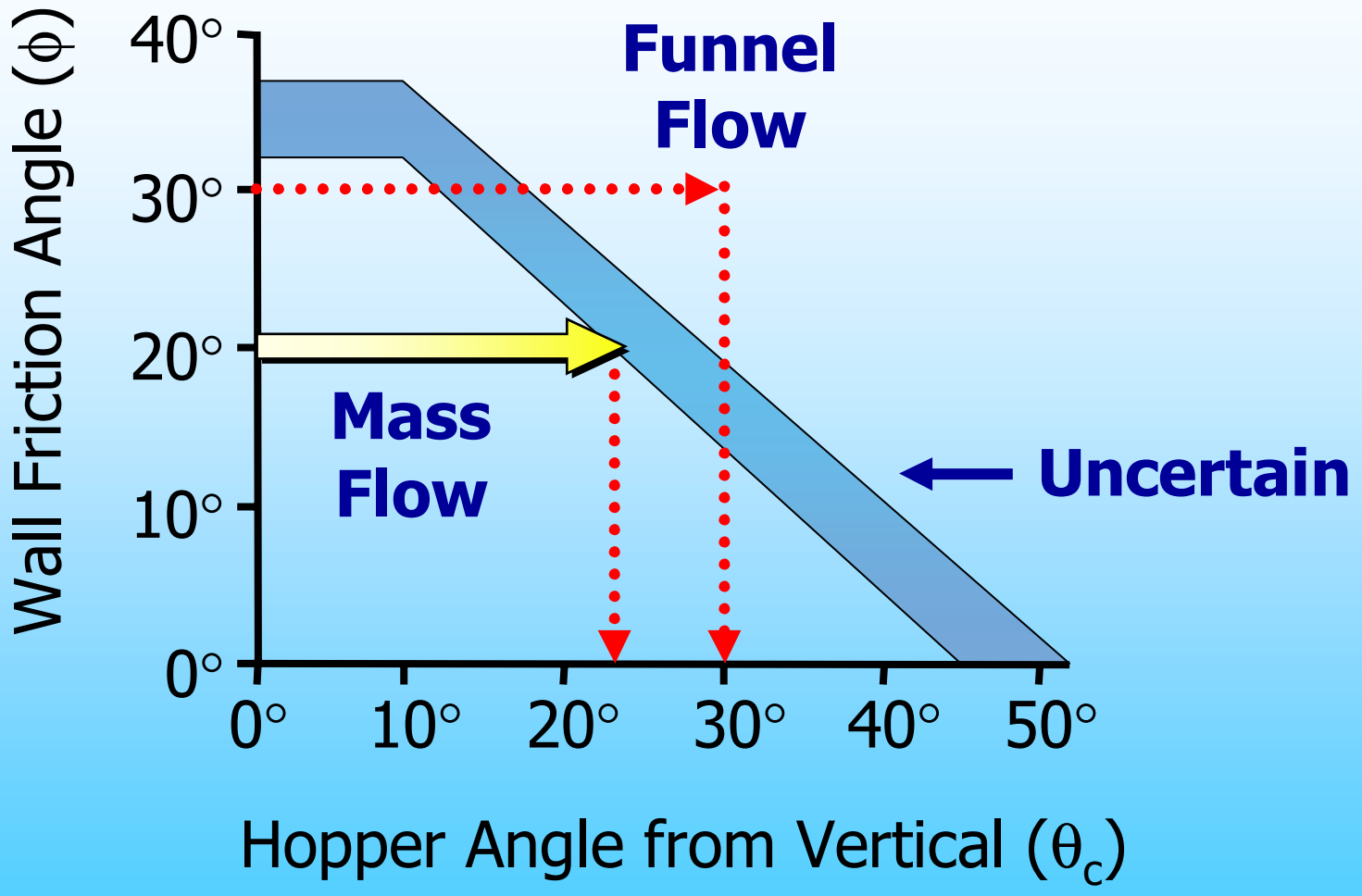
V-type Mixer



Layer-by-layer Loading:
Convection Paces Blend

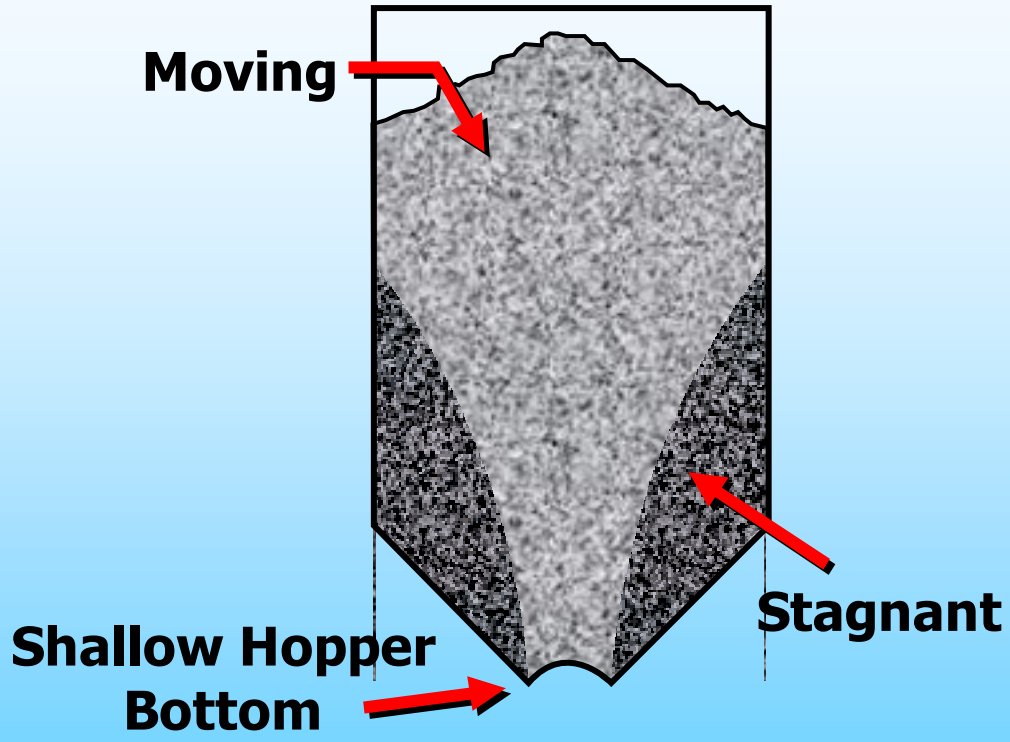
Side-by-side Loading:
Diffusion Paces Blend

Funnel Flow and Mass Flow Patterns



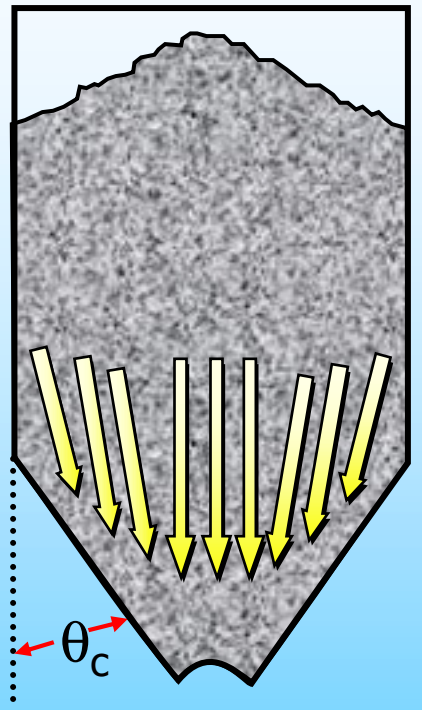
Higher wall friction requires steeper hopper angle (smaller θ_c) to maintain mass flow.

Mass Flow Angle Design for Hopper



Funnel flow

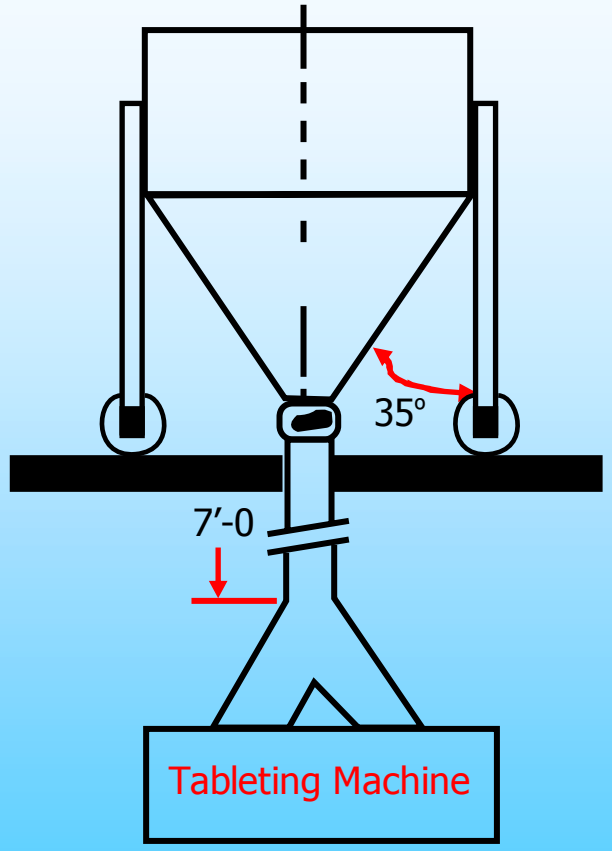
(Segregation is worst)



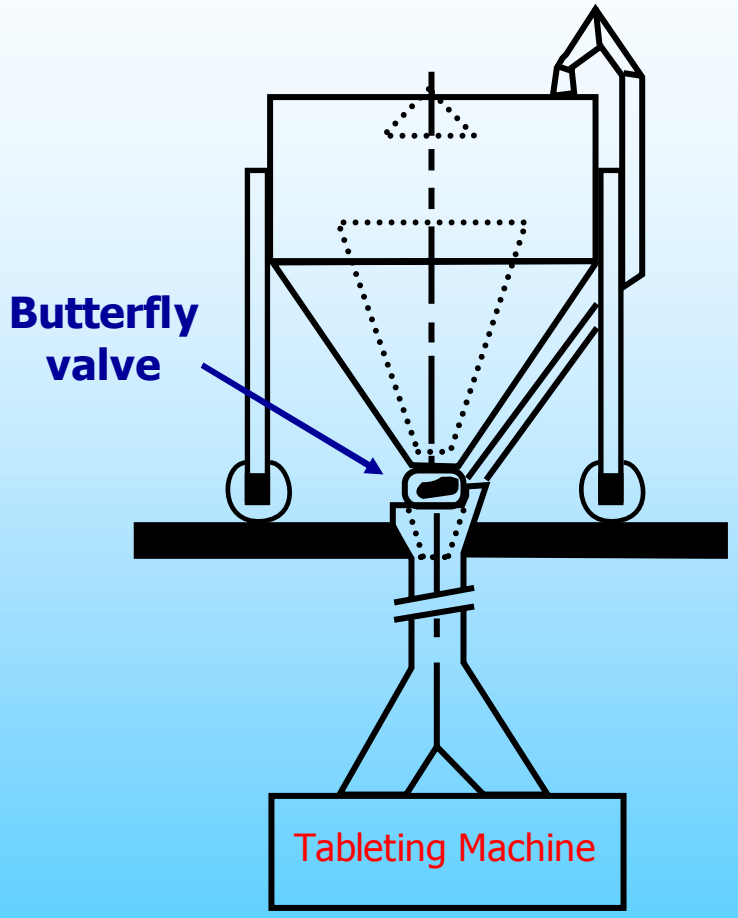
Mass flow

Reference: J. Prescott, Pharm Tech Europe, Jan 2001.

Rapid drop of powder into a Y-branch above tablet press leads to air entrainment



Original Configuration- airstream carried fines



Revised Configuration;

Vent allows air to bypass

Reference: Pharm Tech, June 1994.

Sampling Methods

- Static Bed - sample thieves
  - Globe (side sampling) - most common
  - End
  - Streamline End
  - Core sampling device
- Flow stream (during dynamic discharge)
  - Best to sample entire stream for very short period.

Refs: 1) Chang, R-K. *Drug Dev. Ind. Pharm*., 22 (9), 1031-1035 (1996).

2) Garcia, T.P. *Pharm Dev. Tech.,* 3 (1), 7-12 (1998).

Sample Quantity and Frequency

- In Development phase, pull 1-3x Unit Dose or larger samples.
  If 1-3x is problem, test larger samples to assess bias.
  Justify deviation from 1-3x dose size.
  [Below 1.0x has been problematic, 1-1.5x is optimal.]

- During Validation,
  - Use recommended sample size from Development.
  - Minimum ten locations, three per location (total of 30 samples per batch). Must include worst-case locations.
  - Test 10 samples per batch. Test other 20 samples per USP <905> protocol, if needed
  - If drug content is > 50% (or 50 mg) in dosage form, blend uniformity is not needed. (Dickinson's FDA Review, Nov. 1998)

Sampling Locations in V- Blender

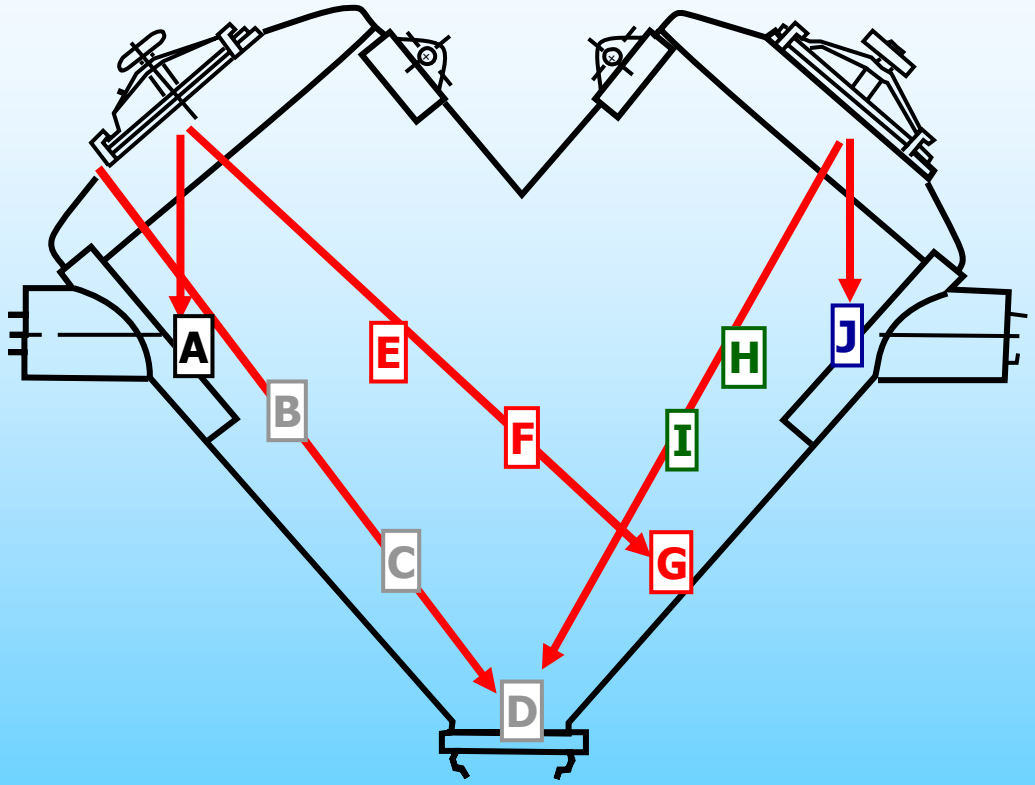


Diagram Shows Approximate Two-Dimensional Sample Locations for a Twin Shell Blender

1st Sample Set

A = Left-Left-Top (left arm)

2nd Sample Set

B = Left arm-Left-Middle
C = Left arm-Left-Bottom
D = Discharge Port

3rd Sample Set

E = Left arm-Center-Middle
F = Center-Center-Center
G = Right-Right-Bottom

4th Sample Set

H = Right-Right-Top
I = Right-Right-Middle

5th Sample Set

J = Right-Right-Top (right arm)

Sampling Locations in Bin Blender

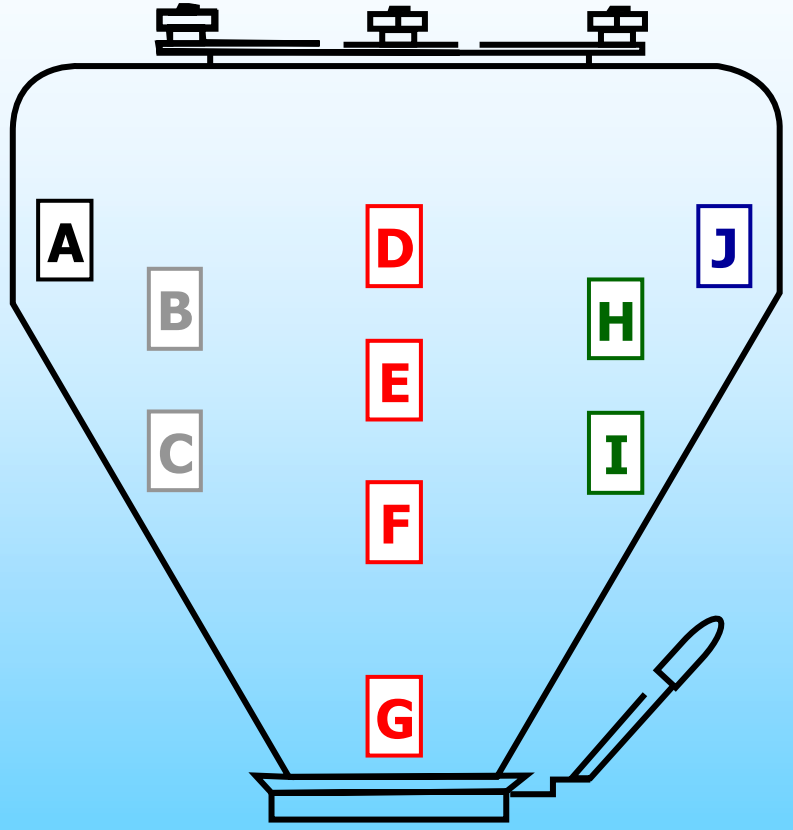


Diagram Shows Approximate Two-Dimensional Sample Locations for a Bin Blender

1st Sample Set

A = Left-Top (left arm)

2nd Sample Set

B = Back-Top

C = Back-Middle

3rd Sample Set

D = Center-Top

E = Center-Middle-Top

F = Center-Bottom

G = Discharge Port

4th Sample Set

H = Front-Top

I = Front-Bottom

5th Sample Set

J = Right-Top (right arm)

Sample Analysis

- Use HPLC where possible, for accuracy.
- HPLC method validation.
  - Precision
  - Reproducibility
  - Sensitivity
  - Spike Placebo - Recovery
  - Solution Stability - Up to 24 hr.
- Blend mean assay is lower than finished product assay. Investigate…..
  - Recovery (dissolving) method, final unit weights, sampling technique (static charge), non uniform mix. May need a powder blend assay or potency test.
- Lab training since blend testing may be uncommon.

Sampling Consistency

- Consistent and standardized sample thief technique
  - Angle of insertion (e.g. 45 °)
  - Swivel (e.g. 3 o'clock)
  - Fast or slow insertion
  - Personnel technique
- Glass vs plastic containers (static).
- Sample separation (coarse/fines).
- Test entire sample (1-3 X); Pull in triplicate (back-up testing)
- Weigh sample containers before sample is added.
- Rinse sample container with extra diluent

Sampling Error/Bias

- Thief design
- Sampling technique
- Physical properties of formulation
  - Flow in sample cavity
- Handling procedure
- Sample size (< unit dose)
- Active content (< 5 mg)

Ref: Carstensen, J.T. Drug Dev. Ind. Pharm., 19 (20), 2699-2708 (1993)

Assay of screen fractions (to assess distribution of active)

- Coarse, medium, and fines (minimum of three fractions)
- On occasion, do not meet theoretical potency
  - Coarse 1-2 % w/w (Theory is 5% w/w)
  - Medium 4 % w/w
  - Fines 10 % w/w
    - May be up to 100% off from expected and still provide acceptable final blend and final product.
    - Use this technique for rough estimation only.

Review

- Mixing mechanisms and equipment
- Component characteristics
- Scale-up of mixing parameters
- Sampling considerations
- Test methods used
- Data interpretation

Thank You!

Questions?

Solid Oral Dosage Forms, Blend Uniformity: Principles and Examples

Turkish Pharmaceutical Society Meeting
June 1, 2001

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Definitions and Terminology

- Powder Blend Uniformity - refers to active ingredient (or preservative) distribution or homogeneity in the "final" blend or mix. Powder Blend is encapsulated, tabletted, or filled into single or multiple dosage units.

- Adequacy of Mixing - satisfactory blending step to assure uniformity and homogeneity. A term used by the US Food and Drug Administration (FDA).

  [21 Code of Federal Regulation 211.110 (a)(3), 1978]

Reasons for Blend Testing

- To optimize the blend time during development phase.
- To demonstrate lack of segregation in bins/drums during material handling.
- To confirm that specified blend conditions produce acceptable uniformity during validation.
- In Australia, blend assays can be used to release finished product.

FDA's position on blend testing

- Use conservative approach: when mixing is critical, blend evaluation is warranted, but may be unnecessary under certain circumstances…
- Validation … may define where it is appropriate, but a conclusion cannot be made before validation is completed and historical data is analyzed.
- 21 CFR 211.110 requires in-process controls and tests…to monitor… those steps responsible for variability...

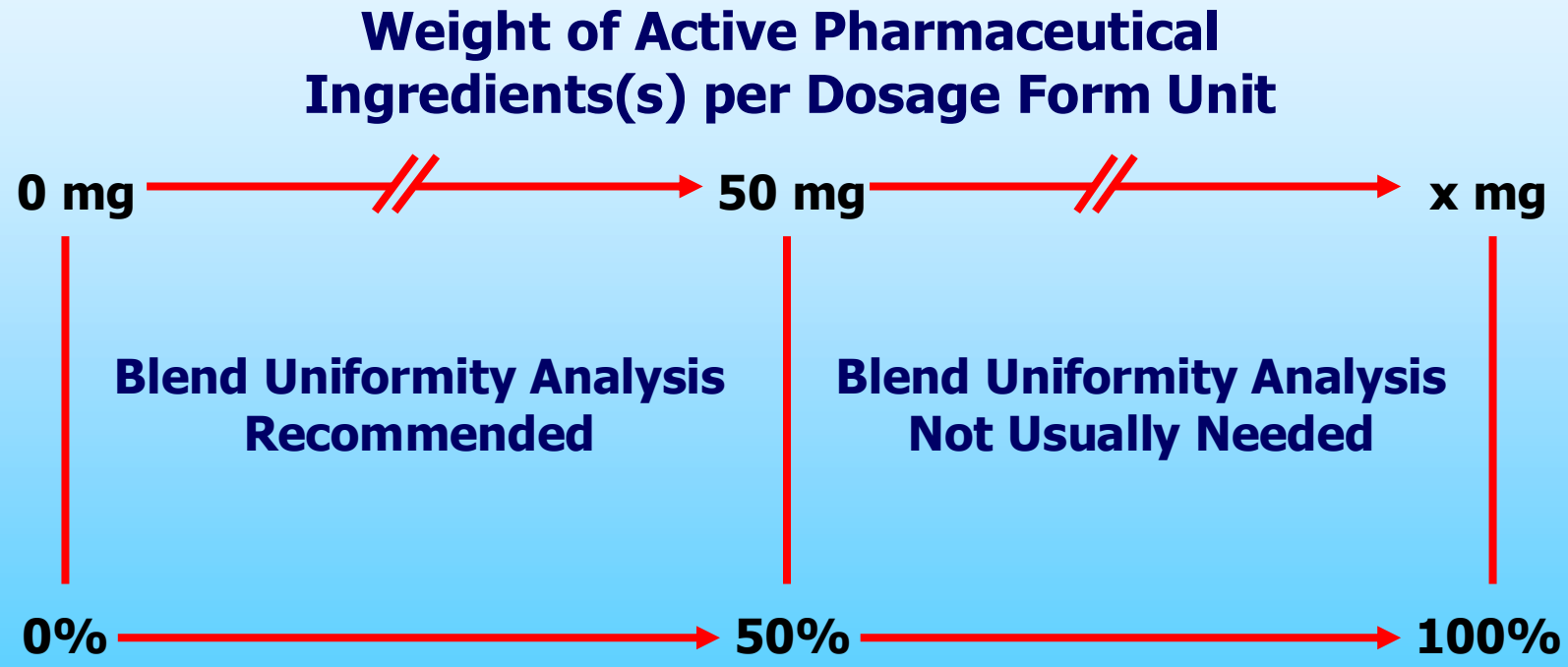
Ref: FDA letter, Aug 29, 1997 in PDA Technical Report No. 25, 1998

Draft FDA Guidance on BUA

- FDA (Office of Generic Drugs - OGD) has issued a Draft Guidance for ANDA Products (August 1999)
  - Conduct BUA on all commercial batches of ANDA drug products with < 50 mg or < 50% active ingredient(s) (Those requiring USP CU test)
  - FDA's interpretation of 211.110 (a)(3) requires BUA (in-process testing for adequacy of mixing)
  - Sample size (less that 3x dosage weight, if bias, up to 10x); N= 6-10 samples; Acceptance criteria: 90.0-110.0% (**mean**), RSD < 5.0%
- Statement that it will extend to NDAs, after another Guidance is revised

The intent of the guidance is clarified in 3/00 edition of Human Drug GMP Notes.

BUA for Simple Dosage Forms



Reference: FDA Draft Guide, Blend Uniformity, Aug 1999.

BUA: Industry Comments to FDA Guidance

- BUA is unnecessary for commercial batches since blending step is validated
  - Evaluated during Development and Validation
  - Blend time and speed specified in manufacturing instructions
  - Raw material control
- Guidance follows USP CU test requirement only part of the way; does not allow testing of additional 20 samples
- Proposed BUA acceptance criteria of 90.0-110.0% mean, <5.0% RSD is looser than USP's 85-115% for individuals, < 6.0% RSD; should be 90.0-110.0% for individuals
- Could lead to unauthorized reblending/retesting procedures
- Firms prefer not to conduct BUA on routine production batches.

FDA court case* on BUA

- Sampling technique should be representative of all portions of blend.
- Blending should not generate weak and/or hot spots in the blend.
- For blend uniformity, sample size must be at most 3 unit dosages.

* FDA vs. Barr, legal action, 1993

Powder Blending Parameters

Variable

- Blending time
- Blender speed
- Intensifier bar

Response

- Blend Content Uniformity
- Assay
- Particle size distribution
- Powder flow
- Densification/Aeration

Lubricant Blending Parameters

Variable

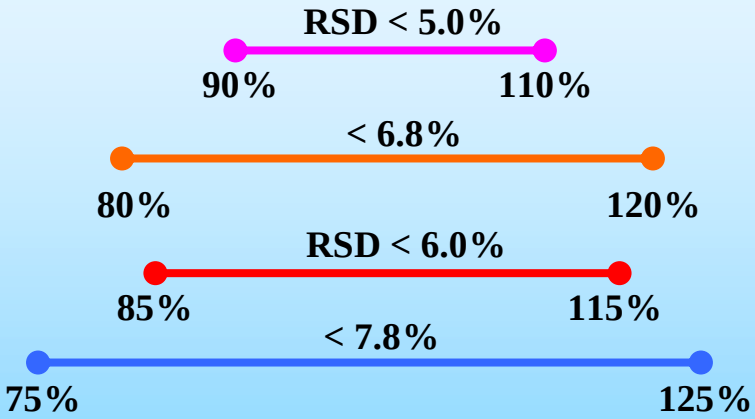
- Blender speed
- Blending time
- Method of addition

Response

- Loose/tapped densities
- Powder flow (from blender/ hopper)
- Tabletting/filling characteristics

Acceptance Criteria for Blend Assay

Samples		Individual Assay
10	Powder Blend - Stage 1	RSD < 5.0% (90% – 110%)
30	Powder Blend - Stage 2	< 6.8% (80% – 120%)
10	Finished Product - Stage 1	RSD < 6.0% (85% – 115%)
30	Finished Product - Stage 2	< 7.8% (75% – 125%)



Blend uniformity acceptance criteria are usually tighter than those for finished product; requirements for Stage 1 are tighter than those for Stage 2.

Standard Deviation Prediction Interval (SDPI)

- Allows calculation of maximum acceptable standard deviation for blend samples (Uses F statistic)
- More conservative approach than the USP

Sample size	% RSD SDPI	% RSD USP
10	3.84	6.0 (Stage 1)
20	4.26	
30	4.40	7.8 (Stage 2)
60	4.55	

Effect of Blending Time on Blend Uniformity

Blend time (min)	Mean (%)	RSD (%)	Range (%)
5	99.7	1.1	98.1-101.8
7	100.0	1.7	97.2-103.3
9	100.0	2.0	95.5-103.1

Sample size: N= 10, 1-2 X (1-2 unit dose); product has 7% active.

- RSD $\leq$ 5.0 % (and 3.84% from SDPI, as well)
- All acceptable and equivalent uniformity at 5- 9 min.
- Seven minutes was chosen and was bracketed.

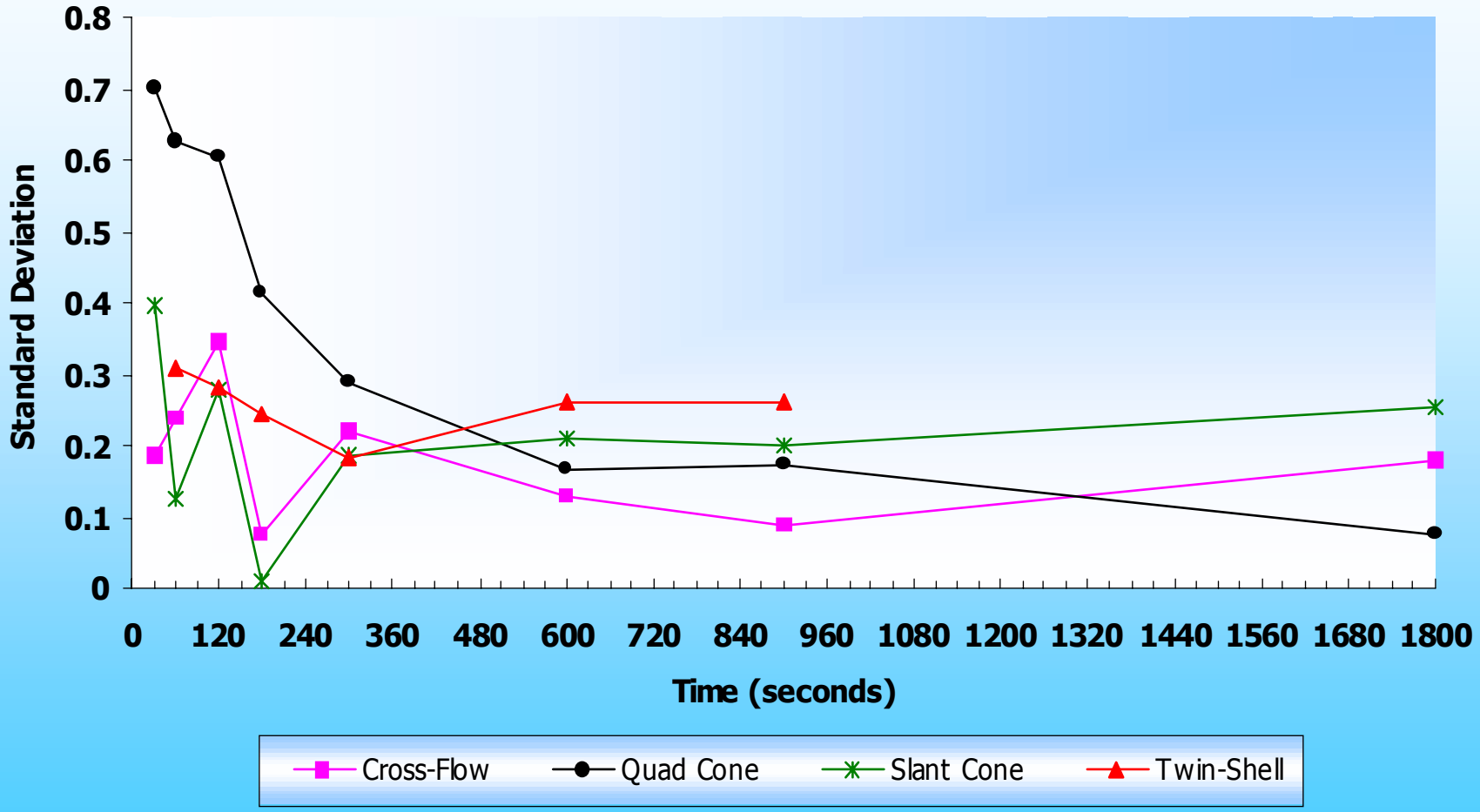
Effect of Physical Properties on BUA

Test	Batch 1	Batch 2	Batch 3	Batch 4
Blend Particle size				
% > 250 µm	15	12	12	12
% < 106 µm	65	72	72	73
Blend Density, g/mL				
Loose (Bulk)	0.53	0.55	0.55	0.54
Tapped	0.63	0.69	0.69	0.69
Blend Uniformity				
Mean, %	99.9	102.3	100.3	101.2
RSD, %	1.7	3.3	1.0	1.1
Core Uniformity				
Mean, %	101	102	101	101
RSD, %	1.1	0.9	1.7	1.5

Effect of Particle Size of a Potent Active (4% w/w)

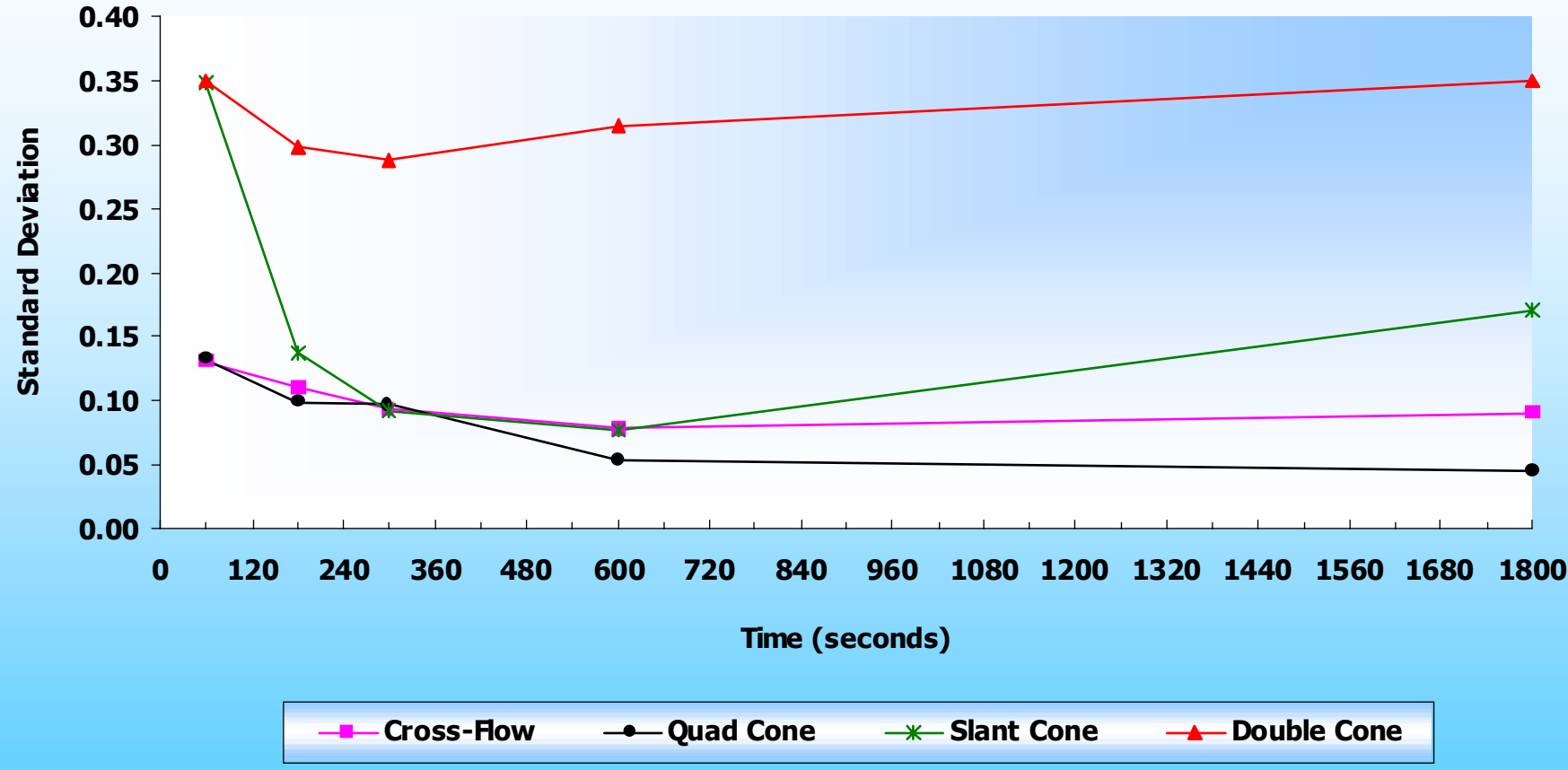
- Scale-up: Blend uniformity RSD was >8% and on occasion, 10%.
- Investigation and screen analysis revealed active had 5-10% of very hard, coarse particles (>1000 μm) that could actually weigh more than 0.8 mg. This lead to poor blend and content uniformity.
- Correction:
  - Controlled milling of active
  - Preblend step added (since active % was relatively low)
  - Use of Comil or conical screening with excipient provides enhanced mixing and dispersion of active.

Choice of Blending Equipment



Blending of 3.5% Citric Acid in Sand; Source: Harsco Co. (Patterson Kelley Blenders Co.), 1997

Choice of Blending Equipment



Blending of 3.5% citric acid in granular Na tripolyphosphate; Source: Harsco Co. (Patterson Kelley Blenders Co.), 1997

Blending more than one active

- All actives must be distributed uniformly
- Focus on minor component-usually the more difficult to disperse
- Literature has equations/calculations: apply same CV or acceptance criteria for each component.

BUA vs CU - 2 Actives

- Active A: 10% w/w, B: 12.5 % w/w
- Both actives are granulated, dried and blended.
- Physical Properties of blend
  - Particle size mean - about 200 μm (10% < 70 μm ; 10% > 800 μm)
  - Density - 0.74 g/mL (loose), 0.83 g/mL (tapped).
  - Angle of repose - 0.65
- Blend 10 min @ 12 rpm (120 revolutions)

	Active A		Active B	
	Mean	RSD, %	Mean	RSD, %
Blend (n = 10)	103.1	1.3	96.8	1.5
Tablet (n = 30)	99.0	1.5	101.5	1.6

BUA vs. CU 3 Actives, Example 1

- Actives A 4% w/w, B 60% w/w, and C 2% w/w
- All actives are granulated, dried and blended.
- Physical Properties of blend
  - Particle size mean - about 110 µm (15% < 55 µm ; 8% > 250 µm)
  - Density- 0.50 g/mL (loose), 0.64 g/mL (tapped).
- Blend- 20 min @ 10 rpm (200 revolutions)

n= 10; All RSDs were < 3.8 % (SDPI) and all met specifications of 5.0%

BUA vs. CU 3 Actives, Example 1, contd.

Blend uniformity, 3 batches

Active	Mean, %	RSD, %
A	99-101	1.0-3.6
B	97-99	0.6-2.0
C	99-102	1.5-2.9

CU, 3 batches

Active	Mean, %	RSD, %
A	99-100	1.4-2.3
B	97-98	0.5-0.8
C	99-102	1.4-1.8

For blend uniformity: n= 10; all RSDs were < 3.8 % (SDPI) and met spec of 5.0%

For tablet CU: n= 10 for 2 batches and n = 30 for third batch; all RSDs were <3.8 % (SDPI) and met specifications of 5.0%

BUA vs. CU 3 Actives, Example 2

- Actives: A 66.7% w/w, B 8.0% w/w, and C 0.33% w/w
- All actives are granulated, dried and blended.
- Preblending (5 min) , Main blending (20 min), and Lubrication (5 min)

BUA vs. CU 3 Actives, Example 2, contd.

Blend uniformity, 3 batches

Active	Mean, %	RSD, %
A	66-68	0.9-3.9
B	7.9–8.0	1.3–1.8
C	0.32-0.34	3.7–4.2

CU, 3 batches

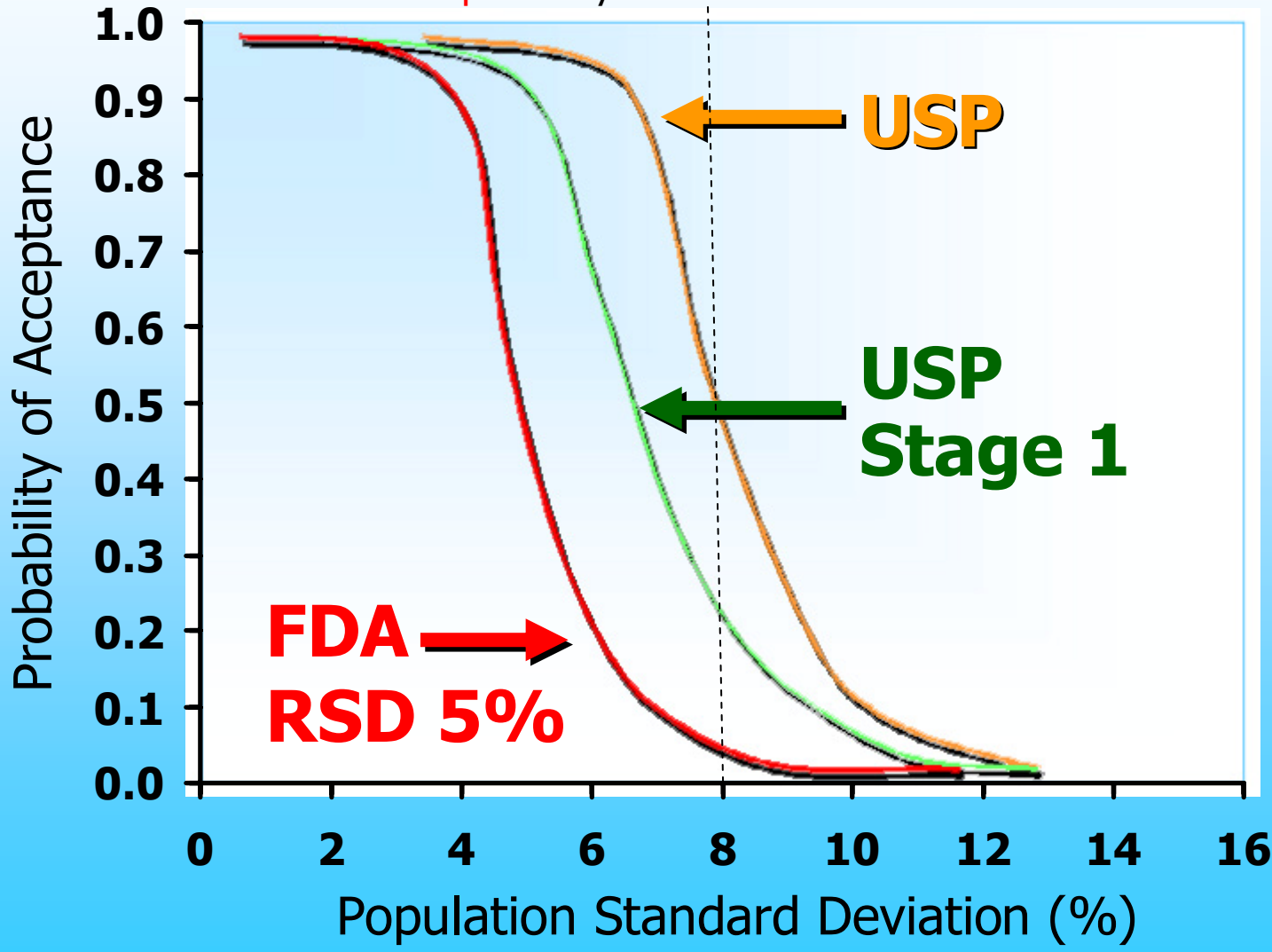
Active	Mean, %	RSD, %
A	**98-100**	**0.4–1.6**
B	**98-102**	**0.5-1.9**
C	**96-103**	**1.2-7.2**

For blend uniformity: n= 10; met spec of 85-115% (and RSD < 5.0%). Test extra tablets as RSD is >3.84 (SDPI)

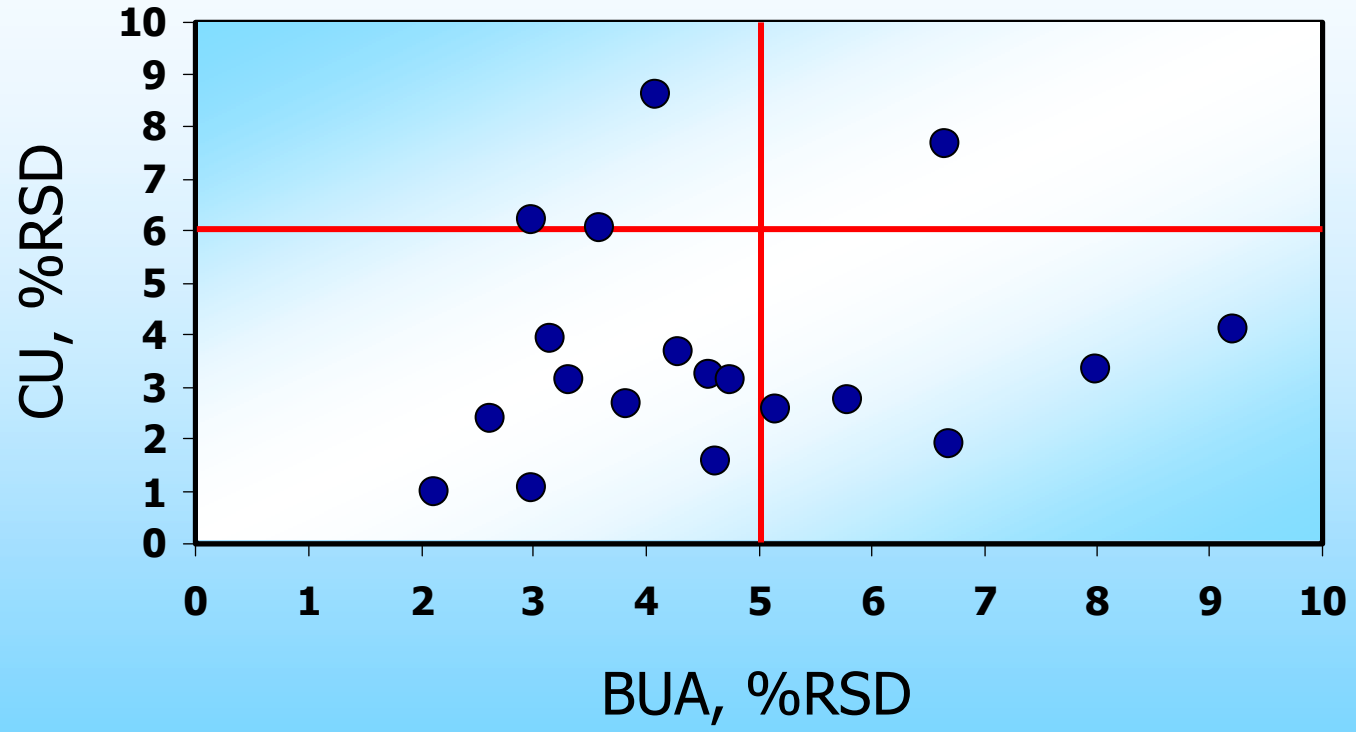
For CU: Each batch had 6 groups of 10 tablets tested (batch total n= 60), RSDs were <3.8% (SDPI) for A and B, C was most difficult but met spec of 85-115% for all tablets

Operating Characteristic Curve for USP and FDA

When Population SD is 8%, USP (Stage 2) accepts about 45%, USP stage 1 about 20 % and FDA plan only 2%.



Comparing BUA to CU



BUA Frequently Does Not Correlate well with CU

Handling Out-of-Specification Result

- Formal investigation per SOP.
- Assignable cause - correct and repeat testing.
- Stage 2 Testing (additional 20 samples).
- Non-assignable cause
  - Different blend sampling method or larger sample size.
  - Extensive and representative tablets/capsule content uniformity to evaluate the blend.

Ref: PDA Technical Report No. 25 (1998), Page 39.

Some Reasons for Inconsistent Results

- Lab handling or calculation errors.
- Sampling errors or bias.
- Wide distributions of particle size or density of ingredients.
- Poor blending, or discharge conditions (segregation, aeration/settling, percolation).
- Active content (< 2% or 5 mg).
- Analytical method not validated for blend.

TGA Position on Microdose Formulations (<5 mg)

- Master record shall describe mixing procedure. Determine parameters to achieve uniform mixing, for each batch size of microdose product.
- Mixing procedure shall be periodically validated. Any significant change requires validation.
- Records of above shall be kept.
- Uniformity of drug content shall be assessed according to written program.

Ref: International GMPs, Australia, TGA, Section 7.8, 1990

Validation Requirements for Blending Equipment Change

Class	Subclass	Example	Recommended Validation Requirements
Same	Same	Same Make/ Model Blender	Ensure sameness*
Same	Same	Tote Bin To Matcon	None*
Same	Different**	V-Blender to Bin Blender	Blend Uniformity Blend Characteristics
Different**	Different	Convection (Planetary) to Diffusion (Bin)	Define Process Parameters Blend Uniformity, Blend Characteristics

* Equipment IQ/OQ; ** Major changes are to be validated

Future Needs and Trends

- More research on blending, such as bin blending, including lubricant blending.
- Study mixing in equipment with different principles such as high shear or air fluidized mixing.
- Improve powder sampling device and procedure.
- Near-Infrared (NIR) method for blend analysis - fast, reliable.
- When blending is shown to be a critical process step, ensure adequate pilot study of the causative factors during process optimization.

References

- US Food Drug Administration
  - Regulation, 21 CFR 211.110 (a)(3), 1978.
  - Proposed rule to 21 CFR 211.110 (d), May 3, 1996.
  - cGMP Human Drug Notes, May 1993, March 2000.
- US vs. Barr Labs; Civil action in New Jersey, Feb 1993.
- Parenteral Drug Association (PDA), Technical Report No. 25, "Blend Uniformity Analysis", 1997.
- International GMPs, Code of Good Manufacturing Practices for Therapeutic Goods (Australia), 7.8 "Microdose Formulations - Validation and Control", 1990.
- Pharmaceutical Technology journal (US and Europe)
  - **US**- Prescott, J. & T. Garcia, Troubleshooting Guide, March 2001
  - **Europe**- Powder Flow I, II- Prescott, J. Jan, Feb 2001

Note of Caution

- **Regulations -** must follow; legal requirements
- **Corporate SOPs -** must follow; Corporate requirements, may be revised.
- **FDA or ICH Guidances -** should follow; good practices; if there is an alternate way justify it (ICH Guides with FDA agreement are as good as regulations)
- **Draft Guidances -** serious consideration, may follow, open for comments
- **Newsletters with Sources -** Consideration - obtain source
- **Newsletters without Sources -** Opinion articles - use caution, source of ideas or "possible" trends to come

Thank You!

Questions?