

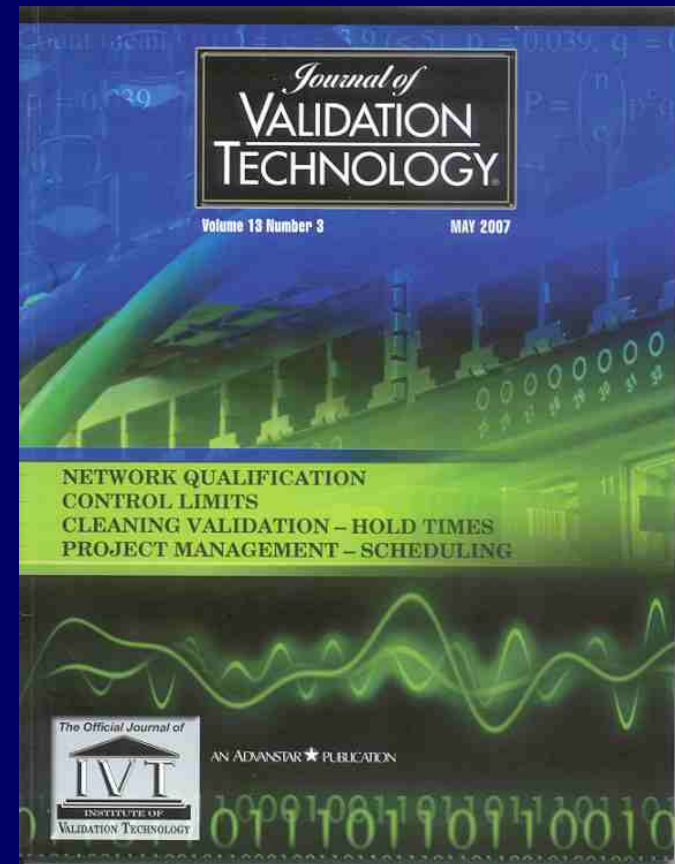
# Benchmarking Process Validation Strategies

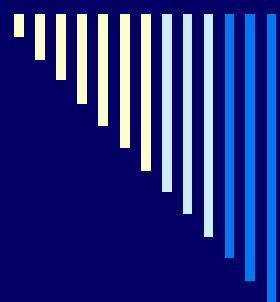
Toronto  
Oct 5, 2007

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# Journal of Validation Technology

- ❑ Published quarterly
- ❑ Benchmarking forum since May 2005
- ❑ Forum poses questions re current industry practice
- ❑ Reader responses anonymously summarized and reported in subsequent issues





# Blend Uniformity

## QUESTION:

Are mixing processes prior to final formulation mixing or blending tested for blend uniformity?

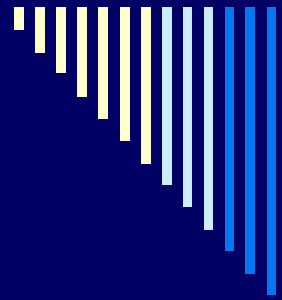


# Blend Uniformity

## Example Process

1. Mix dry ingredients, then wet granulate in ribbon blender
2. Dry granulation
3. Mill granulation
4. Add lubricants
5. Blend in double cone blender

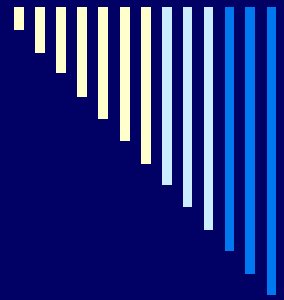




# Blend Uniformity

## Reader Response:

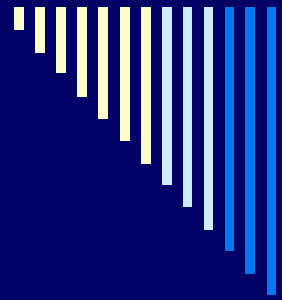
- Unanimous: Only the final mixing process is sampled and tested for blend uniformity
- Mixing processes prior to final mixing are blended for a reasonable time based on technical judgment



# Tablet Compression

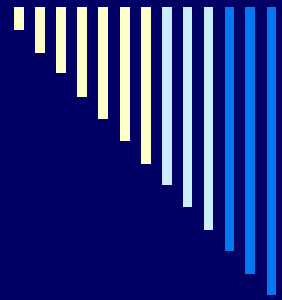
## QUESTION:

How are ranges of tableting parameters such as compression forces and turret speeds handled in process validation?



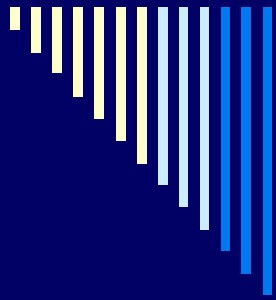
# Tablet Compression

- ❑ Separate runs at high and low parameter extremes?
- ❑ Multiple runs at same settings to demonstrate repeatability?
- ❑ Other options?



# Tablet Compression

- Multiple approaches
- Companies with more modern equipment had the most comprehensive programs



# Tablet Compression

## Reader Response A: (Conventional Validation)

- ❑ 3 lots validated at different speeds to establish a range for subsequent manufacturing.
- ❑ Example: 1 lot low speed and 2 at nominal speed.
- ❑ Favoured over compressing parts of each lot at different speeds
- ❑ If a lot is not able to be pressed within limits, investigate and determine acceptability by extra testing

# Tablet Compression

## Reader Response A: (Manual monitoring & control)

- ❑ No compression force monitor
- ❑ Tablet attributes measured periodically on samples taken manually
- ❑ Press operator makes appropriate adjustments

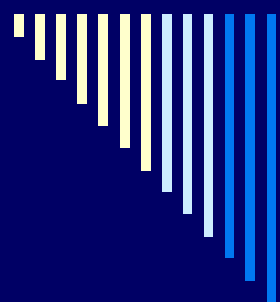


# Tablet Compression

Reader Response A:  
(Automatic control, manual monitoring)

- ❑ Compression force monitor makes automatic adjustments to control tablet weight
- ❑ Tablet attributes measured periodically on samples taken manually





# Tablet Compression

## Reader Response B:

(Automatic monitoring and control)

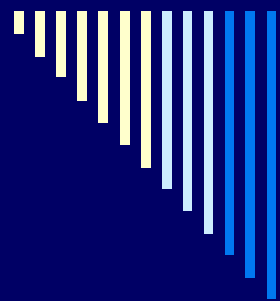
- ❑ 3 lots validated but not at different turret speeds
- ❑ Manufactured with “optimum” process parameters
- ❑ Validation lot data and additional (~10 lots) analyzed statistically to develop in-process parameter limits
- ❑ Data from new lots continuously added to the database for review

# Tablet Compression

## Reader Response B: (Automatic monitoring and control)

- ❑ Compression force monitor makes automatic adjustments to control tablet weight
- ❑ Tablet attributes measured periodically on samples taken automatically

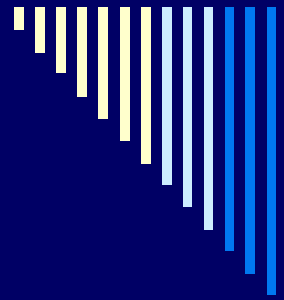




# Tablet Compression

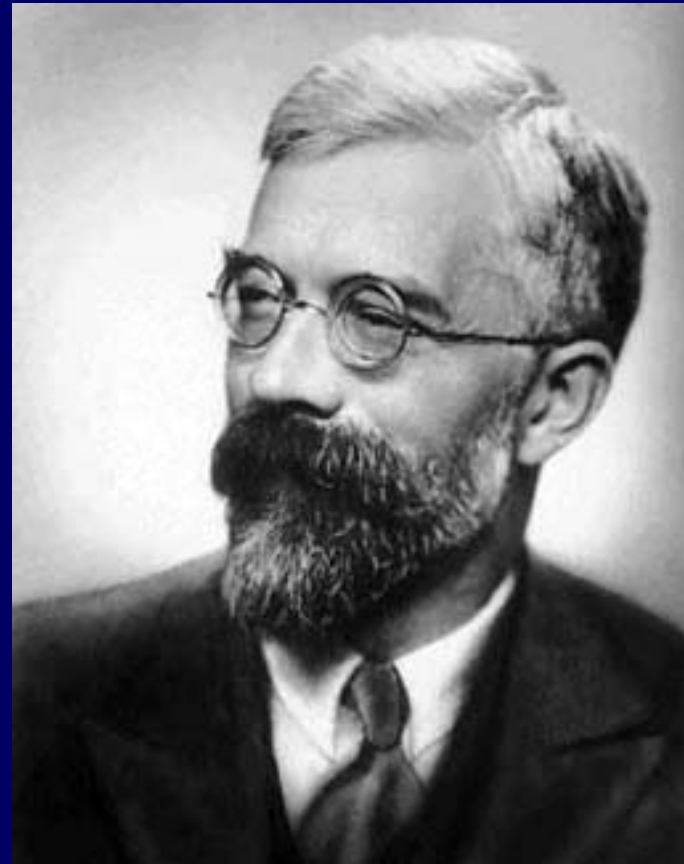
## Reader Response C: (Quality by Design)

- ❑ Effect of compression force and speed on product attributes determined during process development.
- ❑ Proven acceptable range (design space)
- ❑ Normal operating range (control space)
- ❑ Commercial batches run in control space



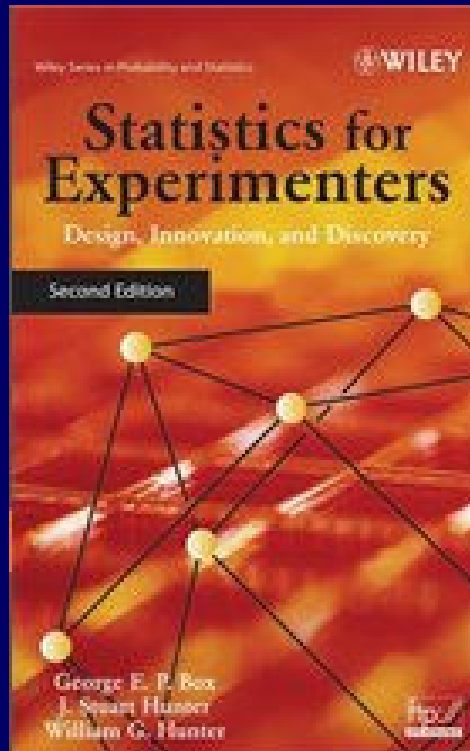
D.O.E.

Sir Ronald Fisher  
(1890-1962)





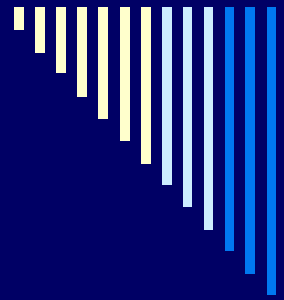
# D.O.E.



Box, Hunter & Hunter, Statistics for Experimenters

# Coating Batch Size





# Coating Batch Size

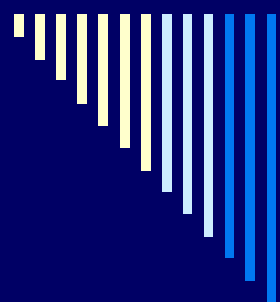
## QUESTION:

How are batch size ranges of individual coating runs validated?



# Coating Batch Size

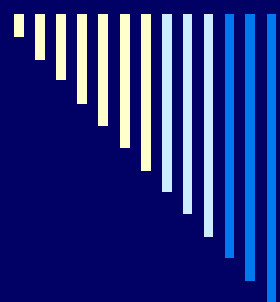
- Separate runs at high and low batch size extremes?
- Is an arbitrary range (e.g.  $\pm 10\%$ ) considered acceptable without testing?
- Any other options?



# Coating Batch Size

## Reader Response:

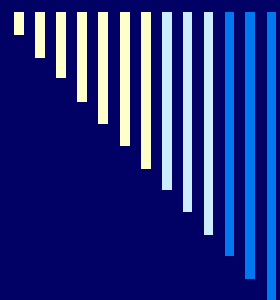
- ❑ In general, pan load ranges are validated.
- ❑ Approach taken depends on batch size and the purpose of the coating.



# Coating Batch Size

## Extended Release Coating

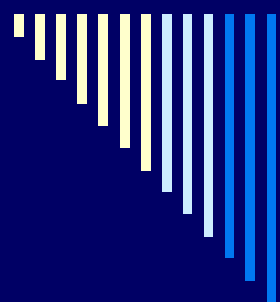
- ❑ 16 pan loads/lot
- ❑ 4 at high load
- ❑ 4 at low load
- ❑ 8 at nominal load
- ❑ Coating parameters same for all loads
- ❑ All tested for drug release
- ❑ Batch record specified max, min and target pan load



# Coating Batch Size

## Non Functional Coating

- ❑ 2000 kg batch
- ❑ Target pan load is 200 kg
- ❑ Coat 1 load at 175 kg
- ❑ Coat another load at 225 kg
- ❑ Coat 8 loads at 200 kg
- ❑ Complete testing on 175 and 225 kg runs
- ❑ Complete testing on composite sample from 200 kg runs
- ❑ Repeated for 3 validation batches
- ❑ Validated range became 175 to 225 kg



# Coating Batch Size

## Small Batches (Only one pan)

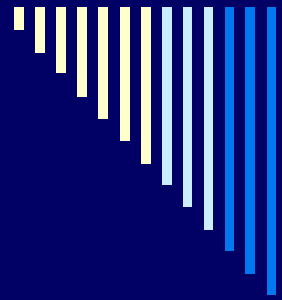
- ❑ Same pan load for 3 validation batches
- ❑ Processing instructions gave a target load with a small arbitrary range
- ❑ If a run must be done outside the range, parameters may need to be changed and validated.

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# Liquid Mixing Processes

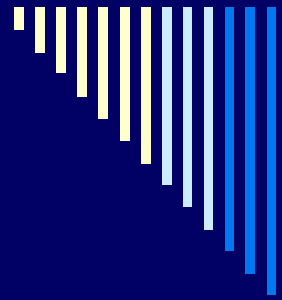




# Liquid Mixing Processes

Question:

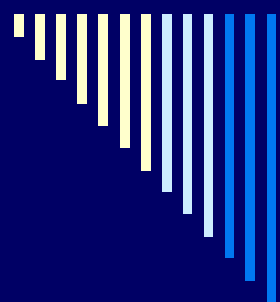
How many samples are appropriate to validate liquid mixing processes?



# Liquid Mixing Processes

Reader Response A:

- 9 samples total; 3 from top, middle bottom regardless of process complexity.



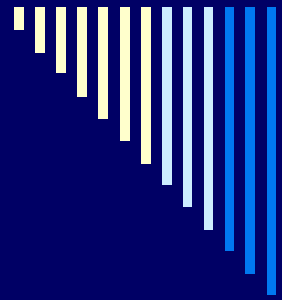
# Liquid Mixing Processes

Reader Response B:

Depends on complexity

Rapidly Dissolving Solutes:

- One or two samples (top and bottom) plus potency determinations from filling operations



# Liquid Mixing Processes

## Reader Response B:

### Slowly Dissolving Solutes:

- Multiple samples, top and bottom
- E.g.: Samples taken every 30 minutes for 8 hours determined that 3 hours at 100 rpm was needed for complete dissolution
- Six hours used for commercial batches



# Have Your Say

- [www.ivthome.com/benchmarking](http://www.ivthome.com/benchmarking)
- Dr Paul Pluta at:  
[editorial@ivthome.com](mailto:editorial@ivthome.com)

