

Thanks to our readers for comments in response to questions in the last issue. Responses demonstrated actual "how to" approaches for practical problems in validation—one of the objectives of "Benchmarking." Excellent examples of actual manufacturing experiences were provided. Discussion of Questions #21 and #22 is reported below.

We continue to receive responses to past "Benchmarking" questions. All "Benchmarking" 2006, 2007, and 2008 questions are listed on the website. Responses and comments on past questions are welcome, and will be published in future updates. Please provide your comments to questions at [info@ivthome.com](mailto:info@ivthome.com) or [www.ivthome.com/benchmarking](http://www.ivthome.com/benchmarking). New questions are also listed on the JVT Forum at [www.IVThome.com](http://www.IVThome.com).

Suggestions from readers for new questions and topics for discussion are also requested.

Several respondents have recommended current expectations for validated processes as a topic for further discussion. Some of the discussion points suggested by respondents have included:

- What is really meant by validation?
- What is really needed to demonstrate a reliable and consistent process?
- Why isn't the usual "three lot" approach to validation sufficient?
- What does FDA mean when they say that "three lots" doesn't tell the whole story on validation?
- Why is the validation group always asking for more—supporting documents, reports, rationales, justifications, plans, and so on?

These points are discussed in the first "Validation Learning Center" in this issue of *JVT*. This discussion provides current thinking on validation as espoused in recent regulatory guidelines and regulatory agency presentations. "Expectations for Process Validation" discusses a comprehensive approach for process validation, beginning with product/process development and continuing after performance of the validation conformance lots throughout the duration of the product lifecycle. See "Expectations for Process Validation" in this issue of *JVT*.

**Respond to  
Benchmarking  
Online!**

The website provides an easy method to respond to questions. Responses to any question may be submitted at any time. Response updates for past questions are planned for future issues of *JVT*. Please provide your comments to questions at [info@ivthome.com](mailto:info@ivthome.com) or [www.ivthome.com/benchmarking](http://www.ivthome.com/benchmarking). New questions are also listed on the *JVT* Forum at [www.IVThome.com](http://www.IVThome.com).

## READER Q & A [∞]

# 21 • Manufacturing Process Validation of Non-Standard Batch Sizes

Manufacturing of non-standard batch sizes may occur for multiple reasons. Non-standard batch sizes may be intentional, i.e., increasing or decreasing market demand may necessitate a new batch size for a product. Non-standard batch sizes may also be unintentional. For example, an unexpected loss of process material during production could necessitate making a non-standard batch.

### Question

What are considerations for the process validation of non-standard batch sizes ?

### Responses [∞]

Respondents commented on the potential for serious and unexpected manufacturing problems that may occur with non-standard batch sizes. The standard batch size is usually the original developed process that is well understood, supported by developed science, and has a long and successful manufacturing history. The non-standard batch size may lack process understanding in certain unit operations, have unknown ranges of acceptable process parameters, and have minimal or no manufacturing experience.

Depending on the processes involved, non-standard batch sizes must not be taken lightly or initiated without consideration of the risks involved. Examples below provided by respondents illustrate unexpected problems with non-standard batch sizes.

Non-standard batch sizes may or may not be cause for concern depending on the processing equipment used in manufacturing and the stage of production at which the non-standard batch occurs. In all cases, manufacturing equipment and processes that are ef-

## Benchmarking.

fective due to the volume of material in the equipment were identified as having greatest potential for process problems in manufacturing non-standard batch sizes.

**Equipment/processes not affected by non-standard batch sizes.** Example unit operations that are not affected by non-standard batch sizes include particle size reduction, separation, continuous fluidized bed drying, roller compaction, extrusion, tablet compressing and encapsulation. These processes are affected only in the duration of time to complete the process. For example, if one container of blended granulation were rejected from a product batch because its storage container had not been cleaned after the previous manufacturing, remaining containers in the lot would be compressed into tablets without impacting the compressing process. Compressing would be completed in proportionately less time. The final yield of acceptable tablets would be less than expected, but all batch material would be reconciled in final accountability. The material loss would also be appropriately documented.

**Equipment/processes affected by non-standard batch sizes.** Example unit operations potentially affected by non-standard batch sizes are those that depend on volume contained in the equipment for acceptable processing. Examples provided by several respondents illustrate.

1. **Liquid mixing.** One respondent described a mixing process for a low-viscosity aqueous solution containing soluble formulation ingredients. The standard product batch was adequately mixed in a tank with one impeller. When the batch size was increased 3x in the same tank, the low-viscosity product was adequately mixed without any process parameter changes. Validation testing involving additional sampling to demonstrate the adequacy of mixing, and uniformity of the increased batch size was acceptable. Smaller batch sizes of product were also adequately mixed as long as the liquid volume was above the level of the impeller in the tank.

The same strategy was attempted with a high-viscosity aqueous product containing polymeric ingredients. The standard batch was adequately mixed in the same tank with one impeller. However, when the batch size of this product was increased 3x in the same tank, the high-viscosity product was unable to be adequately mixed. The single mixing blade was not able to create a vortex in the high-viscosity formulation needed to adequately disperse and dissolve all ingredients.

The 3x increased batch size was ultimately transferred to a mixing tank with additional impellers and was successfully manufactured. The increased batch manufacturing process was validated in the new mixing tank. Additional sampling and testing in validation confirmed the acceptability of the increased batch size in the new mixing tank.

2. **Solids mixing/blending.** Another respondent described several situations involving mixing of granulated solids and other powders in a diffusion (tumble) mixer prior to tablet compressing. These mixtures may contain, for example, granulated solids equaling 85% of the total formulation and powder solids comprising 15% of the total granulation. The granulated solids and powder solids are blended for a specified time to complete the mixing/blending process.

Diffusion mixers are well known to depend on the solids volume being mixed for efficient operation. Acceptable and efficient blending is expected when the solids volume is 50-65% of the actual equipment volume. If the solids volume exceeds 65% of the blender volume, prolonged mixing times are expected because there is inadequate space in the blender for powder mixing to occur. If the solids volume is less than 50% of the blender volume, mixing will also be inefficient because the solids will slide without mixing as the mixer rotates.

The following are example problem situations with proposed corrective actions:

- Loss of 50% of the granulated solids. A lot was manufactured in which 50% of the granulated solids were inadvertently transferred to storage containers that had not been cleaned. The contaminated material was rejected, leaving a 50% non-standard batch. This is a significant loss for future processing. The next processing step was blending in a diffusion mixer. Using the standard mixer with the 50% lower amount of granulated solids would not adequately fill the equipment for acceptable mixing. A smaller mixer appropriate for the remaining batch size was recommended. The amount of powder solids to be mixed with the granulated solids would be adjusted to 50% to maintain the target formulation. Mixing in a smaller blender is a significant process

change unless sufficient knowledge has been established to demonstrate equivalence. New processing parameters would likely be required. Blend sampling and stratified tablet sampling per the US Food and Drug Administration (FDA) guidelines should be conducted to verify the acceptability of the non-standard batch blending and demonstrate acceptability of the compressed tablets.

Another approach would be to manufacture additional granulation runs and then combine these runs with the original granulation. This approach would make up the lost granulation and result in the standard batch size. For example, if the original lot (lot #1) contained four granulation runs and two were lost, remaining granulation would comprise two granulation runs. A new lot (lot #2) containing two granulation runs would be manufactured, and this material would then be combined with the remaining two granulation runs from lot #1 to yield four granulation runs. This combined material could then be processed as a standard batch size with no additional validation testing. There would not be any processing differences in the two granulating runs of lot #2 compared to the standard batch size. This approach would be adequately documented, including explanation, justification, and approvals in the manufacturing batch records of respective lots #1 and #2.

The alternate approach involving manufacture of two new granulating runs and addition to the original batch was preferred because there was no impact on the standard manufacturing process. The processing change (smaller mixing equipment with new process parameters) was not needed and a non-standard batch was avoided.

- Loss of 5% of the granulated solids. A lot was manufactured in which 5% of the granulated solids were spilled and were not recoverable during the particle size reduction process. This should not be a significant loss for future processing. However, the amount of powdered solids to be mixed with the granulated solids would be adjusted to maintain the target formulation. In this case, 5% of each of the powdered solids ingredients would be removed from the amount weighed

to maintain the theoretical formulation. The 95% total solids volume should then be verified to be within the diffusion mixer 50-65% volume for efficient mixing. As long as the solids volume of the batch is within the recommended working volume of the diffusion mixer, the mixing process can be conducted with an expectation of acceptable results. The lot was processed as described. Additional samples of compressed tablets (final product) were tested for content uniformity and dissolution, and successfully verified the acceptability of the 95% batch size mixing process. This approach was adequately documented, including explanation, justification, and approvals in the manufacturing batch records of the lot.

3. **Solids granulating.** Another respondent described the wet granulation of a non-standard batch in a low-shear sigma kneading granulator. The non-standard batch size was smaller than the standard validated batch size. The non-standard batch size volume did not completely cover the sigma blades. The low shear mixing did not adequately granulate the powders in the formulation, resulting in a powdery granulation, serious difficulty in compressing, and broken punches. The non-standard batch was rejected. The importance of the standard batch volume of material in the sigma granulator was not well understood, and an unacceptable granulation was manufactured. The standard batch volume in the granulator completely covered the mixing blades resulting in an acceptable granulation. This example clearly illustrates the importance of process understanding in non-standard batch sizes.

4. **Application to raw material control.** The examples discussed above prompted comments from respondents regarding the proper control of raw material variation. Raw material variation must be considered in the development of a robust manufacturing process. Raw material variation may cause significant problems in the manufacturing process depending on the amount of material and its function. Excipient raw materials often do not have physical specifications. When these materials are a significant percentage of the formulation, control of physical prop-

# Benchmarking.

erties is critical. One respondent described using lactose from a new vendor for cost savings. The new vendor's lactose was much less dense. Use of the new-vendor lactose in the formulation resulted in the blender being over filled. The formulation was not adequately mixed. Tablets compressed had failing content uniformity. The need to identify and control potential sources of variation, as described in recent FDA presentations, is important to maintain a validated process. If the excipient lactose would have had a particle size specification, the new-vendor lactose would likely not have been accepted and the lot failure would have been prevented.

The bottom line to all of the above is that any change-batch size, process, equipment, and raw material-may be significant. The change must be carefully evaluated, understood as best as possible, and potential risks identified and communicated before going forward. Sampling and testing must then be conducted to verify the acceptability of the change. A good understanding of the manufacturing process is fundamental to this evaluation.

## 22. Equipment Information for Cleaning Validation

There is fundamental information on processing equipment that must be compiled in support of the various aspects of cleaning validation. Some of this information is most easily obtained from the equipment manufacturer, and then documented in the equipment installation qualification (IQ). This information is useful for cleaning procedure development, compatibility with cleaning agents, residue level calculations, equipment grouping, and other applications. Equipment grouping is desirable to reduce the number of replicate runs to demonstrate cleaning validation. A clear definition of required information is useful when purchasing new equipment.

### Question

What information on processing equipment is needed in support of cleaning and cleaning validation ?

### Response [∞]

Respondents described information that must be compiled in support of cleaning validation. Equipment vendors to the pharmaceutical industry are well aware of these needs and can be very helpful in obtaining this information. The following describes the equipment information to be compiled:

- 1. Equipment description and design.** The equipment description and design are useful for equipment grouping and for standardization of cleaning procedures. For example, if a facility owns 10 identical impact mills and interchangeably uses the mills in processing, cleaning validation using representative mills will support use of all equipment. There may be groups of equipment that are almost completely identical, but with slightly different features. For example, a grouping of impact mills with screw-feed and without screw-feed attachments would utilize the screw-feed mills as worst-case equipment. The additional design and parts of the screw-feed mill make it the worst-case equipment for cleaning validation. Worst-case equipment in a group of essentially identical equipment would then support the cleaning of all equipment of that equipment group. If worst-case similar equipment can be cleaned, it may be assumed that all equipment in the group can be cleaned. One word of caution: All equipment must utilize the same cleaning procedure. If equipment requires an alkaline cleaning agent for certain residues and an acidic cleaning agent for other residues, each cleaning agent / worst-case residue must be tested for cleaning validation for the equipment group.
- 2. Materials of construction and product-contact materials.** The equipment materials of construction must be known. Most important of these are the materials that will directly contact the product to be manufactured. There are two very important reasons to know the product contact materials:
  - Analytical recovery studies. Product contact materials that will be sampled by swab sampling or rinse sampling must be tested in analytical recovery studies. It must be shown that residual drug is able to be recovered from the equipment surface by swab sampling or rinse sampling. Without demonstrating acceptable recovery from product contact ma-

materials, cleaning validation data is questionable. Recovery studies are usually conducted using coupons that are representative of actual manufacturing equipment. One respondent described recovery studies that demonstrated essentially 100% recovery of the active drug on all but one of the product contact materials, but 0% recovery from cast iron. The tablet machine turret (die table) was constructed of cast iron. A swab sample from the turret that resulted in no active drug residue would be a meaningless result when the recovery study demonstrated that residue could not be detected.

- Material compatibility with cleaning agents and pH. The compatibility of the product contact materials with cleaning agents must be known. Certain polymeric materials and coatings are sensitive to pH extremes (pH less than 2 or pH greater than 10) that are common in cleaning agent preparations. Certain polymers and coatings are sensitive to various solvents. Compatibility information should be available from equipment vendors. Product contact areas with potential compatibility concerns should be specifically cleaned with water or neutral cleaning agent as recommended by the vendor.
3. **Product contact surface area calculations.** The surface area of product contact areas of equipment is necessary for residue level calculations. Equipment vendors are very aware of this need and can often supply this information. Respondents recommended contacting vendors to request this information before initiating the formidable task of calculating surface areas. Vendor calculations of complex equipment, such as compressing machines, are especially helpful.
  4. **Difficult-to-clean areas on equipment.** Equipment and transfer systems must be evaluated to determine potential difficult-to-clean areas. Troublesome cleaning areas, such as inaccessible locations, areas of potential product residue accumulation, and piping with 90° turns leading to residue buildup, should be identified. These areas are the primary areas for consideration as sampling sites in cleaning validation.
  5. **Cleaning procedures.** The cleaning procedure as recommended by the equipment manufacturer or as developed internally must be evaluated. The cleaning procedure should include potential difficult-to-clean areas. Equipment disassembly to enable good cleaning of potential problem areas and thorough evaluation after cleaning are recommended. For example, if a 90° piping turn is necessary, but the piping can be segmented so that the 90° elbow can be immersed in cleaning agent, readily cleaned, and then readily examined after cleaning, the risk of inadequate cleaning and subsequent product contamination may be eliminated. Respondents strongly recommended involving equipment operators or cleaning personnel in this evaluation. These are the people who will be doing the cleaning.
  6. **Recommended sites for cleaning validation swab sampling and rinse sampling.** The areas for sampling in cleaning validation must be identified. This evaluation is based on both the difficult-to-clean areas of the equipment and the cleaning procedure. The final selection of sampling sites for cleaning validation should be documented with rationale for their selection. Approved sampling documents for consistent use in all cleaning validation protocols are recommended.
  7. **Information access and retrieval.** It is recommended that the above information be compiled in an equipment inventory document for cleaning validation. This document should contain a list of all equipment; categorize all facility equipment into appropriate groups; identify worst-case equipment; and include the information discussed above. This compilation will continually be used as a source of information and reference for cleaning validation. This equipment inventory document should be part of the Validation Master Plan or Cleaning Validation Master Plan. This compilation must be a "living" document—It must be updated as new equipment is installed and old equipment is decommissioned and appropriate changes are made.

## NEW QUESTIONS AND DISCUSSION

Questions to be discussed in the upcoming issue of *JVT* are listed below and were suggested by column respondents. Please submit any questions or comments

## Benchmarking.

for inclusion in *JVT* to Dr. Pluta at [info@ivthome.com](mailto:info@ivthome.com) or [www.ivthome.com/benchmarking](http://www.ivthome.com/benchmarking). These questions are also listed in the IVT Forum at [www.ivthome.com](http://www.ivthome.com).

### 23. Tablet Coating Process Validation Testing and Sampling

The process validation of tablet coating processes is accomplished by testing quality attributes, such as tablet potency, dissolution, physical appearance, and other attributes from coating runs as described in the product specifications. There may be other non-specification testing conducted to validate the coating process.

#### Question

What is appropriate testing and sampling for process validation of tablet coating processes ?

### 24. Non-Uniform Contamination in Cleaning

There are two contamination situations to be considered in the cleaning of manufacturing equipment. In one case, contamination from a prior lot may be uniformly dispersed in the subsequent product lot. For example, residue in a mixing tank is uniformly distributed in the next product lot to be manufactured in the same tank. This type of contamination is usually addressed according to the method of Fourman and Mullen. In the second case, contamination from a prior lot is not uniformly distributed in the subsequent product lot. For example, residue in a filling line is distributed primarily to the first few vials to be filled in the next product lot to be manufactured.

#### Question

How is non-uniform contamination handled in cleaning validation ?

#### VALIDATION LEARNING CENTER

"Process Understanding" including identification and control of process variation will be discussed in the next issue of *JVT*.

Process understanding is fundamental to validation and is an expectation for validation processes. Process understanding forms the basis for performance of the validation performance lots and for possible process changes that may be needed during the product lifecycle. See "Process Understanding" in the Spring 2008 issue of *JVT*.

Suggestions for future Validation Learning Center discussion topics are requested. These may be submitted to the *JVT* editors at [www.ivthome.com/benchmarking](http://www.ivthome.com/benchmarking). We need your input to help us make this new feature a successful forum.

#### REFERENCES

FDA, Guidance for Industry, "Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment," Draft Guidance, October 2003.

FDA, "SUPAC-IR / MR: Immediate Release and Modified Release Solid Oral Dosage Forms," Manufacturing Equipment Addendum, Revision 1, January 1999.

FDA, Guidance for Industry, "SUPAC-SS: Nonsterile Semi-solid Dosage Forms," Manufacturing Equipment Addendum, Draft Guidance, December 1998.

FDA, Guide to Inspections, Validation of Cleaning Processes, July 1993.

Fourman, G. L. and M. V. Mullen, "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," *Pharmaceutical Technology*, Vol. 17, #4, 54-60, 1993.

Hart, Sam, and Rebecca Brewer, "Equipment Characterization Documents in Any Facility: A Scientific Rationale of Immeasurable Value," *Cleaning Validation and Critical Cleaning Processes*, Institute of Validation Technology, Chicago, IL 7-24-07.

Lantz Jr., Russell J. and Joseph B. Schwartz, "Mixing," in *Pharmaceutical Dosage Forms: Tablets*, Vol. 2, 40-47, Marcel Dekker, New York, 1990.

LeBlanc, Destin A, *Validated Cleaning Technologies for Pharmaceutical Manufacturing*, Interpharm / CRC Press, Boca Raton, FL, 2000. **JVT**

Please provide your comments on the above questions #23 and #24 at [info@ivthome.com](mailto:info@ivthome.com) or [www.ivthome.com/benchmarking](http://www.ivthome.com/benchmarking).