General Discussion

Examples of primary and secondary packaging validation, both manual and automated operations are provided in this guidance. This also provides guidance on aspects to consider for packaging validation.

Explanations of factors to consider for acceptable packaging validation and lot size are provided with various practical examples.

One of the industry standards in packaging validation indicates that: “A packaging validation lot must be representative of the typical packaging process and be of sufficient length such that packaging validation lot will exhibit normal packaging process variability”. In addition, a packaging validation run (e.g. entire lot or defined portion of a lot) shall be determined by the Validation Committee based on a technical evaluation and experience with the packaging process. For the purposes of validation it should be allowed a lot size to be determined that may not correspond to the full packaging order lot size.

The factors listed in the practice standard are typically associated with packaging runs requiring multiple shifts. However, the principle underlying the practice standard remains applicable to all packaging processes, large or small, automated or manual. This principle is the identification of sources of variability that are likely to occur during routine operation.

Manual packaging processes typically require little or no validation since the output of the process is 100% verified by a trained operator performing the task. However, even manual processes should be evaluated for sources of variability that may lead to unacceptable product which might go undetected. If such a condition exists, then the process should be validated.

Semi-manual and fully automated processes require a similar evaluation for sources of variability. The source(s) of variability should be eliminated or reduced as much as possible prior to validation. The validation itself should focus mainly on errors that may go undetected and demonstration that acceptable product is consistently produced.

Examples are provided below for consideration. These examples are only intended to be illustrative of the rationale for determining factors such as lot size for packaging validation: the example should not be applied at the gmp site without conducting a case-by-case assessment of the process to be validated.

Example 1: Manual packaging process

Batch Size: 2000 units

Process: Sterile units in their sealed primary package are hand-labeled (pre-printed with lot number and expiration date) by 4 operators and then placed on a conveyor which takes the labeled units to a packaging station where 4 units are manually placed into a manually assembled, pre-labeled carton by 2 operators. The cartons are conveyed to a second packaging station where they are manually transferred into a shipping container.

Evaluation: All packaging operations are manual, each step of the process can be 100% verified by the operator conducting the process step. The physical handling of the sealed sterile unit is assessed to determine if the operator can inadvertently induce a sterility breach under routine packaging conditions, no such risk is found. Container closure integrity is assured via separate studies. Placement of the labeled unit into a carton does not impact the quality of the product or affect any batch record specific to labeling of the product. The software and system used to generate the labels has been qualified. The pre-labeled cartons meet specification and are approved for use by incoming inspection. Transfer of the cartons into the shipping container

Example 7: Fully automated packaging process
Batch Size: 250,000 units (Two shifts)
Process: A new product at site. A will be transferred from facility 1 to facility 2. All capsule dosages have a common blend. The difference between dosages is the filling weight. Dosages: 120 mg, 180 mg, 240 mg, 360 mg, and 420 mg. The packaging presentations and capsules sizes are:

Dosage	Capsule size	30's bottle cc
120 mg	2	80
180 mg	2	80
240 mg	1	90
360 mg	1	90
420 mg	00	120

Note: Bottles have the same material composition

Evaluation:
The Bracketing and Matrixing approach can be applied for the packaging process validation. Matrixing of the lower and higher dose is considered in combination with the different capsule sizes. Bracketing will be applied to the different bottle sizes because all the strengths are packaged in the same count (30). Each validation run must be representative of the typical packaging process and be of sufficient length to address the expected variability. The "expected variability" is the variability that would be likely encountered during a "routine" production run such as shift changes. Three validation runs of the following combinations is recommended:

- 80 cc bottle –120 mg
- 90 cc bottle – 240 mg or 360 mg
- 120 cc – 420 mg

One run is conducted for each bottle size, covering the critical feature.

Definition of Validation Lot Size:
In this example each validation run is carried out across three shifts, each shift of 125,000 units is evaluated separately to provide further assurance of reproducibility. This is equivalent to 1.5 of the packaging order (250,000 units). Thus, there are a total of three validation runs.

