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 does not impact the quality of the product or affect any batch record specific to labeling of the product.

Definition of Validation Lot Size: Validation of the process is not required as continuous monitoring is performed at a low-risk. Instead, release of the product will depend on meeting acceptable AQL (Acceptable Quality Level) levels for defects

Example 2: Semi-manual packaging process
Batch Size: 200,000 units
Process: A non-sterile, oral liquid dosage form is filled in pre-labeled plastic bottles, sealed with a tamper-evident seal and capped. The sealed bottle is directly printed with lot number and expiration date using an ink jet printer. The bottles are then placed manually in individual cartons; the cartons are then printed with the same lot number and expiration date. Groups of 6 cartons are shrink-wrapped together. The shrink-wrapped cartons are manually placed in a shipping container. It requires 9 shifts to fill and package all 200,000 units in the batch.

Evaluation: The filling, sealing and capping of the non-sterile liquid should be validated within the scope of the process validation. Subsequent to capping, the packaging process equipment includes a labeler, cartoner, another labeler and shrink-wrapper. The labeling equipment provides batch-record-specific information. Ensuring proper alignment on the bottle/carton is important for legibility.

The potential effect of heat from the shrink-wrapper on the product and packaging materials has already been assessed. The cartoner and shrink-wrapper have no direct impact on product quality. Proper timing of the inter-connected packaging equipment is important not only to the efficiency of the line, but also to prevent damaged bottles, cartons and labeling errors. Transfer of the shrink-wrapped cartons into the shipping container does not impact the quality of the product or affect any batch record specific labeling of the product.

During this operation, potential sources of variation include shift changes, shift breaks, environmental conditions, and material variability. Material variability mostly affects shrink-wrapping, but this is not a critical to product quality or major defect. Variability of the bottle could affect printing, but a range of material types were qualified during the OQ (Operational Qualification) of the labeler so this has been adequately addressed. The environmental conditions in the packaging area are controlled, but tend to run warmer and more humid during the day and

start/stop mode) during system validation (IQ/OQ/PQ) activities. The line is continuous, but utilizes accumulators between some unit operations to manage the flow of product. The function of each unit operation is independent of the previous unit operation in that items that do not meet quality requirements are detected, tracked and removed from the line through qualified checks and reject mechanisms. This is performed before the item could affect the ability of the subsequent unit operation to carry out its defined function. A risk assessment of the line indicates no significant source of variability from environmental conditions, personnel or packaging materials and that the only aspect of the packaging process not yet addressed is the efficiency (e.g. throughput, yields) of the packaging operation. The NOR (normal operating range) is narrow relative to the PAR (proven acceptable range) and automated lot monitoring as described above was suggested as sufficient. Production efficiency per se is not a GMP issue and therefore no packaging validation is required. Instead, acceptance of each batch will be dependent solely on routine release parameters and an Annual Product Review may be relied upon to assess any negative trends in packaging.

Definition of Validation Lot Size:
Not applicable.

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.

