

Potential Critical Packaging Process Parameters and Validation Practices

Regulatory Basis:

FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

This Document provides a tabulation of potential critical process parameters and quality attributes of typical steps of primary solid drug product (i.e. dry products) packaging processes. It also includes packaging validation items such as evaluation of equipment, protocol and report contents, amount of data (e.g. number of runs) and if warranted, microbiological studies.

Some secondary packaging steps are also included which would also apply to sterile products. There are other documents that contain general definitions, guidelines and general principles for selection of Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs). These documents describe how CPPs and CQAs can be used in subsequent packaging process validation or continuous verification studies and the criteria for assessing criticality.

Drug products come in a variety of packaged forms frequently packaged with common steps and equipment. The potential critical process parameters are often the same from process to process and this document captures these common CPPs and CQAs. The specific practices with respect to packaging process validation are described as well.

PACKAGED PROCESS PARAMETERS

Quality risk assessments are suggested to be used for determining the level of criticality of equipment and parameters. See document on Risk Assessment in Validation. Each packaging application should be evaluated on a case-by-case basis to determine impact assessments and which parameters are critical. Critical packaging process parameters and normal operating ranges, including justification or reference for these ranges, are to be determined before validation and included in the packaging validation protocol. Some examples of critical process parameters ranges to be determined in pre-studies, line trials or qualifications may include:

- Time
- Temperature
- Pressure
- Torque
- Speed
- Count quantity
- Fill Weight and Variation
- Inert atmosphere (liquid)
- Environmental Humidity

Steps using packaging equipment should be evaluated to determine which steps or pieces of equipment are considered critical. Examples of potential critical packaging steps/equipment systems may include:

- Reject systems (e.g. vision systems, weighing systems)
- Product and/or lot specific labeling systems
- Bottle and blister filling equipment
- Filling and capping equipment
- Induction seal units
- Tamper resistant packaging equipment
- Tablet and capsule feeding equipment
- Lot and bar coding equipment (both printing and reading of bar codes)

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Process Step	Equipment Type (Examples)	Potential Critical Process Parameters ^{a,b}	Potential Critical Quality Attributes ^{a,b}
Printers	Hot foil, embossing, debossing, flexographic, stamp/pad, laser digital, ink jet, thermal	<ul style="list-style-type: none"> • Speed 	<ul style="list-style-type: none"> • Print quality (accuracy and legibility)
Leaflet Folders/Inserters	MGS Machine, IMA, GUK	<ul style="list-style-type: none"> • Glue temperature (if applicable) • Speed 	<ul style="list-style-type: none"> • Visual inspection- leaflet • Position
Bundling/shrinking/Overwrapper	Pester, Tevopharm	<ul style="list-style-type: none"> • Speed (rate) • Temperature 	<ul style="list-style-type: none"> • Bundles appearance • Number of bottles per bundle
Casepacker Machine	Skinetta, Schubert	<ul style="list-style-type: none"> • Speed and accuracy 	<ul style="list-style-type: none"> • Number of package per case • Low fill
Cartoner	Bosch- Contina, Bedo, Jones, ADCO	<ul style="list-style-type: none"> • Depth and legibility of the emboss/ deboss • Feed mechanism and rate 	<ul style="list-style-type: none"> • Visual inspection- debossing • Units per carton
Bar Coders	Laetus, Kaps, Sartorius	<ul style="list-style-type: none"> • Speed 	<ul style="list-style-type: none"> • Visual inspection- bar code • Readability

^a Potential CPPs and CQAs for filling and sealing steps are also covered in Semi-Solid Dosage Forms

^b Environmental conditions (e.g. temperature, humidity, air cleanliness) may be common to any package operation where product or sensitive materials are exposed to the environment. Change parts and set-up are potentially critical for many operations, but not viewed as “process parameters”. Likewise drug product characteristics such as tablet durability and friability may also be common to any package operation where product handling becomes a potential critical property.

Table 2- Blister Packaging – common critical process parameters.

Process Step	Equipment Type (Examples)	Potential Critical Process Parameters ^{a,b}	Potential Critical Quality Attributes
Thermoformer	Körber Medipak, Uhlmann, Bosch-Servac, Marchesini)	<ul style="list-style-type: none"> • Sealing temperatures (lower, upper, cooling) • Heater plate temperature • Dwell time • Cycle rate/timing cycle • Forming pressure • Filling speed • Blister material characteristics • Quality of tooling • Print register (for pre-pre-printed foils) • Camera function-at filling speed and rate 	<ul style="list-style-type: none"> • Leakage rates • Appearance (e.g. visual inspection, legibility) • Dimensional analysis (including thickness) • Automated inspection (including product control camera) • Security system challenges • Foil registration • Seal strength • Moisture vapor transmission rates (during development)
Feeder	Aylward	<ul style="list-style-type: none"> • Air pressures (frame and pins) • Feed rate 	<ul style="list-style-type: none"> • Potential damage rate • Number of dosage form per blister

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- Discussion of the data compared to their respective acceptance criteria;
- Review of critical process parameters from lot packaging records;
- Description of any deviations or failures, and their impact on the validation; and
- Conclusions.

Matrixing and Bracketing

Matrixing of the packaging processes can be performed when there are significant similarities between products. The rationale for matrixing must be included in the protocol.

Example:

A solid dosage form is compounded in various strengths affecting its overall shape and size. Solid dosage units are packaged with the same tools in the same type of container/closure. One validation run for each tablet strength should be included in the validation matrix.

Bracketing of the packaging processes can be performed when there is a range of process extremes of parameters. Different products may be bracketed due to similarities of package components, critical packaging process parameters, packaging lines, and product attributes.

The rationale for the bracketing approach should be included in the protocol.

Example:

In the case where bottle dimensions for different products are identical except for height and only a minor line adjustment is required.

Example:

Largest and smallest filling amounts, fastest and slowest operating speeds for the packaging process

Number of Validation Runs (or segments)

A packaging validation run should be representative of the typical packaging process and be of sufficient length such that the packaging validation run will exhibit normal packaging process variability such as equipment variability, operator and mechanic variability, material variability, start-ups, shut downs, shift changes, and environmental conditions. Some sites use a minimum run time such as 10 hours to capture any potential effects of a shift change.

However, within a continuous quality verification (CQV) approach, CQAs and/or CPPs may be continuously monitored, evaluated and adjusted (directly or indirectly via critical process parameters). In this approach, the number of packaging validation runs or segments is not applicable. Techniques such as control charting and trending may be performed in an at-line or on-line manner. This approach conforms to the Continued Process Verification (Stage 3) and controls, as described in the FDA's new draft document on process validation.