Overview of Packaging Validation for Drug Products

Numerous guidances are available from regulatory and industry sources concerning process validation; however, very few provide information regarding the packaging process. This paper begins a discussion on the varied ways to implement packaging validation. Focusing on the primary, secondary and tertiary packaging of drug products, it offers available tools and demonstrates, through limited examples, their use in a packaging validation regime. This paper incorporates common validation approaches into the packaging process by offering suggestions for risk mitigation, determining product matrixes and sampling plans, as well as strategies for developing a packaging ongoing process verification program. The author team is interested in receiving feedback, and information about other approaches, including lessons learned.

The paper may be modified or expanded sometime in the future to reflect additional input.

Please direct all feedback to pvpapers@ispe.org.

Overview of Packaging Validation for Drug Products

Authors: Richard Chandler (Unither Pharmaceuticals, USA), Paul Corbishley (AstraZeneca, UK), Walter Harper (Eli Lilly, USA), Matthew McMenamin (GlaxoSmithKline, USA), Dilip Somayajula (Co-Lead) (Boehringer Ingelheim, USA), Erica Stolz (Lead) (Clarke Solutions, USA)

1 Introduction

The ISPE Process Validation Team recognized a potential gap in the knowledge of process validation of packaging processes. In response, the committee enlisted a cross-functional team to 1) seek guidance from similar, well-established industry standards or practices (e.g., International Medical Device Regulators Forum or IMDRF) and 2) formally solicit feedback on packaging process validation from drug manufacturing industry leaders and peers by way of an ISPE discussion paper. This paper looks at recognized process validation definitions, theories, and tools and how they transcend manufacturing and packaging of all dosage forms.

2 Scope

The scope of this paper is the application of process validation methods and tools as they pertain specifically to the drug product packaging process. Packaging processes examined in this paper include primary, secondary, and tertiary packaging operations.

This paper provides some example case studies taken from the experiences of panel members. The case studies are not intended to be authoritative but to encourage thought and discussion. Readers are asked to provide their insights and/or questions about the packaging validation process.

The following topics are not included in the scope of this paper. For most of these topics, published regulatory and/or international industry standards are available.

- Product package design process (e.g., package materials selection, package design or package design validation) [1, 2]
- Filling of sterile injectable products [3, 4]
- System Qualification e.g., Commissioning and Qualification (C&Q) [5], Verification
- Packaging of medical devices [6]
- Package serialization e.g., in accordance with the United States Drug Supply Chain Security Act [7]

For a deeper understanding of these topics, readers may consult the references provided in Section 11.

3 Literature Review

A literature review was performed to understand the availability of guidance and useful information relevant to packaging process validation. Documents reviewed include the publications by several international organizations and regulatory agencies. A summary of each review is presented in Table 1. Full reference information is provided in Section 11.

Table 1: Summary of Existing Publications and Standards for Packaging Processes

Publication or Standard	Content Summary
USP <1136> Packaging and Repackaging-Single Unit Containers [8]	• Discusses requirements of unit-of-use packaging intended for manufacturers, re-packagers and pharmacists. • Describes requirements for container types, packaging fabrication materials, packaging closure types, labelling, repackaging and reprocessing, product information and responsibilities of the dispenser. • Does not provide guidance relevant to packaging process validation.
EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use ANNEX 15: Qualification and Validation [9]	• Discusses principles of qualification and validation applicable to facilities, equipment, utilities, and processes used in the manufacture of medicinal products. • Requires equipment used for primary and secondary packaging to be qualified at minimum and maximum operating ranges defined for the process. • Does not give information on a holistic approach for packaging process validation.
US FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics [2]	• Provides general principles for submitting information on packaging materials. • Does not specify or discuss requirements or expectations for executing packaging process validation.
US FDA Questions and Answers about SUPAC-IR Guidance [10]	• Contains Scale-up and Post-Approval Changes guidance for Immediate Release Products (SUPAC-IR). • Addresses changes made to manufacturing and/or stand-alone packaging sites, and component and composition changes. • Packaging processes, or validation thereof, are not discussed.
ISO 11607-2 Packaging for Terminally Sterilized Medical Devices - Part 2: Validation Requirements for Forming, Sealing and Assembly Processes [11]	• Discusses package design / build processes including forming, sealing, and assembly of sterile barrier systems. • Prescribes qualification of such process equipment to minimally include: initial installation qualification, operational qualification, and performance qualification, followed by on-going process monitoring and control. • Does not discuss process validation of packaging processes.
The Global Harmonization Task Force: Quality Management Systems-Process Validation Guidance Ed. 2, 2004 [6]	• Provides manufacturers general suggestions to approach process validation that are not industry-specific. • Does not discuss packaging process validation, although discussion is made on the statistical significance in a process validation scenario.

Table 1: Summary of Existing Publications and Standards for Packaging Processes (continued)

Publication or Standard	Content Summary
US FDA Office of Compliance: Compliance Policy Guide CPG 7132a.04 Requirements for Expiration Dating and Stability Testing [12]	• Summarizes situations under which the FDA would recommend appropriate action (e.g., warning letter or seizure). • There are no direct references to packaging validation.
European Medicines Agency: Guideline on process validation for finished products – information and data to be provided in regulatory submissions [13]	• Replaces the previous note for guidance on process validation (CPMP/QWP/848/96, EMEA/CVMP/598/99). • Aligns with ICH Q8, Q9 and Q10 documents and allows the possibility to use continuous process verification in addition to, or instead of, traditional process validation. • References the use of pack size as a possible design factor that may be used when considering process validation bracketing strategies; otherwise, there are no direct references to packaging validation.
US FDA Guidance for Industry Process Validation: General Principles and Practices [14]	• Summarizes a lifecycle approach to process validation, as defined by three stages: Stage 1 process design, Stage 2 process qualification and Stage 3 continued process verification. • Discusses process validation methods used for manufacturing of biological products, active pharmaceutical ingredients and drug constituents in combination products for human and veterinary use. • Incorporates ICH quality risk management to assure product attributes are validated commensurate with level of risk to the patient. • Does not explicitly discuss process validation for packaging processes.
ICH Q9 Quality Risk Management [15]	• Defines principles of risk management and the general quality risk management process. • Identifies tools for assessing, evaluating and mitigating risk for pharmaceutical quality aspects (e.g., patient risk, process risk) • Provides example packaging-related uses for risk management, such as secondary package design, choice of container closure system and label control. • There are no direct references to packaging validation.

None of the reviewed publications include direct references to packaging validation. A few publications, however, contain information that may be helpful in defining process design and validation pre-requisites: for example, statistical guidelines from The Global Harmonization Task Force [6].

4 Packaging Process Overview

Before discussing the packaging validation process, the “product” must be clearly understood and defined. The product may be the “drug product”, or the “drug package” that protects the drug product from external damage as well as from outside contamination and spoilage. Packaging implications must be evaluated for risk to both the drug product and the drug package. A discussion and case study on the assessment of these risks are presented in Section 6.

Next, the packaging process must be defined. This paper will only focus on the primary, secondary, and tertiary packaging processes. The drug package, at each of these stages, must be considered both

individually and holistically. For example, in what ways can a secondary packaging operation cause potential damage to the secondary package and/or the primary package inside? Is a drug package defect cosmetic, which may lead to customer complaints (business risk), or does the defect introduce risk to the drug product (consumer risk)?

Figure 1 provides a summary of typical packaging operations, based on product type: sterile parenterals, non-sterile liquid or solid oral dosage forms (bottles and blister packs), and non-sterile lotions and creams. It is noted that sterile filling processes are not within scope of this paper; hence, these operations are shaded in gray.

Figure 1: Generic Packaging Operations by Product Type

Packaging Type	Sterile (Parenteral)	Non-Sterile (Oral Solid/Liquid Bottle)	Non-Sterile (Lotions/Creams)	Non-Sterile (Blister Packs)
Primary	Vial Unscrambling	Bottle Unscrambling	Pre-labeled Tube-Feed Loading	Forming (of Base Foil)
	Vial Air-blow	Bottle Air Blow		
	Vial Washing			
	Vial Drying			
	Vial Depyrogenation			
	Vial Filling	Tablet (or Liquid) Dispensing	Tube Filling	Tablet Feed & Fill
	Plugging/Stopper Insertion	Insert Component (i.e. desiccant)		
				Lid Foil Printing
		Bottle Sealing	Tube Crimping	Blister Sealing
			Tube Cutting	
	Capping	Capping		
	Labeling	Labeling	Variable Data Embossing or Printing	Variable Data Embossing or Printing
	Printing (Variable Data)	Printing (Variable Data)		Blisterstrip Punching
Secondary	Cartoning (insert)	Cartoning (insert)	Cartoning (insert)	Cartoning (insert)
Tertiary	Case Packing	Case Packing	Case Packing	Case Packing
	Case Labeling and Printing	Case Labeling and Printing	Case Labeling and Printing	Case Labeling and Printing
	Palletizing	Palletizing	Palletizing	Palletizing
Items shaded gray constitute sterile filling operations that are outside the scope of this paper.				

Challenges with validating packaging operations include the variety of technologies available for use. New packaging technologies further drive the equally varied means of performing packaging quality control (QC), whether in-line or off-line, destructive or non-destructive. Due to its location in the overall product lifecycle, a manufacturer's risk may be more costly if product non-conformances affecting drug quality or efficacy are encountered during packaging (e.g., liquids or ointments), rather than in earlier stages of drug manufacture. Packaging and quality control equipment manufacturers are responding to this need for right-first-time packaging by creating package designs and equipment from which product can be more easily verified by in-line, non-destructive means. In-line vision inspection systems, barcode scanners, and ultrasonic seal-integrity testers are some examples of quality control methods in use.

The type of data obtained and evaluated during packaging validation creates a significant challenge. Success or failure of a packaging unit operation is often determined by a drug package's defects (tears, holes, smudges or leaking seals). This lack of measurable (variable) data often requires very large sample sizes for a packaging process to be statistically validated. This paper will demonstrate in later sections that the validation of packaging processes, beyond the product definition, risk level, and the technologies used, differ little from the validation of processes used for drug manufacture. Similarly, equipment used in the packaging process may be commissioned and qualified by following the same general guidelines as those used for drug product manufacturing equipment.

In some cases, it may be advantageous to follow an equipment validation lifecycle approach to packaging operations, using commissioning and qualification (C&Q) rather than a process validation lifecycle. This approach may be employed if it is determined that there are no product critical quality attributes (CQAs) impacted by packaging equipment and/or operations (see ICH Q8(R2) [16]). Although acceptable, this approach must be carefully justified. The reader may consult Section 11 for literature that discusses the C&Q process.

5 Developing a Product Matrix

In order to prepare for packaging process validation, it is necessary to understand the breadth of formats that the validation will cover. For the purpose of this discussion, a format is a combination of different drug/package attributes and equipment/process parameters that, when combined, constitute a unique pack/process. Packaging lines can be dedicated or very diverse in terms of how different the processes are configured and different components are used. Typically, the packaging formats are bracketed to improve the efficiency of the validation effort; however, bracketing might not be accepted in some markets, or may not be appropriate, such as when there is limited knowledge or experience on the product or process. The latter may be mitigated with strong process knowledge up-front, which may allow for more bracketing and a more efficient process validation. In all cases where bracketing is used, care must be taken to follow regulations for the intended market (e.g., EU Annex 15 reference to packaging and bracketing [9]).

This is often accomplished by developing a matrix. Selection of the attributes to be used in the matrix should consider the effect on critical quality attributes, process parameters, and the equipment set

used. For example, the matrix would not have instances where the only differences between formats are artwork. Table 2 contains an example matrix for a single primary packaging line.

Table 2: Example format matrix primary packaging on a bottle line

Format	Type	Strength	Bottle Size	Cap Size	Child Resistant	Count	Filler	Desiccant Feeder	Capper	Induction Seal	Speed (bottles per min)	Label
1[1]	A	5 mg	20 cc	28 mm	Y	30	Y	Y	Y	Y	200	C
2[1]	A	5 mg	20 cc	28 mm	Y	30	Y	Y	Y	Y	200	C
3	A	10 mg	20 cc	28 mm	Y	30	Y	Y	Y	Y	220	C
4	B	60 mg	20 cc	28 mm	Y	30	Y	N	Y	Y	200	D
5	B	60 mg	50 cc	28 mm	Y	30	Y	N	Y	Y	200	E
6	B	60 mg	100 cc	33 mm	N	60	Y	N	Y	Y	100	F

[1] Only difference between formats "1" and "2" is the secondary package presentation. For brevity, secondary packaging is not discussed in detail here.

5.1 Determining Which Formats to Include in the Validation Exercise

The goal of the validation effort is to prove that the process creates products meeting or exceeding a previously determined quality level. It is recommended to ensure that all of the equipment sets and critical quality attributes are used in the effort. Combinations may be determined and tested during equipment qualification (e.g., OQ, PQ) and, depending on the extent of testing performed during qualification, may be exempt from the packaging validation process. Some attributes lend themselves to validation based on a worst-case approach, like speed. Others may require bracketing smallest and largest sizes. For some attributes, each combination may be chosen.

From the list of products in Table 2, the following assumptions may be considered when determining which formats to use in the validation effort.

- It does not matter what the product is for the purposes of packaging validation, A or B, as the validation is for packaging and not product.
- With the assumption that each product strength has a different size tablet, validation needs to be performed on formats 1 or 2 (5 mg), format 3 (10 mg), and format 4, 5 or 6 (60 mg).
- Assuming that for each primary packaging size there is a different height bottle, and the size could have an impact on the amount of heat transferred to the induction heat seal (and machine set-up), each size should be validated. The validation needs to be performed on formats 1, 2, 3 or 4 (20 cc), format 5 (50 cc), and format 6 (100 cc).
- Each cap size should be validated; thus, validation on formats 1, 2, 3, 4 or 5 (28 mm cap) and format 6 (33 mm) needs to completed.
- Packaging with the child resistant feature is the worst case; therefore, ensuring validation is performed on formats 1, 2, 3, 4 or 5 will meet this requirement.
- Assuming each product count is independent and needs to be independently verified, the 30-count bottle can be validated by using format 1, 2, 3, 4 or 5, and the 60-count bottle

validated using format 6. Dependent on technology, it may be acceptable to validate a worst-case product count, i.e. the greatest number, therefore only format 6.

- The filler is used on all formats; so, validating any format will capture this piece of equipment.
- The use of the desiccant feeder is the worst case and only used on formats 1 and 3; therefore, validation needs to capture one of those formats.
- The capper and induction seal are used on all formats, consequently validation of any format will capture this equipment.
- A decision needs to be made on the impact of speed on the operation of the process. Typically, a worst-case approach is appropriate, which is the fastest speed; thus, any validation conducted should be completed at the fastest speed, i.e. 220 bpm. An assumption is made that all equipment in the process is operating at the same speed.
- Labels for product A differ only for strength; otherwise labels are identical in size and layout. Each label should be validated (i.e., formats 1, 2 or 3, 4, 5 and 6).

Taking all of the above into consideration, the validation activities can be bracketed and completed on formats 1 or 2, 3, 4, 5 and 6. It may be appropriate to reduce further the number of formats by creating a "hybrid" primary package. Although it is not a format specifically created for a customer, it could be used to capture the worst-case requirements of the process in a fewer number of validation runs. NOTE: As with the selection of any bracketing strategy, the choice of a hybrid must be scientifically justified, since the format does not result in an actual product intended for sale. Additionally, the bracketing strategy will need to be constantly evaluated as new products are introduced in the facility. This will ensure it consistently covers the worst-case configuration.

5.2 Number of Batches

A risk analysis should be used to determine the number of batches required. Some of the factors that a risk analysis should focus on include, but are not limited to:

- experience and understanding of the product and process
- control strategies adopted *
- complexity
- Impact to the patient, as evidenced by impact to product and package CQAs
- level and length of PQ
- knowledge of similar line/equipment/processes
- evaluation of exposed product hold times

- good packages are produced, and primary dosage unit is preserved (i.e., unit not damaged during packaging)

* Since the aim of packaging process validation is to demonstrate a robust process, the control strategy should detail and manage the level of variation from product and process inputs, including, for example, the number of operators, different shifts, and different sources/batches of input materials. The potential variation in these examples could be controlled by a robust operator training program, and the material variation controlled with tight tolerances detailed in controlled and approved material specifications.

A low residual risk product/process may need only one batch for validation, if very similar to an existing packaging process is used; whereas, a product/process with a high residual risk may need several batches.

6 Packaging Validation Risk Assessment

Assessing the risk for packaging can occur at several points in a project. Obvious time points are before purchasing of the equipment and again prior to the packaging validation. The conclusion of the packaging validation may discuss the risk, while pointing to the ongoing monitoring approach.

6.1 Equipment Risk Assessment

Equipment risk assessments following good engineering practices are discussed in detail through ISPE guides, *Applied Risk Management for Commissioning and Qualification* [17] and *Science and Risk-Based Approach to the Delivery of Facilities, Systems and Equipment* [18].

Equipment is most often purchased with at least one or more products in mind. It can also be purchased with the expectation of future purposes. In other situations, the equipment exists and is to be moved to another place and/or used in a different process. Risk should be evaluated around the equipment's intended use(s) through user requirements. With more complicated equipment, revisiting the equipment risk assessment should be done at different stages of the project (after specification/design phase and after FAT/Commissioning/Qualification phase).

6.2 Process Risk Assessment

Once the expected products are known, and the equipment purchased, installed and qualified, the entire packaging equipment train should be assessed. The more that is known of the specific packaging materials and process, the better the risk assessment. Because of this, this risk effort ideally should be done after a good portion of the development work has been completed. Performance of the packaging process risk assessment just prior to the packaging validation can be used with the goal of justifying the packaging validation approach (e.g., the number of runs, representative presentations used, materials, sampling schemes, etc.). Complexity, variability, knowledge of the process, and data recorded to date should be considered in determining the number of and approach to the packaging validation runs.

For the purposes of process validation, risk assessments should consider the risk to the patient, risk to the product, and risk of GMP non-compliance (reference ISPE quality risk categories from *Applied Risk Management for Commissioning and Qualification*, p. 73 [17]). Other non-quality related risks that may be considered at this time include business, safety, or efficiency risks; however non-quality risks should not be included in the validation. These would not need to be evaluated in detail within the packaging validation, but addressed prior to the packaging validation or the first commercial lots (unless addressing them affects the process itself, i.e., speed for efficiency).

6.3 Primary vs. Secondary Packaging

Primary packaging, where there is open product, is typically where higher risks (risk to patient) are expected. Secondary packaging is also important due to regulatory requirements for label printing, lot, and date code (and serialization). From a true risk to patient or product, risks in secondary packaging should be minimal with equipment that has been properly specified, purchased and thoroughly tested.

6.4 Evaluation of All Expected Situations

Table 3 provides a high-level example of expected scenarios to consider for a drug packaging facility. The table depicts, in time-relative terms (NEW, EXISTING/SIMILAR and EXISTING), the introduction of product, package presentation, or packaging line, and its resulting risk to the patient. Placement of scenarios in the table, if reading the table from left-to-right and top-to-bottom, should allow the viewer to quickly discern the relative risk of each scenario. Addition of color is made to the table to demonstrate this practice. Here, red represents the highest risk to the patient, followed by yellow and then green. The table should be reviewed and/or updated whenever any element of a scenario is introduced, modified or retired.

Procedures for risk assessments should remain generalized enough to accommodate unforeseen situations. Further variations of packaging risk should be expected based on business needs and expectations. Each situation could present different risks and require a different approach to packaging validation. Not all situations are represented in Table 3, and risk levels are left for each company to determine.

Table 3: Packaging Scenarios – High Level

Scenario	Product	Presentation	Packaging Line
a	NEW	NEW	NEW
b	NEW	NEW	EXISTING/SIMILAR
c	NEW	EXISTING/SIMILAR	NEW
d	NEW	EXISTING/SIMILAR	EXISTING/SIMILAR
e	EXISTING	NEW	EXISTING/SIMLAR
f	SIMILAR	SIMILAR	SIMILAR
g	EXISTING	SIMILAR	EXISTING

Familiarity (existing or similar) would mean it would be easier to mitigate known risk. All products and/or processes should be mapped out, as something may be different enough to increase risk in a specific portion of the packaging line. For example, the active ingredient may be the same between two tablets, but differences in the coatings may disqualify them from being considered “similar”. Assessing risks helps to further understand and improve the packaging process. Depending on the process, more experience may mean more risks are seen requiring attention during testing (development or validation). All reasoning around the conclusions drawn and approaches to be followed in the packaging validation should be explained at the time of the assessment. Providing detail helps to eliminate questions during audits or updates.

7 Validation Sampling Plans and Case Study

Much of packaging data is attribute data (e.g., pass/fail, legible/illegible). In comparison to variable or continuous data, attribute data requires a significant number of samples to make a statistically-based inference about a population (e.g., lot) of packaged products. The term “lot” as used here may involve multiple production batches, as necessary, to accept or reject the validation of the process. A carefully chosen sampling plan for packaging attributes is paramount. A 100% inspection of the lot may be used. If destructive testing is involved in the sample inspection process, however, this sampling plan is the most resource intensive and should be reserved for the most critical attributes.

Acceptance sampling for attributes is commonly used by product packagers as an alternative to 100% inspection. In acceptance sampling, a pre-specified sample of the lot is selected to represent the entire lot. An ideal sampling plan results in the rejection of all "bad" lots and acceptance of all "good" lots. As the sampling plan bases its decision on a sample of the lot, however, there is some risk of making an incorrect decision. The decision to accept a lot that should have been rejected is known as a Type II error (also known as consumers’ risk, β). Conversely, the decision to reject a lot that should have been accepted is a Type I error, or producers’ risk (α). Although an optimized sampling plan means a low risk outcome to both the consumer and producer, minimizing the consumers’ risk is most critical to patient safety.

A sampling plan is defined by its Operating Characteristic curve (OC curve), which shows how well a particular sampling plan discriminates between good and bad lots. It is summarized by two parameters: acceptance quality limit (AQL), the minimum level of quality routinely accepted, and rejectable quality level (RQL) (or limiting quality (LQ)), the level of quality routinely rejected.

Applying AQL and RQL to validation acceptance sampling plans allows one to make either of two confidence statements.

- **If passed**: to a defined confidence level (e.g., 1-β), the batch/process defective rate is below the defined RQL
- **If failed**: to a defined confidence level (e.g., 1-α), the batch/process defective rate is above AQL

As can be seen from these statements, the quality level is only known from an AQL viewpoint if the process fails, and known only to be above that defined AQL level. Only RQL provides statistical assurance that the batch defect level is below the defined level. Therefore, a typical approach for balancing AQL and RQL is to set the validation RQL level as the planned routine release criticality level (often termed AQL level). This approach provides statistical confidence (to the defined confidence level) that the defect level within the batch is no higher than the allowed routine release criticality level.

Once the confidence and highest possible defect rates have been defined, single or double acceptance sampling plans may be considered to balance the level of intensity of the validation sample plan.

This paper provides an example of how developmental stage testing, involving attribute data, may be performed and later used to qualify a vision inspection system in a packaging and labeling process.

7.1 Case Study: System Description

A continuous packaging and labeling process consists of two on-line label printers and two inspection cameras, among other packaging equipment and inspection systems. One printer prints human-readable variable data such as lot number and expiration date. The second printer prints a machine-readable barcode depicting the same variable data. Similarly, one camera reads the human-readable label content and the other camera decodes the barcode variable data. Before initiating a packaging run, both cameras are "trained" (i.e., provided a control standard label by which to compare test samples) to read its respective label content within a specified two-dimensional area on the label. Both human-readable and machine-readable characters read by the cameras are transmitted to a system PLC (programmable logic controller) for the packaging line. The PLC compares the data transmissions from each camera and makes the decision to pass or reject the labels based on a data match to production lot data entered into the PLC before the process is started.

7.2 Attributes Studied

Product labels are inspected by the cameras for the following defect types: 1) label misaligned/misapplied to the product (failure to detect printed information); 2) label print partially outside the bounds of the specified label print area; 3) incorrect lot number; 4) incorrect expiration date; 5) erroneous lot number (too few or too many numbers); 6) erroneous expiration date (too few or too many numbers); 7) print legibility, too faint; and 8) print legibility, too dark (causing characters to appear to run together). Attribute 7 presents the greatest test challenge. As such, this attribute is the primary focus of this discussion.

7.3 Approach

Before validation activities are begun on the vision inspection system, a method for "measuring" print legibility is determined. A single 2x2 full-factorial DOE (design of experiments) is conducted to examine print-head temperature and print-head pressure effects on print quality (or legibility) for both printers. The DOE test reveals a positive relationship between print-head temperature and print quality, although at a 95% confidence level, a relationship between print-head pressure and print quality is not discerned.

A logistic regression study is performed to examine further the minimum print-temperature at which the label print is 100% accepted by both vision inspection cameras when operating at production line speed using actual production materials, and by experienced packaging inspectors working off-line. For this study, all five trained inspectors are each provided a controlled workstation (common lighting, instructions for inspection angle, distance from label, etc.) in which to perform his/her inspection. No acceptance criteria for label acceptance or rejection are provided. Cameras and human inspectors are presented labels in the same random order. Results of the regression study lead to a minimum print temperature of 6°C for passing print legibility by both human inspectors and cameras. Print temperatures less than 6°C result in some passing camera inspections, though almost all human inspections are failures.

A standard operational qualification employing a 100% inspection plan is conducted for the vision inspection system. Package labels generated at the minimum passing print temperature of 6°C (i.e., at edge of failure) are among those used in the qualification. Upper-bound print temperature settings do not apply, as print is still legible at the maximum design print temperature (determined from a second logistic regression study). With the packaging process running at production line speed, the vision system is presented with 75 labeled packages, of which 60 samples have known defects falling into one of the defect categories (see Section 7.2 “Attributes Studied”). An RQL of 5.0% is chosen, as the product risk is low. Successful completion of the qualification with n=60 defects and a=0, therefore, assures with 95% confidence that the vision system will falsely accept defective labels no more than 5% of the time.

8 Ongoing Process Verification (OPV) for Packaging

Major global regulators expect industry to be evaluating the performance of the process to identify issues and to determine whether action must be taken to correct, **anticipate, and prevent problems** so that the process remains in control. This is accomplished through Ongoing Process Verification (OPV), also known as Continued Process Verification (CPV). When developing an OPV trending plan for packaging operations, there are many factors to consider; however, these tend to be similar considerations when developing a product-based trending plan.

A packaging-data trending plan may consider the elements below identified at the design and development stage:

- Identify stage/packaging step (i.e. primary, secondary or tertiary).
- For each step identified, list all of the following:
    - CQAs for components and product
    - Critical process parameters (CPPs)
    - Critical material attributes (e.g., tablet inputs such as thickness or weight)
    - Location and type of in-process checks (IPCs)

- Required and/or allowed yields/rejects/downtime (optional)

- Justify which of these may be trended and which may not, using a risk-based approach:
  - Where CPPs are held to a set point (e.g. by automated recipe driven control systems) may trend for common cause variability
  - May trend IPC data
  - May trend rejects
  - May trend defects
- Define and justify the frequency of trending and reporting for critical items to be reviewed using development/manufacturing history, risk assessment, process capability, etc. Packaging attributes from processes demonstrating process stability and high process capability may be trended less frequently because the risk to product quality is low. Control limit lock through the quality systems (e.g. LIMS, alert alarms) may also be used to maintain awareness of process outliers.
- Review following the implementation of change control activities and, at least quarterly, to ensure updates are made according to data trends observed, outcomes of mitigation plans, change controls, revalidation activities, and new requirements from a risk assessment or corrective and preventive actions (CAPA).

For packaging operations, consideration should also be given to the following:

- Critical process parameters having system alarms, especially with warning alarms. If alarms are within the validated specification limits, they can provide a trigger to investigate a potential departure from a state of control before impacting the release of product and therefore the patient.
- External factors that affect the packaging operation (e.g., differing lots of packaging material from outside suppliers) should be part of the OPV plan. The required process capability, trend rule breakage criteria, and frequency of review for these attributes should be rationalized.

Additional items to consider are:

- The initial critical data trending and review period after process validation where critical process control limits are established and sample sizes may be larger than routine. The reduction of samples for both process inputs (components, etc.) and outputs (packaged product) from validation to routine should be rationalized.
- Higher criticality/risk elements (input/output) that display higher intra/inter lot variability may warrant continued validation-level sampling plans until variability estimates are well understood.

- Sudden or gradual changes in trend should be reviewed for root cause, significance to the process, and impact to the final product/packaging and therefore, not necessarily trigger a Quality System deviation unless warranted by the investigation.
- A set period of time (i.e. annual review) or trigger (i.e. change control) to reassess process control limits should be established.
- Critical attributes with low process capability should be targeted for process improvements.

9 Conclusions

Drug product packaging helps in protecting the contents from environmental effects, contamination, and physical damage as well as sealing the contents until ready for use; thus, preserving product quality. The packaging process is part of the manufacturing process, and the process validation effort should demonstrate that the manufacturing process consistently produces products that meet attributes related to safety, identity, strength, purity, and quality. This paper provides insight into packaging process validation and presents a methodology that can be adapted by readers.

Development of a product matrix to bracket packaging formats is discussed as an efficient approach. A risk-based approach for validation strategy is presented to help focus on the areas that could impact product quality and employ mitigation controls to reduce residual risk levels. Sampling plans that may be used in the process validation effort are put forth. Recommendations for an ongoing process verification program are offered to help the reader in the establishment/implementation of an effective program. The authors' intention is to develop this paper as an overview or high-level discussion and to solicit feedback from other members knowledgeable in the drug product packaging industry.

10 Key Terms

AQL	Drug Substance	Process Validation
Commissioning	Package	Process Validation Protocol
Critical Process Parameter	Packaging Component	Qualification
Critical Quality Attribute	Packaging Material	Secondary Packaging
DOE	Primary Packaging	
Drug Product	Process Performance Qualification	

Reference ISPE Glossary for definitions. www.ispe.org/glossary.

RQL	Rejectable Quality Level
Tertiary Packaging	Outer packaging (e.g., case or wrapped pallet) used for the commercial shipping of one or more secondary packages of drug product

11 References

1. WHO Technical Report Series, No. 902, 2002, Annex 9, Guidelines on Packaging for Pharmaceutical Products, World Health Organization.
2. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, US Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) 1999.
3. Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA), September 2004, Pharmaceutical CGMPs.
4. Technical Report, Current Practices in the Validation of Aseptic Processes – 1992, 1996 and 2001, Parenteral Drug Association.
5. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 – Commissioning and Qualification,* International Society for Pharmaceutical Engineering, First Edition, March 2001, www.ispe.org.
6. The Global Harmonization Task Force: Quality Management Systems-Process Validation Guidance Ed. 2, 2004.
7. Title II of the Drug Quality and Security Act, SEC. 202. Pharmaceutical Distribution Supply Chain, Chapter V (21 U.S.C. 351 et seq.), Subchapter H--Pharmaceutical Distribution Supply Chain, United States Food and Drug Administration.
8. United States Pharmacopeia <1136> Packaging – Unit-of-Use, USP34-NF29, 1 December 2011.
9. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, EudraLex, Volume 4, October 1, 2015, European Commission Directorate-General for Health and Food Safety.
10. SUPAC-IR Questions and Answers about SUPAC-IR Guidance, 18 February 1997, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm, United States Food and Drug Administration.
11. BS EN ISO 11607-2:2006+A1:2014, Packaging for terminally sterilized medical devices. Validation requirements for forming, sealing and assembly processes, 31 May 2006, British Standards Institution.
12. Compliance Policy Guide, Section 480.100, Requirements for Expiration Dating and Stability Testing, http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074408.htm, United States Food and Drug Administration, Issued 20 June 201985, Reissued 4 September 1987 and March 1995.
13. Guideline of process validation for finished products – information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012, Rev 1, Corr.1, 21 November 2016, European Medicines Agency.
14. Guidance for Industry, Process Validation: General Principles and Practices, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), January 2011, Current Good Manufacturing Practices (CGMP), Revision 1.
15. International Council for Harmonisation (ICH), ICH Harmonised Tripartite Guideline, *Quality Risk Management – Q9,* Step 4, 9 November 2005, www.ich.org.
16. International Council for Harmonisation (ICH), ICH Harmonised Tripartite Guideline, *Pharmaceutical Development – Q8(R2),* August 2009, www.ich.org.
17. *ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification,* International Society for Pharmaceutical Engineering, First Edition, October 2011, www.ispe.org.
18. *ISPE Guide: Science and Risk-Based Approach to the Delivery of Facilities, Systems and Equipment,* International Society for Pharmaceutical Engineering, First Edition, June 2011, www.ispe.org.