



Technical Report No. 60-2

Process Validation: A Lifecycle Approach

Annex 1: Oral Solid Dosage/ Semisolid Dosage Forms



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Process Validation: A Lifecycle Approach — Annex 1: Oral Solid Dosage/Semisolid Dosage Forms Technical Report Task Force

Authors and Contributors

José Toro, Ph.D., Tolmar Inc. (Team Co-Lead)

Michael N. Blackton, Eli Lilly & Co. (Team Co-Lead)

Scott Bozzone, Ph.D., Pfizer (Retired)

David Brown, Pfizer

Igor Gorsky, Valsource

Susan Griesemer-Murphy, Mallinckrodt
Pharmaceuticals

Miguel Hernandez, Teva Pharmaceuticals

Steven Ostrove, Ph.D., Ostrove Associates

Darius Pillsbury, UltraGenyx

Michael O. Skidmore, Pharmaceutical Quality
Consulting, Inc.

Bob Wissert, Yoh, A Day & Zimmermann Company

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1.0 Introduction

This document is an annex to *PDA Technical Report No. 60: Process Validation: A Lifecycle Approach* (TR 60). It applies the process validation lifecycle to oral solid dosage and semisolid dosage products.

TR 60-2 is organized in a manner that illustrates how the entire process validation lifecycle presented in TR 60 relates to oral solid and semisolid dosage forms, with their unique technologies and well-characterized processes. This includes a brief explanation of the technologies associated with oral solid and semisolid products, as well as a discussion of the lifecycle stages—Stage 1: *Process Design*; Stage 2: *Process Qualification*; and Stage 3: *Continued Process Verification*. Legacy product validation and validation lifecycle enablers, such as risk and knowledge management, are also presented. Finally, but more importantly, TR 60-2 outlines some specific case studies that illustrate how these concepts are specifically addressed for each dosage form.

1.1 Purpose

The purpose of this annex is to illustrate how concepts from TR 60 can be applied to oral solid and semisolid dosage drug products so the reader can gain a clear understanding of the application of the process validation lifecycle to these technologies (1).

1.2 Scope

The scope of this document is limited to the application of the concepts outlined in TR 60 to oral solid dosage forms, such as tablets and capsules (excluding liquid-filled capsules), and semisolid dosage forms, which includes creams, ointments, and suppositories.

2.0 Glossary of Terms

Terminology may differ by company and some terms may be subject to change over time. Those terms used in a validation program should be clearly defined, documented, and well understood. When establishing internal definitions, terminology definitions that are widely recognized by the industry should be considered. These can be found in regulatory guidance documents. Definitions of company-specific terminology should also be included in the validation documents to provide clarity and context. This technical report uses the terms below, which are accompanied by their definitions, synonyms, and references where applicable:

Attributes

Critical Quality Attribute (CQA)

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (2).

Process Performance Attribute (or Process Performance Parameter)

An output variable or outcome that cannot be directly controlled but is an indicator that the process performed as expected (3).

Quality Attribute

A molecular or product characteristic that is selected for its ability to indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency, and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected

subset of the quality attributes (4).

Continued Process Verification (CPV)

US FDA

Assuring that during routine production the process remains in a state of control (5).

Continuous Process Verification

ICH

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (2).

Critical Process Parameter (CPP) (or Critical Operational Parameter)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (2).

Lifecycle

All phases in the life of a product, from the initial development through marketing until the product is discontinued (2).

Normal Operating Range (NOR)

A defined range, within the Proven Acceptable Range, specified in the manufacturing instructions as the target and range at which a process parameter should be controlled, while producing unit operation materials or final product meeting release criteria and CQAs (6).

Process Analytical Technology (PAT)

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (2).

Process Performance Qualification (PPQ)

Confirming that the manufacturing process, as designed, is capable of reproducible commercial manufacturing (5).

Process Validation

EMA

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes (7).

US FDA

The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products (5).

Proven Acceptable Range (PAR)

A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (2).

Quality

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength, and purity (8).

Quality Target Product Profile (QTPP)

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product (2).

Target Product Profile (TPP)

A format for a summary of a drug development program described in terms of labeling concepts to facilitate communication regarding a particular drug development program (8).

Verification

A systematic approach to verify that manufacturing systems, acting alone or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses types of approaches such as qualification, commissioning and qualification, verification, and system validation (9).

Worst Case

A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure (10).

2.1 Abbreviations

APC	Advanced Process Control
API	Active Pharmaceutical Ingredient
CMA	Critical Materials Attribute
CPP	Critical Process Parameter
CPV	Continued Process Verification
CQA	Critical Quality Attribute

DOE	Design of Experiments
DP	Drug Product
DS	Drug Substance
FMEA	Failure Mode Effects Analysis
LIF	Laser-induced Fluorescence
NIR	Near Infrared

NOR	Normal Operating Range	QbD	Quality by Design
OSD	Oral Solid Dosage	QTPP	Quality Target Product Profile
PAR	Proven Acceptable Range	SSD	Semisolid Dosage
PAT	Process Analytical Technology	TPP	Target Product Profile
PPQ	Process Performance Qualification		

3.0 Oral Solid Dosage Forms

Tablets and capsules are among the most popular and convenient methods of drug delivery. The three main oral solid dosage (OSD) processing methods are direct compression (dry powder blending), wet granulation, and dry granulation. Tablets and capsules are solid pharmaceutical dosage forms containing active and inactive pharmaceutical ingredients, with or without excipients, that are prepared either by compression or encapsulation. Common tablet and capsule forms are shown in **Table 3.0-1** and **Table 3.0-2**, respectively.

Table 3.0-1 Common Tablet Forms

Form	Description
Compressed Tablets (CT)	Formed by compression with no special coating.
Sugar-coated Tablets (SCT)	Compressed tablets with a sugar coating and added color in some cases.
Film-coated Tablets (FCT)	Compressed tablets that are covered with a thin layer or film of a water-soluble material and added color in some cases.
Enteric-coated Tablets (ECT)	Compressed tablets coated with substances that resist dissolution in gastric fluid but disintegrate in the intestine.
Multiple Compressed Tablets (MCT)	Compressed tablets made by more than one compression cycle.
Layered Tablets	Bilayered and trilayered compressed tablets made by more than one compression layer; each layer may contain an active or inactive ingredient(s).
Press-coated Tablets	Dry-coated; prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets (i.e., enteric-coated tablet within the center of a compressed tablet).
Controlled-release Tablets	Compressed tablets that are formulated to release the drug slowly over a prolonged period of time (e.g., laser-drilled or slow-dissolving tablets).
Oral Powders	Preparations consisting of solid, loose, dry particles of varying degrees of fineness. They contain one or more active ingredients, with or without excipients and, if necessary, approved coloring matter and flavoring substances. They are generally administered in or with water or another suitable liquid. They may also be swallowed directly. They are presented as single or multi-dose preparations.

Table 3.0-2 Common Capsule Forms

Form	Description
Gelatin Capsules	Soft gelatin capsules are solid dosage forms in which the medication is contained within gelatin shells. The medication may take the form of a liquid, with dissolved or suspended active ingredient; a semisolid mass; or pellets or beads. The capsules are formed, filled, and hermetically sealed in a simultaneous, continuous operation. Hard gelatin capsules consist of two pieces in the form of cylinders: the shorter piece, the "cap," and the longer piece, the "body." They are typically filled with powders, pellets, beads, or tablets. Assembly typically has multiple steps.
Pellets	Small cylinders implanted subcutaneously for continuous absorption.
Beads	Solid dosage form in the shape of a small ball.
Sustained-release Capsules	In general, a sustained-release dosage form consists of filled materials with one or more parts composed of an immediate- and/or sustained-release portion which gradually dispenses the medication.

4.0 Semisolid Dosage Forms

Semisolid dosage (SSD) forms comprise creams, gels, ointments, suppositories, and other special topical dosage forms. SSD formulations share many common properties including consistency, dosage uniformity, preservative requirement, and route of administration (membrane crossing). SSD forms present the challenge of delivering the drug's active ingredient across the patient's skin or other physical membrane to reach the targeted system. Common SSD forms are shown in **Table 4.0-1**.

Table 4.0-1 Common SSD Forms

Form	Description
Creams	Creams are viscous semisolid emulsion products with an opaque appearance as contrasted with translucent ointments. Consistency and rheological character depends on whether the cream is water in oil (W/O) or oil in water (O/W). The type of cream may be defined by the emulsifier used and the phase (water or oil) that is dispersed.
Suspensions and Gels	Suspensions and gels are semisolid systems in which a liquid phase is constrained within a polymeric matrix having a high degree of physical or chemical cross-linking. Suspensions and gels are aqueous colloidal suspensions of the hydrated forms of insoluble compounds. These SSDs vary physically from transparent to turbid in appearance.
Ointments	Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Ointments are normally classified into four types by base: hydrocarbon, absorption, emulsion or water-miscible, and water-soluble.
Suppositories	Suppositories are a solid body drug delivery system of various weights and shapes, adapted for introduction into the rectal, vaginal, or urethral orifices of the human body.

5.0 Application of the Process Validation Lifecycle To OSD Products

5.1 Stage 1: Process Design

This section discusses the major points to be considered during Stage 1 of the process validation lifecycle defined in PDA TR 60, as applied to OSD forms **(1,5)**. One of the main goals of this stage is to determine CQAs and CPPs that will be used to define the commercial manufacturing process and to ensure the CQAs and CPPs are documented in the development report. In addition, the design of the sampling plan/technique/technology must be defined at this stage. The following studies are conducted with compendial as well as R&D sampling methods (which typically require many more samples than compendial methods). The sampling plan is further refined as the control plan is developed.

For the purposes of this discussion of Stage 1, the unit operation of powder blending will be discussed. Two of the most prevalent characteristics (powder characteristics and flow patterns) are described below. In addition to the specific areas of study outlined in this section, common process design characteristics such as cleanability and microbial control should also be evaluated.

5.1.1 Powder Characteristics

Manufacturing of OSD forms is contingent upon proper powder-blending processes to consistently produce uniform finished dosage units. There are many characteristics of the materials and process that impact particle–particle interactions **(11–13)**. For the formulation being studied, it is important to understand those interactions that have the potential to impact the quality of the finished dosage form. Properties that are subject to study may include:

- Particle size distribution
- Powder density (bulk and tap)
- Powder angles of repose
- Particle morphology
- Moisture
- Stability
- Dissolution

5.1.2 Flow Patterns

Process design should consider powder flow pattern and its impact on material segregation in a vessel (i.e., blender, hopper, storage container, drum, etc.) **(14,15)**. The powder characteristics described above are linked, such that changing one property may have an impact on one or more flow characteristics. Flow pattern characteristics subject to study may include:

- Bulk powder flow properties, e.g., mass flow or funnel flow
- Impact of outlet orifice size, e.g., formation of arches
- Powder shear strength
- Agglomeration
- Sifting or percolation
- Air entrapment
- Microbial control and cleanability
- Particle entrapment

5.1.3 Effect of Scale on the Powder Flow and Segregation

In general, the types of processes involved in both OSD and SSD manufacture, particularly the mixing/blending steps, could typically present some challenges when being scaled up throughout the lifecycle of the product. It is important to carefully examine scale-up considerations and plan process control strategies appropriately. The scale-up modeling and actual studies could be considered to achieve consistent processing and transfer to a larger or smaller scale. These scale-up considerations apply to all three stages of the process validation continuum.

The effect of scale on the powder flow and segregation, for instance, should be thoroughly studied during the process design stage. Measurements of sifting and fluidization are two methods currently used for these investigative studies (16). The propensity of powders to segregate should be addressed within the process design. For example, as the process is scaled, equipment is added, or recipe sequences are changed, powder segregation should be re-examined as powder flow and the potential for segregation can impact the dosage uniformity, which is typically considered a CQA.

ASTM D6940: Standard Practice for Measuring Sifting Segregation Tendencies of Bulk Solids provides useful standard practices for the process designer to more fully understand powder segregation properties and the effect of different processing strategies within a set of design options (17).

5.1.4 Blending Process Parameters

When designing the process for blending, the following should be taken into consideration:

- Blender size and technology (working capacity, sanitary design, etc.)
- Rotational rate (typically considered critical for scale-up)
- Powder characteristics, including particle size distribution and morphology (applies to granulated and non-granulated blend components)
- Acceleration rates
- Blend time (typically considered critical for scale-up and may impact microbial control, cleanability, etc.)

Additional consideration should also be given to the correlation of particle velocities to vessel rotation rate and radius, which can be investigated using the Rayleigh's Method (18). To adequately develop and scale up the blending process, efforts should focus on those parameters (e.g., dissolution, dissolution rate, potency, stability, cleanability, etc.) that have significant impact on the final result.

5.1.5 Sampling Methods and Schemes

Methods and plans for sampling must be studied in advance of establishing the control strategy to avoid sample bias and ensure consistent results. Each component of the sampling plan design, including technique, frequency, and relevance, must be considered as they relate to the parameters under study. Sampling should therefore address:

- Sampling tools
- Sampling tool orientation (including angle and action)
- Location of the sample within the vessel
- Sample size
- Sample frequency
- Sufficient samples for retest, if required
- Sample handling and storage
- Time between sample collection and analysis

The sampling process must be properly detailed in written procedures with associated operator training to ensure consistency. The sampling plan and statistical significance should be considered when determining the sample size, sample locations, and sampling tool to be used for data analysis.

5.2 Stage 2: Process Qualification

Finalized process design requirements and CPP/CQA information from Stage 1 will provide the information and data needed to move into Stage 2: Process Qualification (PQ). This stage verifies the process reproducibility at commercial-scale in a real-world production environment and design of the facility and qualification of the equipment and utilities. Given the nature of a dynamic environment, operations that are ancillary to the process design may have an impact on the PQ and must be addressed. Therefore, factors to consider include, but are not limited to, the items outlined in Table 5.2-1.

Table 5.2-1 Considerations for Transition from Stage 1 to Stage 2

PPQ Aspect	Considerations
Equipment/system design	CPPs and how they will be controlled (critical aspects) Equipment working capacity and capabilities Process sampling requirements (e.g., PAT, conventional sampling, parametric release) Product strengths (mass/dosage unit) API potency/toxicity/particle characteristics (e.g., milled, micronized, dust generation) Temperature/humidity/light/oxidation sensitivity Weighing, dispensing, containment Granulation/blending process (e.g., wet granulation, dry blend) Drying conditions Blend/filling/compression or encapsulation characteristics (e.g., sticky, free-flowing, subject to bridging or rat-holing, compressibility) Coating process (e.g., active, sugar, modified release, enteric coating) Printing and sorting process Bulk storage (conditions and/or time) Sanitary design, ease of cleaning, microbial control Primary packaging (bottles, blister packs)
Equipment qualification	Temperature sensitivity Cleaning and/or sanitizing Spray rates and patterns for granulation and coating Granulation drying characteristics Ability to meet microbial control strategy requirements Milling/micronizing conditions Tablet press tooling differences and tooling maintenance lifecycle Additional OQ/PQ work that may be required on tablet press to expand upon original qualification based on tableting optimization work (multifactorial compression trials)
Introduction of new materials or material source	Particle size differences Particle characteristics Blending, compression, and drying requirement changes
Facility qualification/cleaning validation	Product changeover and line clearance Utilities Unique requirements of new materials (API, excipients, dyes) upon existing cleaning validation and procedures Dust collection and containment requirements (potent compounds) Waste disposal Personnel gowning Personnel training Material flow Material segregation/separation

5.2.1 Process Performance Qualification (PPQ) Study Design

The PPQ study design is determined based on many factors including prior product knowledge, data collected during Stage 1 development activities, risk assessment, and identified areas of known process and product variability. Upon completion of Stage 1 activity, CPPs and CQAs will be determined, justified, and documented as part of development reports and the product/process control plan. The PPQ will verify process control as determined through the collection and assessment of CPP and CQA data.

The level of PPQ-required enhanced sampling and CQA testing at any given manufacturing unit operation should be based on the risk assessment and process variability as documented during Stage 1.

It is important to note that the risk assessment results will vary greatly based on the specific product. For example, if an immediate-release coated tablet has an active coat rather than a non-active coat, the coating unit operation would have a risk ranking of high for assay, rather than low.

5.2.2 Manufacturing Operational Requirements

Operational requirements, such as duration of manufacturing processing times and impact of different operators performing manufacturing operations, should also be taken into consideration when developing the PPQ study design. If a manufacturing operation will typically run over multiple manufacturing shifts using different operators, then the PPQ should specify that additional samples and testing are required to provide process data across all shifts and operators.

5.2.3 Bracketing, Matrix, and Family Approaches

Product data gathered from Stage 1 may be used to provide justification for utilizing a bracketing, matrix, or family approach to PPQ. If data from Stage 1 provides information that represents the extremes of process variables, then the data can be potentially leveraged to justify a reduction in the number of PPQ batches required. **Table 5.2.3-1** shows an example of bracketing. The approach shown is valid, provided the tablets at each strength have similar geometrical characteristics. Further information on bracketing, matrix, and family PPQ approaches is detailed in PDA TR 60 (1).

Table 5.2.3-1 Example of Bracket Approach for Tablet from a Master Blend

Blend Concentration	API Content/ Tablet	Total Tablet Weight	PPQ Runs	Rationale
25 mg API/ 100 mg powder	25 mg	100 mg	Multiple	Lowest DP Strength /Lowest Tablet Wt.
	50 mg	200 mg	1 batch	Covered by Matrix
	100 mg	400 mg	1 batch	Covered by Matrix
	150 mg	600 mg	Multiple	Highest DP Strength /Highest Tablet Wt.

5.2.4 Process Analytical Technologies/Advanced Process Control

Process analytical technologies (PAT) and advanced process control (APC) systems may be used to monitor and control OSD processes. These systems may provide more accuracy in controlling critical quality attributes such as API homogeneity, moisture content, and particle size. Processing times may be optimized, such as blending and drying times, due to the real-time nature of the measurements. Examples are near infrared (NIR) and software-model sensors, which are in-line (in the process stream). Ultimately, the use of PAT can simplify PPQ efforts.

5.2.5 Homogeneity or Uniformity within Bulk Vessels

Homogeneity, or uniformity of bulk solutions, blends, or core tablets is a critical element of the PPQ that must be clearly demonstrated. When developing a sample plan to confirm solution homogeneity (e.g., of a Wooster coating) or powder blend uniformity as part of PPQ, it is important to consider factors that are likely to have an impact on the homogeneity of the pharmaceutical ingredients. Variables that should be considered in determining sample size and location include:

Vessel configuration

This includes such things as the shape of the vessel (e.g., V-Blender vs. a cylindrical tank) and presence or absence of impellers, baffles or, in the case of blenders, intensifier bars. Samples should be taken from areas within the vessel where blending conditions may not be optimal and would potentially result in nonhomogeneous solutions or powder blends. Stratified samples should be taken across the vertical and horizontal planes of the vessel to ensure all portions of the vessel are sampled and tested.