IPEC FEDERATION

The International Pharmaceutical Excipients Council

Validation Guide

For Pharmaceutical Excipients

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This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this Guide may be used to achieve an equivalent level of assurance for excipient quality.

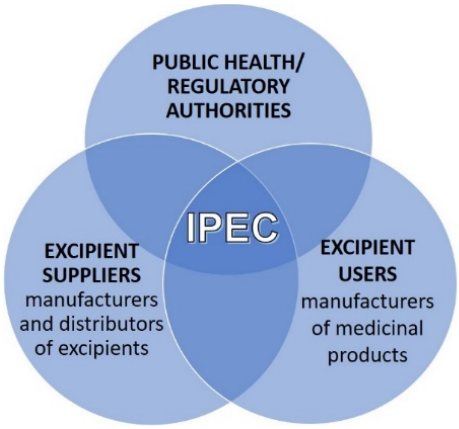
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and users. At the current writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the international excipient standards development and harmonization, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient manufacture.

IPEC has three major stakeholder groups:

1. excipient manufacturers and distributors, defined as suppliers in IPEC documents,
2. pharmaceutical manufacturers, defined as users in this document, and
3. public health and regulatory authorities.



This Guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the rules and regulations applying to excipients will vary from region to region and country to country. In addition, the rules and regulations are continually evolving. It is the responsibility of users of the Guide to determine whether there are

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

any additional legal or regulatory requirements, in addition to the recommendation given in this Guide, applicable to a particular region or country in which they are doing business.

This document offers best practice and guidance on the validation of excipient processes and product. It is the responsibility of, and expectation for, each company to determine/extrapolate the applicable level of validation activities necessary for their processes and/or products and to document their strategy, as appropriate, in their quality policies and procedures manual.

NOTE: Refer to the "International Pharmaceutical Excipients Council Glossary: General Glossary of Terms and Acronyms" for definitions [1]. The first use of a term found in the glossary will be in **BOLD**.

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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This Guide was developed by representatives from International Pharmaceutical Excipients Council (IPEC) member companies. IPEC is an industry association whose members consist of excipient manufacturers, distributors, and users. The company representatives who worked on this Guide are listed below:

List of Contributors from IPEC-Americas

Jane N. Bono, Ashland Specialty Ingredients

Dale Carter, Evonik

George Collins, Vanderbilt Chemicals LLC

Elizabeth Febbo, Henkel Corporation

Luke Grocholl, MilliporeSigma

Ann Gulau, DuPont

David B. Klug, Sanofi

Lucien Sergile Jr., Eli Lilly and Company

Paul Smutz, Henkel Corporation

Katherine Ulman, KLU Consulting

Priscilla Zawislak, DuPont

List of Contributors from IPEC Europe

Karsten Diehl, BASF

Ulrich Fechtel, Merck KGaA

Astrid Stockrahm, DFE Pharma

Martin Fink, DFE Pharma

Jens Woeltinger, Evonik

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

1 INTRODUCTION

1.1 Background and Purpose

Validation is a term commonly used in the pharmaceutical industry to describe a program that tests and evaluates systems, processes and methods to provide a high degree of assurance that they consistently produce results meeting predetermined acceptance criteria. Validation activities, in addition to all other GMP activities provide the evidence that the process is in a state of control. The **excipient manufacturer** may not perform these activities in the same manner or to the same extent as the pharmaceutical industry, however, many activities leading to the same degree of assurance are performed. This guide will attempt to address how to document the activities that are currently used by an excipient manufacturer to successfully produce excipients in a manner that meets the **excipient user's** expectations.

Current excipient **Good Manufacturing Practices (GMP)** standards and guides (NSF/IPEC/ANSI 363 [2], EXCiPACT® [3] and the IPEC/PQG Guide [4]) do not require validation of manufacture, however they require demonstration of consistent operation of the excipient manufacturing process based on knowledge of process parameters, product attributes and their inter-relationship.

ISO 9001:2015 [5] requires validation of processes where resulting outputs cannot be verified by subsequent measurement (i.e., where a required excipient attribute cannot be ensured by testing samples from the final product). In addition, the referenced excipient standards refer to the need for demonstrating consistent operation of computer systems and effectiveness of cleaning.

According to the U.S. FDA Guidance on Process Validation [6]: General Principles and Practices, GMPs require that manufacturing processes for Active Pharmaceutical Ingredients (APIs) and finished drugs be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.

This guide provides potential approaches that could be used to meet the intent of the clauses referencing validation or similar terms for excipients (e.g. verification, **commissioning**) in the current excipient GMP Standards [2,3] and Guide [4].

This guide is not intended to convey additional requirements beyond what is contained in the references above. Rather, it is intended to explain how an excipient manufacturer might meet expectations using work processes that may already be in place.

1.2 Definitions

- Commissioning: A systematic approach to the start-up and turnover of facilities, systems, and equipment to end-users and ensuring that user requirements and design specifications are met [7]. Activities within this phase may include design reviews, factory

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

acceptance testing, installation verification, and functional testing. Summary reports are generated at the conclusion of commissioning activities and include an overview of the results and any deviations encountered during testing. Commissioning, if well documented, may be leveraged to reduce or eliminate qualification testing.

- Qualification: Action of proving and documenting that equipment or systems that can impact the quality or compliance of the final product are properly installed, work correctly, and lead to the expected results (i.e. installation, operational, and performance qualification).
- Validation: A documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criterion.
- Validated state: The status of a GMP relevant system or process that is achieved after having provided documented evidence that the system or process is capable (i.e. in a state of control) for the intended use in the manufacturing of pharmaceutical excipients.
- Continuous Verification: Assuring that during routine operation the process, method or system remains in a state of control.

1.3 Application to Excipients

Although the term “validation” is referenced in current excipient standards, the processes that are often used by the excipient manufacturer to perform validation may not be familiar to their excipient user(s). In addition, these processes may not readily generate the type and level of documentation customarily expected by excipient users.

Many excipients are produced in large industrial facilities such as chemical plants or mining operations that produce materials for a variety of markets (including, but not limited to pharmaceutical, food, cosmetic, and industrial uses). Manufacturing operations within these facilities have often been in place for many years and were not originally intended for the production of pharmaceutical excipients. Activities such as equipment qualification would have been done in accordance with chemical or mining industry standards and may not have generated documentation that looks like a pharmaceutical industry qualification. However, years of successful operation are evidence of the adequacy of the work that was completed.

Although the excipient manufacturer may not have a process validation report, other documents may be used to demonstrate a state of control. In general, the excipient manufacturer controls their processes to maintain quality and profitability. They often utilize sophisticated process automation systems, designed for handling highly hazardous materials to meet industrial safety requirements. In addition to safety, these automated systems typically provide a high degree of quality control.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
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2 GENERAL GUIDELINES

Excipient manufacturers may choose to follow a traditional pharmaceutical approach. However, this is not a requirement, and, in many cases, validation may be successfully demonstrated by existing work processes

Collection and interpretation of critical process data that can impact critical quality attributes are measures for determining product quality and process robustness. The comparison of these data with specifications defined in the manufacturing protocol or monograph is often used as the first step in estimating process consistency and to evaluate if the processes are in a state of control, which may allow the manufacturer to claim that a validated state is achieved for all systems and processes.

Validation activities should be described in the excipient manufacturer's quality management system. Good documentation practices should be followed in the records created in the planning and execution of validation studies (see IPEC-PQG The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients [4]).

2.1 Validation and/or Study Approaches

The manufacturer should consider processes, systems and procedures that may have an impact on product quality and where a validation would be needed. Documented risk assessments should be used to identify where the quality may be impacted.

Typical validation approaches may include:

- Prospective validation is usually applied to new processes or in conjunction with significant changes and/or new products. Execution of defined studies, collection/analysis of data and assessment/documentation of conclusions are completed prior to commercial release of the excipient product(s).
- Concurrent validation is usually applied to established processes and is performed in parallel with on-going production. Validation batches are released upon successful completion of confirmatory testing.
- Retrospective validation is usually applied to established processes where no further operation validation activities are anticipated. Historical data is used to support the validation. This approach is not usually recommended but is common for long-established processes.
- Continuous verification which uses ongoing monitoring and evaluation of parameters and controls to demonstrate that the process, system or procedure remains in a state of control may be appropriate when they have been developed based upon engineering design

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

principles (e.g. QbD, DOE). A continuous verification may be an alternative to (re)validation.

Regardless of the strategy, excipient manufacturers should have procedures defining the validation approach.

2.2 Activities

2.2.1 *Initiation of activities*

Excipient manufacturers should identify and assess their GMP relevant systems and processes to determine whether sufficient capability has been demonstrated and documented. This assessment can be achieved by following the relevant sections of this guide for such validation activities as process, computer, method, cleaning, etc.

2.2.2 *Validation Master Plan*

A Validation Master Plan is a commonly used term in the pharmaceutical industry [6, 8] for a high-level document outlining the manufacturer's approach to validation. A Validation Master Plan is not a requirement for excipient manufacture but may be a useful reference or tool.

For the excipient manufacturer, a validation master plan may be used to identify the existing work processes, data, metrics, etc. that, when taken together, provide the evidence to justify that the manufacturing plant commissioning, process operation, computerized systems, analytical methods and cleaning procedures operate in a state of control.

2.2.3 *Preparation*

Prior to performing a validation or robustness study, a validation plan or other suitable documentation, such as a protocol, might be created to support and document the upcoming validation activities. The following items should be considered, as appropriate:

- Objective
- Scope
- Process description and risk evaluation
- Critical process parameters and acceptance criteria or tolerances
- Definition of data which should be collected and evaluated
- Sampling and testing plan
- Analytical methods
- Number of validation batches
- Roles and responsibilities

These should be considered for each planned validation activity regardless of whether they are applied to manufacturing plant commissioning, process operation, computerized systems, test methods and/or cleaning procedures.

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2.2.4 *Reporting*

After the execution of the validation or robustness study all collected data should be evaluated and interpreted. This collection, evaluation and interpretation should be documented in a validation report or other suitable documentation. All topics outlined in preparation (planning) should be covered.

The validation report or other suitable documentation should indicate the result of the study and conclude whether the process meets the acceptance criteria.

2.2.5 *Change Management*

If the validation activities conclude that GMP relevant systems and processes are in a state of control, the excipient manufacturer may claim that a validated state is achieved. However, change management is essential to secure the validated state once achieved.

In case of a change to a GMP relevant system, this change should be assessed within the change management program [9] to determine the impact to the validated state. If the change impacts the validated state of the system, related activities as described in this guide should be initiated.

2.3 Qualification and Commissioning of Equipment and Instruments

The purpose of qualification and commissioning is to demonstrate that the system is suitable for the intended use and that it fulfills the user requirements.

The commissioning of equipment before using it for commercial production is good engineering practice and should also be conducted by excipient manufacturers after an installation of process equipment. Steps for these commissioning activities are often comparable to those taken for equipment qualification and may, therefore, be used to demonstrate suitability of equipment.

Things to consider when qualifying and commissioning equipment or instruments (based on their potential to impact consistency and reliability of predetermined quality requirements) might include:

- Process flow diagrams
- Equipment lists
- Equipment and instrumentation (diagrams, drawings, labeling, P&IDs), manuals, specification sheets
- Calibration and Preventive Maintenance SOPs
- Maintenance plans or records
- Cleaning procedures, including frequency
- Operating Procedures
- Utility requirements
- Equipment verification activities (operation, user acceptance test, functionality, etc.)

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The qualification or commissioning of equipment and instruments that have been in use for many years can be supported by a retrospective review of the historical operation (for example, frequency of failure and failure types) against the current procedures and work processes used to maintain them. The protocol should list the information to include in the qualification report; for example, it might include the list shown above as well as the period of time that is being reviewed. The protocol could include a requirement to review the performance of the equipment, for example, "Maintenance and repair records from January 2020 to the current date will be reviewed and the results of the review summarized in the qualification report."

A retrospective qualification could also include a list of products that have been produced or tested with the equipment and any relationship to required maintenance or repairs. If the instrument or equipment can have a significant impact on a particular excipient attribute, the protocol should require a review of that attribute for a specific period of time. The protocol should be reviewed and approved by appropriate personnel.

2.4 Computerized Systems

Computerized systems may be used for a variety of purposes in the excipient industry, for example:

- controlling the manufacturing process
- controlling inventory,
- management of documents
- managing analytical data,
- creating certificate of analysis (COA),
- generating labels and transportation documents,

These systems are designed, commissioned and verified to meet employee, environmental and equipment safety as well as regulatory requirements and functionality. Excipient manufacturers can use risk assessments to determine which computer systems are critical to excipient quality, and the validation requirements for these systems should be considered. The context and the extent of the validation should be commensurate with the risk to excipient quality.

Validation of computer systems for process controls may be performed as part of process validation activities, including continuous process verification or process capability studies, which demonstrate that the entire system is in a validated state and performs as intended.

Commissioning and verification demonstrate that the system is capable of operating in a state of control and performs as intended. Continuous process verification or process capability studies are also used to demonstrate the process control computer system continues to perform as intended.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

For system changes or upgrades, assurance that these will not impact excipient quality should be documented within the change management program.

Computerized systems that may impact excipient quality should have evidence of controls to ensure consistent operation. Things to consider when evaluating a computer system, based on their potential to impact consistency and reliability of predetermined quality requirements, might include:

- Function – Evaluation that includes a description of the functions it performs and an assessment of data and checks that demonstrates that the system operated as intended.
- System Security – Data integrity, maintenance, access control, back-up or archiving, disaster recovery, and evaluation that demonstrates the security functioned as designed and did not allow changes to the system by unauthorized individuals.

  NOTE: Process control systems that manage excipient quality critical parameters are often subject to restricted access control; however, these systems often require access by multiple operators for safety reasons and may have shared passwords based on roles and responsibilities. Such a practice would not for example, be common in quality control laboratories but in both instances where passwords have to be shared an adjuvant paper log could be used to make data captured attributable.
- Change Management - Evaluation that provides a description of how changes to the system are managed. Subsequent computer systems changes, such as software version upgrades, would require verification that the system performs as intended. Changes that do not alter the computer system function may not require further computer system evaluation.

Additionally, paper-based and computerized system information for example, SOPs, can be used to support that a computer system is adequately verified.

2.5 Analytical Methods

Test methods (analytical or otherwise) used for quality control and product release should be evaluated and verified to demonstrate they provide reliable test results and are fit for purpose.

Methods generally used by excipient manufacturers include: compendial methods, American Society for Testing and Materials (ASTM), Association of Official Analytical Chemists (AOAC), other standard methods, and/or in-house methods.

Several pharmacopeias, e.g. USP-NF and European Pharmacopoeia (Ph. Eur.) have General Chapters on test method validation and verification. If compendial methods are implemented as described in these documents, the following activities are recommended:

- Verification that the current version of the method is being used

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
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- Verification that any associated equipment is properly installed and operates correctly
- Evidence that personnel are appropriately trained on the method and the equipment use and operation
- Evidence that results are accurate and repeatable (i.e. testing standards, verify personnel performance over multiple days and multiple shifts)
- Evidence of system suitability where applicable, such as chromatographic methods

In-house methods, in addition to the above activities, might also be evaluated (as appropriate) for:

- Accuracy
- Precision
- Specificity
- Detection Limit
- Quantitation Limit
- Linearity
- Range
- Robustness

2.6 Process

Effective process control is key for achieving consistent quality in the manufacturing of pharmaceutical excipients; therefore, excipient manufacturers should have procedures defining their approach to demonstrate this effectiveness.

Various approaches may be utilized, including process capability studies, continuous process verification, design of experiments statistical techniques, etc. The method(s) used should provide a high degree of assurance that a specific process or system will consistently produce the desired results.

Since excipients are typically manufactured in industrial equipment used to produce similar materials (e.g. families of polymeric materials) and may be marketed for other applications, process capability studies/data across the product family are often used to confirm the validated state.

Many excipient processes were designed and commissioned years and even decades ago, long before validation of excipients was considered. For these situations, an excipient manufacturer should evaluate what historical activities may have taken place (e.g. process capability studies) and how results from these activities could be documented to support the state of control for a

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

process and/or product. Use of historical records (e.g. minimum **%** right first time [1]or CpK) to demonstrate that a process can achieve the desired output is often referred to as retrospective validation. For a retrospective review of production, the time period for assessment/review of data should be justified (e.g. after the last significant change was made).

For continuous process verification, excipient manufacturers may use ongoing monitoring and evaluation of process parameters and controls to demonstrate that the process remains in a state of control. Excipient manufacturers should define critical process parameters that impact quality. These parameters should be monitored, assessed, and documented to demonstrate that the manufacturing process continually and consistently produces the desired product.

Statistical techniques can be used to demonstrate that the process is in a state of control. A useful and effective means of describing process capability are statistics such as Cp and Cpk.

Supportive evidence of a state of control may include a combination of these elements:

- Development and scale up reports
- Process capability studies
- Retrospective evaluation of process and test parameters
- Statistical analysis of historical process and product data
- Product quality reviews / campaign reviews
- Management reviews
- Change management
- Corrective and preventative actions (CAPA) measures to eliminate causes of deviations and complaints

Often, these elements are readily available, but may not be tied together as an assessment of the state of control. Therefore, excipient manufacturers should have procedures defining their approach to demonstrate this effectiveness.

2.7 Cleaning

The cleaning approaches applied in excipient manufacturing vary greatly and depend on multiple considerations such as type of excipient, history of use, equipment capabilities, continuous or batch manufacturing, etc. While current excipient standards [2, 3] do not require formal cleaning method validation**,** understanding cleaning effectiveness is necessary to ensure the level of cleanliness meets predetermined acceptable levels based on risk assessment [10] and to determine where cleaning is required, to ensure equipment is suitable for use and will not

[1] When a batch is successfully produced as it is intended and meets all specifications without deviations or need for adjustments to the process as written.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

adversely impact the product quality. Therefore, the excipient manufacturer should demonstrate that the cleaning procedure and frequency are effective.

Items to consider for a cleaning effectiveness assessment include:

- The production equipment design (e.g. flow, dead legs, construction material, seals)
- Multi-purpose or dedicated equipment
- Utensils and secondary equipment (e.g. hoses, transfer vessels)
- The manufacturing and packaging environment
- Hygienic practices (e.g. gowning, PPE, loose items, food and drink)
- The cleaning process (e.g. cleaning equipment, risks derived from water, cleaning agents, degradation of agents or solvents, method capability for detection as needed)
- Maintenance / return to service activities
- Cleaning study acceptance criteria based on worst case scenarios

  NOTE: Worst case scenarios should consider, as appropriate: bioburden, cleaning difficulty due to design, blind spots that hinder visual inspection, product ingredient toxicity, cleaning agent toxicity, ease of residue removal, production sequence, etc.
- Data and conclusions demonstrating that potential contamination levels meet the predetermined acceptance criteria.

  NOTE: Sources of contamination can include residual cleaning materials, residue material, cross-contamination, hygienic practices, environmental and / or microbiological.

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Rue Marie de Bourgogne 52 - 1000, Brussels, Belgium
W: ipec-federation.org T: +32 2 213 74 40 E: info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73363068125160 - RPM Brussels Capital Region

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