



REVIEW ARTICLE

A Comparative Evaluation of Process Validation Requirements for Multivitamin Tablet Formulations in Nutraceutical and Drug Categories

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ABSTRACT

Process validation plays a critical role in ensuring the quality, safety, and consistency of multivitamin tablet formulations across both pharmaceutical and nutraceutical sectors. Despite serving similar end-user needs, these two categories are governed by distinct regulatory frameworks, resulting in divergent validation requirements. This review presents a comparative evaluation of process validation approaches applicable to multivitamin tablets classified as either drugs or nutraceuticals. Key focus areas include differences in regulatory expectations, validation lifecycle stages, identification and control of critical process parameters (CPPs), documentation practices, and the application of quality risk management tools. The review also highlights emerging trends such as digitalization, real-time monitoring, and the adoption of Quality by Design (QbD) principles, particularly in high-risk nutraceuticals. By analyzing these aspects side by side, the article aims to assist quality assurance professionals, regulatory experts, and manufacturers in aligning validation strategies for improved compliance, product uniformity, and consumer safety. The insights provided may also support regulatory harmonization and the development of integrated quality systems across both product categories.

Keywords: Process Validation; Multivitamin Tablets; Nutraceuticals; Pharmaceuticals; Critical Process Parameters (CPPs); Quality Risk Management; GMP Compliance; Regulatory Frameworks; FSSAI; FDA; Lifecycle Approach; Quality by Design (QbD)

INTRODUCTION

Multivitamin tablets are widely consumed dietary products that serve diverse roles ranging from general nutritional supplementation to therapeutic applications. Their categorization as either a drug or a nutraceutical depends on factors such as composition, intended use, claims, dosage, and regulatory jurisdiction. In India, products classified as drugs are regulated under the Drugs and Cosmetics Act and Rules, while nutraceuticals fall under the purview of the Food Safety and Standards Authority of India (FSSAI)¹. Globally, regulatory bodies such as the US FDA², EMA, and Codex Alimentarius³ provide frameworks that influence local policies. Given this divergence, process validation strategies vary significantly across these two classifications².

The present review undertakes a detailed comparison of the process validation requirements for multivitamin tablet formulations in these two categories. The goal is to

provide clarity on best practices, expectations, and critical differences, ultimately contributing to effective compliance and assurance of product quality.

Concept and Importance of Process Validation

Process validation (PV) is a documented, evidence-based activity that establishes a high level of assurance that a specific process consistently produces a product meeting its pre-determined specifications and quality attributes^{2,4,5}. It ensures that product quality is not tested into the product but is built into the process².

The critical objectives of PV include^{2,4}:

- Ensuring reproducibility and uniformity of product characteristics.
- Identification and control of critical process parameters (CPPs).



- Enhancing regulatory compliance and operational efficiency.
- Mitigating risk through early identification of deviations.

Regulatory Framework Comparison

Pharmaceutical (Drug) Regulations

- Governed by stringent regulations like US FDA 21 CFR Part 210/211², EMA GMP Guidelines⁶, WHO TRS 986 Annex 2⁷, and Indian Schedule M⁷.
- ICH Guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System) form the backbone of modern process validation principles⁸.
- Emphasis on lifecycle approach to validation including Process Design, Process Qualification, and Continued Process Verification (CPV)².
- Requirement of three consecutive successful batches during Process Performance Qualification (PPQ)⁷.

Nutraceutical (Food Supplement) Regulations

- Governed under FSSAI notifications¹, ISO 22000:2018⁹, FSSC 22000 v6¹⁰, Codex guidelines³, and focused on Hazard Analysis and Critical Control Point (HACCP), Preventive Controls, and verification activities.
- PV requirements are relatively flexible; however, there is increasing emphasis on validation of sanitation, hygiene, CCPs (Critical Control Points), and product consistency^{1,9}.

Critical Process Parameters and Validation Considerations

Key Manufacturing Steps in Multivitamin Tablets

- Blending: Uniformity of micronutrient distribution; risk of segregation in low-dose vitamins⁴.
- Granulation: Control of binder levels, mixing time, and granule homogeneity (especially critical in hygroscopic or thermo-labile vitamins)^{4,11}.
- Drying: End-point moisture critical to tablet stability^{4,5}.
- Compression: Weight variation, hardness, friability—all influencing dissolution and stability^{4,11}.
- Coating: Film uniformity, visual appearance, moisture protection (especially for B-complex vitamins)^{4,11}.

Pharmaceutical Validation Focus

- Use of statistically designed experiments (DoE) to define design space^{4,8}.
- Validation of analytical methods (e.g., HPLC, UV for vitamin quantification)^{5,8,11}.
- Cleaning validation to avoid cross-contamination^{2,4}.
- Strict traceability and deviation management^{2,8}.

Nutraceutical Validation Focus

- Consistency of ingredient mixing (especially natural or herbal components)^{1,9}.
- Validation of hygienic design and cleaning protocols^{9,10}.
- Label claim validation (e.g., vitamin levels till end of shelf life)^{1,3}.
- Use of metal detectors, sieves, and environmental monitoring as part of PRPs (Prerequisite Programs)^{9,10}.

Table 1: A comparative summary of validation lifecycle stages for pharmaceutical and nutraceutical multivitamin tablet formulations^{1,2,4,5,7-11}

Lifecycle Stage	Pharmaceutical Category	Nutraceutical Category
Stage 1: Process Design	Based on Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), and risk assessment (FMEA) ⁸ .	Based on product profile, hazard analysis, and risk categorization (HACCP, VACCP) ^{1,9,10} .
Stage 2: Process Qualification	Detailed IQ, OQ, and PPQ; Use of conformance batches and statistical process control ^{2,4,5,7,8,11} .	Equipment and sanitation validation, control of CCPs and PRPs ^{1,9,10} .
Stage 3: Continued Process Verification (CPV)	Ongoing batch monitoring, trending of CPPs and CQAs, annual product quality review ^{2,8} .	Periodic internal audits, sanitation record review, control of deviations ^{1,9,10} .

Documentation Practices and Statistical Application

Pharmaceutical

- Validation Master Plan (VMP), individual validation protocols and reports^{2,4,5,7,8}.
- Use of control charts, process capability indices - Cp (Process Capability) & Cpk (Process Capability Index), regression models^{4,5,8,11}.
- Documentation required for every process change, deviation, or revalidation trigger³.

Nutraceutical

- FSMS Manual, PRP validation records, SOPs, and cleaning logs^{1,10}.
- Use of checklists and verification records instead of statistical analysis^{1,9}.
- Less emphasis on predictive statistics, though trending is encouraged^{2,7,9,10}.



Challenges and Implementation Gaps

Pharmaceutical Sector

- High cost of compliance and analytical testing^{5,11}.
- Need for real-time monitoring tools (PAT)^{2,8}.
- Managing process drift across global manufacturing sites^{4,11}.

Nutraceutical Sector

- Heterogeneity of raw materials (especially botanical extracts)^{1,10}.
- Lack of harmonized global regulations^{1,2,7,10}.
- Limited technical expertise in small-scale nutraceutical firms^{1,10}.

Emerging Trends and Integration Strategies

- Convergence of quality systems under risk-based models^{4,8}.
- Use of Quality by Design (QbD) principles in high-risk nutraceuticals^{4,8}.
- Implementation of digital twins, real-time monitoring, and cloud-based validation platforms^{2,8}.
- Increasing demand for transparency and traceability in supply chains^{2,7,10}.

Case Illustrations and Best Practices

Case Study 1: Process Performance Qualification (PPQ) for a Multivitamin B-complex Tablet

- Conducted in a GMP-compliant facility^{2,4,7}.
- Critical Process Parameters (CPPs): Granulation time, drying endpoint, compression force^{4,5,8}.
- Critical Quality Attributes (CQAs): Uniformity of dosage units, dissolution, stability^{4,8,11}.
- Outcome: All three conformance batches met the specifications with low variability^{2,4}.

Case Study 2: Process Validation in a Nutraceutical Multivitamin Tablet Formulation

- Conducted under ISO 22000:2018 and FSSC 22000 v6 guidelines^{1,9,10}.
- Prerequisite Programs (PRPs) validated: Sieving, weighing, blending operations, granulation process, drying parameters, compression force, and sanitation procedures (Validated cleaning and sanitation protocols for equipment and production area, ensuring control of microbial load and allergen contamination)^{1,9,10}.
- Label claims verified through both in-house and third-party laboratory testing^{1,3}.
- Emphasis on sanitation effectiveness, cross-contamination control and allergen management^{3,9,10}.
- Documentation of batch manufacturing records and PRP monitoring records maintained as per FSMS

requirements^{1,9}.

- Outcome: Consistent batch conformity observed with verified safety and compliance to declared nutrient content^{1,3,9}.

CONCLUSION

A comprehensive process validation program is indispensable for ensuring the safety, efficacy, and regulatory compliance of multivitamin tablets. Pharmaceutical-grade validation demands in-depth statistical evaluation, protocol-driven documentation, and lifecycle-based oversight. In contrast, nutraceutical validations emphasize product consistency, food safety, and hygiene practices. Despite the divergent paths, an integrated, risk-based approach that considers scientific principles and global standards can bridge the compliance gap and facilitate robust product development and commercialization.

Abbreviations

API: Active Pharmaceutical Ingredient, **CDSCO:** Central Drugs Standard Control Organization, **CQA:** Critical Quality Attribute, **CPP:** Critical Process Parameter, **CPV:** Continued Process Verification, **DoE:** Design of Experiments, **EMA:** European Medicines Agency, **FAO:** Food and Agriculture Organization, **FSMS:** Food Safety Management System, **FSSAI:** Food Safety and Standards Authority of India, **GMP:** Good Manufacturing Practice, **HACCP:** Hazard Analysis and Critical Control Points, **HPLC:** High-Performance Liquid Chromatography, **ICH:** International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, **IQ:** Installation Qualification, **ISO:** International Organization for Standardization, **OQ:** Operational Qualification, **PAT:** Process Analytical Technology, **PPQ:** Process Performance Qualification, **PRP:** Prerequisite Program, **QbD:** Quality by Design, **QTPP:** Quality Target Product Profile, **SOP:** Standard Operating Procedure, **TRS:** Technical Report Series, **US FDA:** United States Food and Drug Administration, **VACCP:** Vulnerability Assessment and Critical Control Points, **VMP:** Validation Master Plan, **WHO:** World Health Organization.

Conflict of Interest

The authors declare no conflict of interest.

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