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HARMONIZING ANALYTICAL METHOD AND PROCESS VALIDATION: A COMPARATIVE STUDY OF ICH AND ASEAN GUIDELINES

B. Dinesh Kumar[1], Dr. K. Jaganathan[2], Dr. B. Senthil kumar[3], Dr. N. Senthil kumar[4]

[1,2,3,4]Department of Pharmaceutical Regulatory Affairs, JKKMRF's Annai JKK Sampoorani Ammal College Of Pharmacy, Komarapalayam, Nammakkal – 638183, Tamil Nadu, India.

Corresponding Author: Dr. B. Jaganathan, M. Pharm, Ph. D

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ABSTRACT

The pharmaceutical industry operates in a highly regulated environment, where analytical method and process validation play pivotal roles in ensuring product quality and safety. To facilitate global harmonization and streamline regulatory requirements, international organizations like the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Association of Southeast Asian Nations (ASEAN) have developed guidelines for these critical aspects.

This comparative study aims to comprehensively analyze the similarities and differences between the ICH and ASEAN guidelines pertaining to analytical method and process validation. By examining key elements such as scope, principles, requirements, and acceptance criteria, the study seeks to provide a clear understanding of the harmonized and divergent aspects of these guidelines. The comparison will cover a wide range of topics, including:

- Analytical method validation: This includes aspects such as specificity, linearity, accuracy, precision, range, detection limit, and quantification limit.
- Process validation: This encompasses topics like design of experiments, process performance qualification, and continued process verification.

Ultimately, this study will contribute to a better understanding of the regulatory landscape for pharmaceutical manufacturing and quality control. By highlighting the commonalities and differences between the ICH and ASEAN guidelines, it will provide valuable insights for pharmaceutical companies, regulatory authorities, and industry stakeholders seeking to ensure compliance with international standards and best practices.

Key Words: Regulatory affairs, Regulatory Agencies, FDA, ICH and ASEAN guidelines

1. INTRODUCTION

In the rapidly evolving landscape of pharmaceutical and biotechnological industries, the validation of analytical methods and processes is crucial for ensuring the safety, efficacy, and quality of medicinal products. Regulatory bodies across the globe have established guidelines to standardize these validation processes, ensuring that pharmaceutical companies adhere to rigorous quality standards. Among these, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Association of Southeast Asian Nations (ASEAN) have developed comprehensive frameworks that guide the industry in maintaining consistent and reliable validation practices.

The ICH guidelines are globally recognized and widely adopted, providing a harmonized approach to pharmaceutical regulation across major markets, including the United States, Europe, and Japan. These guidelines emphasize a science- and risk-based approach to validation, aiming to ensure that pharmaceutical products meet the necessary quality standards throughout their lifecycle.

On the other hand, the ASEAN guidelines, while aligned with global standards, reflect the unique regulatory environment of the Southeast Asian region. They cater to the specific needs of ASEAN member states, considering regional variations in manufacturing practices, regulatory frameworks, and market dynamics. This results in a distinctive approach to validation that, while harmonious with global standards, addresses the unique challenges and opportunities within the ASEAN region.

This comparative study aims to harmonize the analytical method and process validation parameters outlined in the ICH and ASEAN guidelines. By identifying similarities and differences between these two regulatory frameworks, this study seeks to provide a deeper understanding of how global and regional guidelines converge and diverge in their approach to validation. The insights gained from this comparison will be invaluable for pharmaceutical companies operating across multiple regions, helping them navigate the complexities of regulatory compliance in a globalized market.

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Comparison of Process Validation Requirements: Process validation is a crucial aspect of quality management systems across various industries, ensuring that manufacturing processes consistently produce products meeting predetermined specifications and quality attributes. The requirements for process validation can vary depending on the industry, regulatory body, and specific standards being followed. Below is a comparison of process validation requirements in some key industries:

Pharmaceutical Industry- Regulatory Guidelines: U.S. FDA's 21 CFR Part 211 (cGMP for Finished Pharmaceuticals), EU GMP Annex 15, ICH Q7.

Stages of Validation:

Process Design

- Purpose: Define the process objectives, identify critical process parameters, and establish control limits.
- Comparison: While the general approach is similar across regulatory bodies, the level of detail and documentation required may vary. For example, the FDA's guidelines may be more specific about risk assessment and control strategy.

Process Qualification

- Installation Qualification (IQ): Verify that equipment and facilities are installed and configured correctly.
- Operational Qualification (OQ): Demonstrate that the equipment operates as intended under specified conditions.
- Performance Qualification (PQ): Establish that the process can consistently produce products that meet specifications.
- Comparison: The specific tests and criteria for IQ, OQ, and PQ may differ slightly between regulatory bodies. For example, the EU GMP guidelines may emphasize the need for a risk-based approach to process qualification.

Continued Process Verification

- Monitoring: Continuously monitor process parameters to ensure they remain within control limits.
- Revalidation: Periodically revalidate the process to address changes or identify potential issues.
- Comparison: The frequency of revalidation and the specific monitoring methods may vary depending on the nature of the process and regulatory requirements.

Focus Areas:

- Risk management is integral, especially with the introduction of ICH Q9 (Quality Risk Management).
- Emphasis on using science-based approaches and ensuring product quality throughout the product lifecycle.
- Regulatory Bodies: Compare the guidelines from different regulatory bodies, such as the FDA, EMA, and ICH.
- Industry-Specific Requirements: Consider any industry-specific standards or guidelines that may apply.
- Risk-Based Approach: Evaluate the extent to which a risk-based approach is emphasized in the guidelines.
- Documentation: Compare the documentation requirements, including the types of records that need to be maintained.
- Change Control: Examine the guidelines for managing changes to the process.

Medical Devices Industry- Regulatory Guidelines: U.S. FDA's 21 CFR Part 820 (Quality System Regulation), ISO 13485:2016.

Validation and verification are critical components of the medical devices industry, ensuring that products meet the intended use and are safe for patients. These processes are guided by various regulatory bodies, including:

- FDA (Food and Drug Administration): The FDA has specific guidelines for medical device validation and verification, particularly for devices submitted for approval in the United States.
- CE Marking: Medical devices intended for sale in the European Union must comply with CE marking requirements, which include validation and verification protocols.
- ISO Standards: International Organization for Standardization (ISO) publishes standards related to quality management systems (ISO 13485) and medical device risk management (ISO 14971), which provide guidance on validation and verification activities.

Validation Process- Validation in the medical devices industry involves demonstrating that a medical device meets its intended use and performs as specified. It typically includes the following steps:

1. Design Verification: Ensuring that the design meets the specified requirements and is suitable for its intended use.
2. Process Validation: Demonstrating that the manufacturing process can consistently produce devices that meet specifications.
3. Installation Qualification (IQ): Verifying that the equipment and facilities are installed and configured correctly.

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4. Operational Qualification (OQ):: Confirming that the equipment operates as intended under specified conditions.
5. Performance Qualification (PQ): Establishing that the device performs as intended in its intended use environment.

Verification Process

Verification in the medical devices industry involves ensuring that the design and manufacturing processes comply with established requirements. It typically includes:

1. Design Review: Reviewing the design to identify potential risks and ensure compliance with regulatory requirements.
2. Process Review: Evaluating the manufacturing process to identify potential risks and ensure compliance with regulatory requirements.
3. Inspection and Testing: Conducting inspections and tests to verify that the device meets specifications and regulatory requirements.

Focus Areas:

- Risk-Based Approach: Medical device validation and verification should be conducted using a risk-based approach, focusing on critical aspects of the device and process.
- Documentation: Detailed documentation is essential to demonstrate compliance with regulatory requirements and traceability.
- Continuous Improvement: Validation and verification should be an ongoing process, with regular reviews and updates to address changes or identified issues.

Food Industry

Validation and verification are essential components of quality assurance in the food industry, ensuring that products meet safety, quality, and regulatory requirements. These processes help to protect consumers from foodborne illnesses and maintain brand reputation. Regulatory Guidelines: HACCP (Hazard Analysis and Critical Control Points), FDA's FSMA (Food Safety Modernization Act), ISO 22000.

Validation Process

Validation in the food industry involves demonstrating that a process or system consistently produces the desired results. It typically includes:

Design Validation: Ensuring that the design of a process or system meets the specified requirements and is capable of producing the desired output.

Process Validation: Demonstrating that a manufacturing process can consistently produce products that meet specifications. This may involve conducting trials and collecting data to evaluate process performance.

Equipment Validation: Verifying that equipment is installed and configured correctly and can perform as intended. This may include calibration and testing.

Verification Process

Verification in the food industry involves confirming that a process or system is being implemented as intended. It typically includes:

Document Verification: Ensuring that documentation, such as standard operating procedures (SOPs) and quality records, is accurate and complete.

Inspection: Conducting regular inspections to verify that processes are being followed correctly and that facilities are maintained in a sanitary condition.

Testing: Conducting tests to verify that products meet specified quality standards and are free from contaminants.

Specific Areas of Validation and Verification

Sanitation Validation: Demonstrating that sanitation procedures are effective in reducing microbial contamination.

Allergen Management Validation: Ensuring that procedures are in place to prevent cross-contamination of allergens.

Hazard Analysis and Critical Control Points (HACCP) Validation: Verifying that the HACCP system is implemented effectively and controls critical control points.

Food Safety Plan Validation: Ensuring that the food safety plan is comprehensive and addresses all potential hazards.

Regulatory Requirements

Food safety regulations vary by country and region, but common requirements include:

Good Manufacturing Practices (GMPs): Adhering to GMP guidelines to ensure that food is produced under sanitary conditions.

HACCP: Implementing a HACCP system to identify and control potential food safety hazards.

Allergen Labelling: Providing clear allergen labelling on food products.

Traceability: Maintaining records that allow for tracing food products from the farm to the consumer.

Automotive Industry

Regulatory Guidelines: IATF 16949, AIAG (Automotive Industry Action Group) standards.

Stages of Validation:

Design Validation: Ensures that the design meets the customer's requirements.

Process Validation: Ensures that production processes consistently produce products that meet specifications.

Production Part Approval Process (PPAP): A comprehensive approach to validating both the product and the process before full-scale production.

Focus Areas:

Strong emphasis on defect prevention and continuous improvement.

Validation often includes statistical analysis, such as Process Capability (Cp, Cpk) studies.

Biotechnology Industry

Regulatory Guidelines: Similar to pharmaceuticals, often governed by FDA and EMA, with additional guidelines from organizations like the International Council for Harmonisation (ICH).

Stages of Validation:

Process Development: Critical for processes involving living organisms.

Process Qualification: Often involves complex analytical testing and may include validation of the cell culture process.

Ongoing Process Verification: Continual monitoring is essential due to the variability in biological processes.

Focus Areas:

Control of biological variability and ensuring the consistency of biological products.

Detailed characterization of the process and product, with a focus on maintaining sterility and preventing contamination.

Commonalities Across Industries:

Documentation: All industries require rigorous documentation of the validation process, often including protocols, test data, and final reports.

Risk Management: Increasingly integrated into validation processes, especially in regulated industries.

Change Control: Any changes to validated processes require revalidation to ensure that the changes do not negatively impact product quality.

Continued Monitoring: Ongoing monitoring and review of processes are essential to ensure that they remain in control and continue to produce products that meet specifications.

Key Aspects of Analytical Method Validation

Analytical method validation typically involves assessing several key parameters to ensure that a method is suitable for its intended purpose. The specific parameters may vary depending on the type of analysis (e.g., quantitative or qualitative), the matrix being analyzed, and the regulatory requirements. Below are the commonly validated parameters:

Accuracy

The closeness of agreement between the value obtained by the method and the true value or an accepted reference value. Typically assessed by analyzing a known reference standard and comparing the measured value to the true value. It is often expressed as a percentage of the true value.

Precision

The degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogeneous sample.

Types:

- **Repeatability:** Precision under the same operating conditions over a short time interval.
- **Intermediate Precision:** Precision when variations are introduced within the laboratory (e.g., different days, analysts, equipment).
- **Reproducibility:** Precision under different laboratories or with different equipment. Measured by calculating the standard deviation (SD) or relative standard deviation (RSD, also known as the coefficient of variation, CV).

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Specificity (Selectivity)

The ability of the method to unequivocally assess the analyte in the presence of other components like impurities, degradation products, or matrix components. Demonstrated by comparing test results from samples containing the analyte with those from samples containing potential interferences.

Linearity

The ability of the method to obtain test results that are directly proportional to the concentration of the analyte within a given range.Typically evaluated by analyzing different concentrations of the analyte and plotting a calibration curve. The linearity is assessed by the correlation coefficient (r) or the coefficient of determination (R^2).

Range

The interval between the upper and lower concentration of the analyte that has been demonstrated to be determined with precision, accuracy, and linearity.Determined during the linearity study and is the range over which the method is valid.

Detection Limit (LOD)

The lowest amount of analyte in a sample that can be detected, but not necessarily quantified, under the stated experimental conditions.Often calculated based on the standard deviation of the response and the slope of the calibration curve (using methods such as the signal-to-noise ratio).

Quantitation Limit (LOQ)

The lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy. Similar to LOD, but typically with a higher signal-to-noise ratio, ensuring quantifiable results.

Robustness

The capacity of the method to remain unaffected by small, deliberate variations in method parameters, providing an indication of its reliability during normal usage.

Tested by varying parameters such as temperature, pH, or reagent concentrations and observing any effects on the method's performance.

Ruggedness

Similar to robustness, but refers to the reproducibility of the method under different conditions, such as different analysts or different laboratories.Usually assessed during inter-laboratory studies.

System Suitability Testing

The performance of the analytical system to ensure it is working properly before analysis.Usually involves running standard samples or controls before sample analysis to check parameters like resolution, peak symmetry, and column efficiency.

Table 1. The comparison table for each parameter of Analytical Method Validation according to ICH, ASEAN guidelines is depicted below

Validation Parameter	ICH Guidelines	ASEAN Guidelines
Specificity	Defines acceptance criteria for interference and selectivity	Sets limits for selectivity and interference
Accuracy	Establishes acceptance criteria for closeness of test results to true values.	Sets limits for accuracy compared to reference or known values
Precision	Specifies acceptance criteria for repeatability and intermediate precision.	Sets limits for repeatability and intermediate precision.
Robustness	Outlines acceptable variation in method performance under varied conditions	Sets limits for acceptable variations in method performance under varied conditions
Linearity	Establishes acceptance criteria for linearity over a range of concentrations.	Sets limits for deviation from linearity over the concentration range
Intermediate Precision	Specifies acceptance criteria for intermediate precision under varied conditions	Sets limits for intermediate precision under varied conditions.

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Analytical Method Validation Summary Report	
Parameter	**Results**
Product Name	Tadalafil
Active Ingredient	Tadalafil (Cialis)
Analytical Method	HPLC
Instrument Used	XYZ Model HPLC System
Column	C18 , 3.5 mm X 150 mm, 5µ
Mobile Phase	50:50 (ACN: Water)
Flow Rate	1.0 mk/min
Injection Volume	20 µL
Wavelength	230 nm
Retention Time	2.4 Minutes
Linearity	2-10
LOD	2.4001
LOQ	7.2732
Accuracy(mean %recovery) 80% 100% 120%	 0.29 0.21 0.15

Process Validation

Similarly, in process validation, differences may arise in the requirements for process design and qualification, as well as the frequency and scope of ongoing process verification and monitoring activities. The comparison table for each parameter of Process Validation for solid dosage form (tablet) according to ICH and ASEAN guidelines is depicted below

Parameter	ICH	ASEAN
Critical Process Parameters (CPP)		
Temperature	20-25°C ±2°C	20-30°C ±3°C
Pressure	1-3 bar	Not specified
Sterilization	121-134°C, 15- 30 psi	121-134°C, 15- 30 psi
pH	5.5-8.5	6.0-8.0
Drying	40-80°C,	40-80°C,
Homogeneity	≤2% RSD	≤3% RSD
Critical Quality Attributes (CQA)		
Physical Attributes	Tablet hardness: within ±5% of target Disintegration time: ≤20 minutes	Tablet hardness: within ±5% of target Disintegration time: ≤15 minutes
Chemical Attributes	Assay: within ±5% of label claim Impurities: NMT 0.1%	Assay: within ±2-5% of label claim Impurities: NMT 0.%
Microbiological Attributes	Bioburden: NMT 100 CFU/gS terility: no growth in 14 days	Bioburden: NMT 100 CFU/g Sterility: no growth in 14 days
Biological Attributes	Potency: within ±10% of label claim	Potency: within ±10% of label claim
Stability Attributes	Shelf-life: ≥24 months	Shelf-life: ≥24 months

Control Limits		
Temperature	±2°C around set point	±1.5°C around setpoint
Pressure	±0.2 bar	±0.1 bar
Flow Rate	±5%	±3%
pH	±0.2	±0.1
Mixing Time	±2 minutes	±1 minute
Granulation Moisture	±0.5%	±0.3%
Process Performance Qualification (PPQ) Parameters		
Assay	> 95% yield	≥ 90% yield
Impurities	<0.1%	≤ 0.2%
Dissolution Rate	> 80%	≥ 75%
Content Uniformity	90-110%	95-105%
Disintegration Time	≤ 30 minutes	≤ 20 minutes

Despite these challenges, there are significant opportunities for alignment and harmonization. By recognizing shared principles and best practices across various guidelines, stakeholders can simplify validation processes, leading to greater efficiency and consistency in product development and manufacturing. Collaborative efforts among regulatory bodies, industry associations, and other key stakeholders are crucial for advancing harmonization and creating a more unified regulatory framework

2. CONCLUSION

In summary, the comparative analysis of analytical method validation and process validation guidelines from ICH and ASEAN highlights the need to navigate the complex regulatory environments within the pharmaceutical and analytical sectors. Although the guidelines differ in certain aspects, they share common principles focused on ensuring product quality, safety, and efficacy.

Pharmaceutical companies must pay close attention to both the differences and the shared elements of these guidelines to achieve compliance and maintain high standards in manufacturing and quality assurance. Harmonization efforts and collaboration among stakeholders are essential for simplifying validation processes and enhancing global market access for pharmaceutical products. By fostering alignment and consistency in regulatory requirements, stakeholders can help build a more efficient and effective regulatory framework that ultimately serves the best interests of patients and consumers worldwide.

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