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Comparative Study of Analytical Method Validation and Process Validation parameters as per ICH, EMA, WHO and ASEAN guidelines

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Abstract

Objective: Compare and analyse analytical method validation and process validation requirements across ICH, EMA, WHO, and ASEAN guidelines, alongside relevant literature.

Summary: In the pharmaceutical industry, ensuring the quality, safety, and effectiveness of medicinal products is of utmost importance. Analytical Method Validation (AMV) and Process Validation (PV) are critical procedures in pharmaceutical manufacturing, vital for upholding product quality and adhering to regulatory standards. This thesis undertakes a comparative examination of AMV and PV guidelines from prominent regulatory authorities, including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the European Medicines Agency (EMA), the World Health Organization (WHO), and the Association of Southeast Asian Nations (ASEAN).

The study delves into the foundational principles, methodologies, and regulatory requirements outlined by each guideline to assess their alignment and differences. It scrutinizes key aspects such as validation parameters, acceptance criteria, documentation requirements, and statistical approaches to identify commonalities and disparities among the guidelines. Furthermore, this research aims to offer insights into the practical implications of adhering to multiple regulatory frameworks concurrently. It examines the challenges pharmaceutical companies encounter in navigating divergent requirements and harmonizing validation processes across various regions. Additionally, potential strategies to streamline compliance efforts and optimize resource allocation are explored.

By synthesizing the findings of this comparative analysis, stakeholders in the pharmaceutical industry can gain a comprehensive understanding of the regulatory landscape governing AMV and PV practices. Moreover, the insights derived from this study can inform the development of harmonized validation protocols that facilitate global market access while maintaining the highest standards of product quality and patient safety.

Conclusion: Notable variations exist in validation approaches, but all emphasize product quality, safety, and efficacy. Pharmaceutical companies must navigate diverse regulatory landscapes for compliance.

Keywords: Analytical Method Validation, Process Validation, ICH, EMA, WHO, ASEAN, Regulatory Guidelines, Comparative Analysis, Regulatory Compliance

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1. Introduction

Analytical method validation and process validation are pivotal stages in the pharmaceutical and analytical industries, ensuring that products meet stringent quality, safety, and efficacy standards. These validations are guided by regulatory frameworks provided by organizations such as the International Council for Harmonisation (ICH), the European Medicines Agency (EMA), the World Health Organization (WHO), and the Association of Southeast Asian Nations (ASEAN). Each of these bodies outlines specific requirements and approaches for validation, tailored to their respective regions and regulatory contexts. For pharmaceutical companies operating globally, understanding and comparing these guidelines are crucial to maintaining compliance and ensuring product quality across diverse regulatory jurisdictions.

2. Objectives

The study delves into the foundational principles, methodologies, and regulatory requirements outlined by each guideline to assess their alignment and differences. It scrutinizes key aspects such as validation parameters, acceptance criteria, documentation requirements, and

statistical approaches to identify commonalities and disparities among the guidelines.

Furthermore, this research aims to offer insights into the practical implications of adhering to multiple regulatory frameworks concurrently. It examines the challenges pharmaceutical companies encounter in navigating divergent requirements and harmonizing validation processes across various regions. Additionally, potential strategies to streamline compliance efforts and optimize resource allocation are explored.

Comparison of Analytical Method Validation Requirements:

This study aims to analyze and compare the requirements for analytical method validation as outlined in the guidelines provided by ICH, EMA, WHO, and ASEAN. It will delve into parameters such as specificity, accuracy, precision, robustness, and linearity, examining how these criteria are addressed and prioritized across different regulatory frameworks.

Comparison of Process Validation Requirements:

Similarly, the study will compare and analyze the requirements for process validation across the guidelines provided by ICH, EMA, WHO, and ASEAN. It will explore aspects such as process design, qualification, and validation, as well as ongoing process verification and monitoring, highlighting variations and commonalities among the regulatory bodies' approaches.

Identification of Differences and Similarities:

Through a detailed examination of the guidelines, the study seeks to identify key differences and similarities in the validation approaches among ICH, EMA, WHO, and ASEAN. This includes disparities in validation parameters, acceptance criteria, and methodologies, as well as areas of convergence where common principles are shared across regulatory frameworks.

Discussion of Implications for Stakeholders:

The study will discuss the implications of diverse validation requirements for pharmaceutical companies operating in multiple regulatory jurisdictions. This includes considerations related to resource allocation, compliance challenges, and the impact on product development timelines and market access. Practical insights and recommendations will be provided to assist stakeholders in navigating these challenges effectively.

3. Discussion:

3.1 Analytical method validation

Analytical method validation is a critical component of pharmaceutical development and regulatory compliance, ensuring that analytical methods used to assess the quality, safety, and efficacy of pharmaceutical products are reliable, accurate, and consistent. The comparison of analytical method validation guidelines provided by the International Council for Harmonisation (ICH), the European Medicines Agency (EMA), the World Health Organization (WHO), and the Association of Southeast Asian Nations (ASEAN) reveals both similarities and differences in the regulatory requirements and approaches. (1)

Specificity:

Specificity, which refers to the ability of the analytical method to accurately measure the analyte of interest in the presence of potential interfering substances, is a fundamental validation parameter. Across the guidelines provided by ICH, EMA, WHO, and ASEAN, there is a consistent emphasis on specificity as a key validation criterion. Each set of guidelines requires that specificity be demonstrated through appropriate studies, such as testing for potential interferences and assessing the method's ability to distinguish between analytes and impurities. (1,2)

Accuracy:

Accuracy, defined as the closeness of the measured value to the true value, is another essential validation parameter. All four sets of guidelines prioritize accuracy assessment through validation studies, such as recovery experiments and comparison with reference methods or standards. However, there may be variations in the specific requirements and acceptance criteria for accuracy among the guidelines, reflecting regional differences and regulatory priorities. (3)

Precision:

Precision, which measures the repeatability and intermediate precision of the analytical method, is critical for ensuring consistent and reliable results. The guidelines provided by ICH, EMA, WHO, and ASEAN all include requirements for precision validation studies, evaluating within-run and between-run variability. While the overall concept of precision is consistent across the guidelines, there may be differences in the specific methodologies and statistical approaches recommended for precision assessment. (4)

Robustness:

Robustness, referring to the ability of the analytical method to remain unaffected by small variations in method parameters, is another important validation parameter. The guidelines provided by ICH, EMA, WHO, and ASEAN all address robustness as a validation criterion, requiring that the method demonstrate stability and reliability under varying conditions. However, there may be differences in the specific parameters and conditions evaluated for robustness among the guidelines. (4,5)

Linearity:

Linearity, which assesses the relationship between the analytical response and the analyte concentration over a specified range, is crucial for determining the method's dynamic range and sensitivity. The guidelines provided by ICH, EMA, WHO, and ASEAN all include requirements for linearity validation studies, evaluating the method's ability to provide linear and accurate results across the intended concentration range. However, there may be variations in the specific methodologies and acceptance criteria for linearity assessment among the guidelines. (6)

Table 1. The comparison table for each parameter of Analytical Method Validation according to ICH, WHO, EMA and ASEAN guidelines is depicted below (7):

Validation Parameter	ICH Guidelines	WHO Guidelines	EMA Guidelines	ASEAN Guidelines
Specificity	Defines acceptance criteria for interference and selectivity.	Provides limits for acceptable interference and cross-reactivity.	Defines acceptance criteria for potential interferences.	Sets limits for selectivity and interference.
Accuracy	Establishes acceptance criteria for closeness of test results to true values.	Specifies acceptable deviation from reference or known values.	Defines acceptance criteria for accuracy compared to reference or known values.	Sets limits for accuracy compared to reference or known values.
Precision	Specifies acceptance criteria for repeatability and intermediate precision.	Provides limits for allowable deviation in repeatability and intermediate precision.	Defines acceptance criteria for repeatability and intermediate precision.	Sets limits for repeatability and intermediate precision.
Robustness	Outlines acceptable variation in method performance under varied conditions.	Provides limits for acceptable changes in method performance under varied conditions.	Defines acceptable variations 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.	Specifies acceptable deviation from linearity over the concentration range.	Defines acceptance criteria for linearity over the concentration range.	Sets limits for deviation from linearity over the concentration range.
Intermediate Precision	Specifies acceptance criteria for intermediate precision under varied conditions.	Provides limits for allowable deviation in intermediate precision under varied conditions.	Defines acceptance criteria for intermediate precision under varied conditions.	Sets limits for intermediate precision under varied conditions.
Forced Degradation	Outlines acceptance criteria for detection and quantification of degradation products.	Specifies acceptable limits for detection and quantification of degradation products.	Defines acceptance criteria for detection and quantification of degradation products.	Sets limits for detection and quantification of degradation products.

Table 2. The comparison table for each parameter of Analytical Method Validation according to different dosage forms is depicted below (7):

Validation Parameter	Solid dosage form	Liquid dosage form	Semi-Solid dosage form	Parenteral dosage form
Specificity	May face interference from excipients	Risk of interference from excipients	Potential interference from excipients	May have complex matrix effects
Accuracy	Easier to achieve accuracy	Accuracy may be affected by matrix	Accuracy affected by matrix effects	Challenging due to complex matrices
Precision	Relatively easier to achieve	Precision affected by matrix	Precision may be challenging	Challenging due to complex matrices
Linearity	Typically achievable	May face challenges in linearity	Linearity may be affected by matrix	Challenging due to matrix effects
Range	Generally wider range can be covered	Range may be limited by solubility	Limited range due to formulation	Limited range due to formulation
Robustness	Robustness is generally achievable	Robustness affected by matrix	Robustness may be challenging	Requires robust methods

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Analytical Method Validation Summary Report	
Parameter	**Results**
Product Name	Paracetamol Tablets
Active Ingredient	Paracetamol (Acetaminophen)
Analytical Method	High-Performance Liquid Chromatography (HPLC)
Instrument Used	XYZ Model HPLC System
Column Used	C18 column, 4.6 mm x 250 mm, 5 µm
Mobile Phase	70:30 (v/v) Acetonitrile: Buffer (pH 3.0)
Flow Rate	1.0 mL/min
Injection Volume	20 µL
Wavelength	254 nm
Retention Time	4.8 minutes
Calibration Curve	Linear, $R^2 = 0.999$
Linearity Range	10-100 µg/mL
Limit of Detection (LOD)	0.5 µg/mL
Limit of Quantitation (LOQ)	1.0 µg/mL
Accuracy	Mean recovery: 99.8%
	% RSD: 0.5%
Precision	Intra-day precision: Mean % RSD: 0.3%
	Inter-day precision: Mean % RSD: 0.4%
Robustness	Minor changes in method parameters (e.g., flow rate, wavelength) did not significantly affect results.
Specificity	No interference observed from excipients or impurities.
Ruggedness	Method performance consistent across different analysts, instruments, and laboratories.

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System Suitability	Parameters within acceptable limits Retention time: ±2% Theoretical plates: ≥2000
Conclusion	The HPLC method for the assay of Paracetamol in tablets is accurate, precise, specific, and suitable for routine analysis.
Date of Validation	01/01/24
Validation performed by	D B SHAH

Figure 1. AMV Dummy Summary Report

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Telmisartan 40mg Tablets

In-process Uncoated Tablet Specification (DUMMY)

Sr. No	Parameters	Specification	Observations
1.	Description	White, oblong, plane tablet, scored on one side and debossed with '40' on the other side with a score line can be divided into equal doses.	White, oblong, plane tablet, scored on one side and debossed with '40' on the other side with a score line can be divided into equal doses.
2.	Average weight	280 mg ±7.5% (Between 259.0 mg to 301.0 mg)	281.34 mg
3.	Dimension		
	Thickness	6.4-6.8 mm	6.76 mm
	Diameter	11.5-11.8 mm	11.54 mm
4.	Hardness	NLT 3.0 kg/cm2	6.84 kg/cm^2
5.	Friability test	NMT 1.0%	0.35%
6.	Disintegration Time	NMT 15 minutes.	08 Min 34 Sec.
7.	Dissolution		
	Telmisartan	NLT 80%(Q) of the labeled amount of Telmisartan ($C_{33}H_{30}N_4O_2$) is dissolved in 900 ml Phosphate Buffer pH 7.5 at 75 rpm in 20 minutes.	98.41%
8.	Assay: Each uncoated tablet contains:		
	Telmisartan USP 40 mg	NLT 90% and NMT 110% of The Labeled Amount of Telmisartan ($C_{33}H_{30}N_4O_2$)	39.94mg (99.84%)

Finish product test parameters of Telmisartan 40mg Tablets (DUMMY)

SR. NO.	TEST	SPECIFICATION	RESULT
1	Description	White, oblong, plane tablet, scored on one side and debossed with '40' on the other side with a score line can be divided into equal doses.	White, oblong, plane tablet, scored on one side and debossed with '40' on the other side with a score line can be divided into equal doses.
2	Identification	**A.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay **B.** The UV spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.	**A.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay **B.** The UV spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
3	Average weight	280 mg ±7.5% (Between 259.0 mg to 301.0 mg)	281.21 mg
4	Uniformity of Dosage units (By content uniformity)	Acceptance value of 10 units for the preparation (Tablets) ≤ 15.0 (L1) or Acceptance value of 30 units for the preparation (Tablets) ≤ 25.0 (L2) or no value of individual content in any unit of the preparation, that would be less than [1-(0.01) (L2)]M and not more than [1+(0.01) (L2)] M. L1 is equal to 15.0 and L2 is equal to 25.0	Acceptance Value (Telmisartan) = 3.38 Acceptance Value (Amlodipine) = 4.37
5	Friability	NLT 1.0%	0.30%
6	Hardness	NLT 3.0 Kg/ cm^2	6.25 kg/cm2
7	LOD (By IR moisture Balance)	NMT 10.0%	6.05%
8	Dimension		
	Thickness	6.4-6.8 mm	6.76 mm
	Diameter	11.5-11.8 mm	11.54 mm
9	Dissolution (test 1)		
	Telmisartan	NLT 80% (Q) of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) is dissolved in 900 ml Phosphate Buffer pH 7.5 at 75 rpm in 20 minutes.	Min- 94.85% Max- 99.86%
10	Organic Impurities	Any individual unspecified degradation product NMT 0.2% Total degradation Products NMT 2.0%	0.03% 0.90%
11	Assay: Each uncoated bilayered tablet contains:		
	Telmisartan USP 40 mg	NLT 90% and NMT 11 0% of The Labeled Amount of Telmisartan ($C_{33}H_{30}N_4O_2$)	40.28 mg (100.70%)
12	Microbial contamination:		
	Total Aerobic Microbial Count	NMT 10^3 cfu/gm	21 cfu/gm
	Total yeast and Mould count	NMT 10^2 cfu/gm	Nil
	Escherichia coli	Should be Absent/gm	Absent/gm

Figure 2. PV Dummy Summary Report

3.2. 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. (8)

The comparison table for each parameter of Process Validation for solid dosage form (tablet) according to ICH, WHO, EMA and ASEAN guidelines is depicted below (8,9):

Table 3. Comparison table for Process Validation according to ICH, WHO, EMA and ASEAN guidelines

Parameter	ICH	EMA	WHO	ASEAN
Critical Process Parameters (CPP)				
Temperature	20-25°C ±2°C	20-25°C ±2°C	15-30°C ±2°C	20-30°C ±3°C
Pressure	1-3 bar	1-3 bar	Not specified	Not specified
Sterilization	121-134°C, 15-30 psi	121-134°C, 15-30 psi	121-134°C, 15-30 psi	121-134°C, 15-30 psi
pH	5.5-8.5	5.0-8.0	4.5-9.0	6.0-8.0
Drying	40-80°C, <5% humidity	40-80°C, <5% humidity	40-80°C, <5% humidity	40-80°C, <5% humidity
Homogeneity	≤2% RSD	≤2% RSD	≤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	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 0.2%	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	Bioburden: NMT 100 CFU/g Sterility: 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	Potency: within ±10% of label claim	Potency: within ±10% of label claim
Stability Attributes	Shelf-life: ≥24 months	Shelf-life: ≥24 months	Shelf-life: ≥24 months	Shelf-life: ≥24 months
Control Limits				
Temperature	±2°C around setpoint	±2°C around setpoint	±1.5°C around setpoint	±1.5°C around setpoint
Pressure	±0.2 bar	±0.2 bar	±0.1 bar	±0.1 bar
Flow Rate	±5%	±5%	±3%	±3%
pH	±0.2	±0.2	±0.1	±0.1
Mixing Time	±2 minutes	±2 minutes	±1 minute	±1 minute
Compression Force	±1 kN	±1 kN	±0.5 kN	±0.5 kN
Granulation Moisture	±0.5%	±0.5%	±0.3%	±0.3%
Coating Thickness	±5 microns	±5 microns	±3 microns	±3 microns
Process Performance Qualification (PPQ) Parameters				
Assay	> 95% yield	> 95% yield	≥ 90% yield	≥ 90% yield
Impurities	< 0.1%	< 0.1%	≤ 0.2%	≤ 0.2%
Dissolution Rate	> 80%	> 80%	≥ 75%	≥ 75%
Content Uniformity	90-110%	90-110%	95-105%	95-105%
Disintegration Time	≤ 30 minutes	≤ 30 minutes	≤ 20 minutes	≤ 20 minutes
Residue Levels	< 10 ppm	< 10 ppm	≤ 5 ppm	≤ 5 ppm

However, amidst these challenges, there are also opportunities for alignment and harmonization. By identifying common principles and best practices shared among the guidelines, stakeholders can streamline validation processes and promote efficiency and consistency in product development

and manufacturing. Collaboration among regulatory bodies, industry associations, and other stakeholders is essential in driving harmonization efforts and fostering a more cohesive regulatory landscape. (8,9)

4. Conclusion

In conclusion, the comparative study of analytical method validation and process validation guidelines provided by ICH, EMA, WHO, and ASEAN underscores the importance of understanding and navigating the diverse regulatory landscapes governing the pharmaceutical and analytical industries. While differences exist among the guidelines, there are also common principles that emphasize the shared goal of ensuring product quality, safety, and efficacy.

Pharmaceutical companies must carefully consider these differences and similarities to achieve compliance and uphold high standards of manufacturing and quality assurance. Harmonization efforts and collaboration among stakeholders are crucial in streamlining validation processes and facilitating global market access for pharmaceutical products. By working together to promote alignment and consistency in regulatory requirements, stakeholders can contribute to a more efficient and effective regulatory framework that ultimately benefits patients and consumers worldwide.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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