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CONCURRENT PROCESS VALIDATION OF VORICONAZOLE TABLETS IP 200 MG

NEHA SHAH*, SUNITA ARYA, SONI MATELA, DR. PRAVEEN KUMAR ASHOK
Gyani Inder Singh Institute of Professional Studies, Dehradun, Uttarakhand, India

ABSTRACT
Validation is widely recognized as a crucial parameter in Good Manufacturing Practices (GMP). The process validation of pharmaceutical manufacturing processes is of significant importance, aiming to ensure the reproducible quality of drugs. This study provides an overview of process validation, emphasizing the need to build quality into every stage of production rather than relying solely on end-product testing. Process validation, in line with ISO 9000:2000, serves as a vital tool for quality management in the pharmaceutical industry. It is conducted before product release, during product changes, and continuously to verify the proper functioning of the process. A well-defined protocol should be established, outlining monitored parameters, sample collection, and acceptance criteria for results.

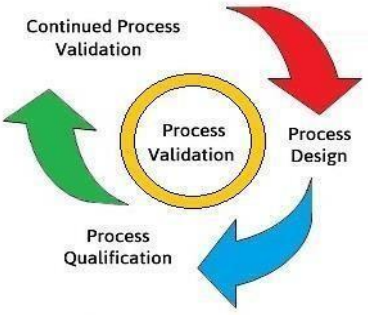
Keywords: Process validation, Quality, Protocol, Quality Management, Voriconazole

1.INTRODUCTION
Validation refers to the process of verifying and documenting that a process, procedure, or method consistently produces the intended outcomes. Process validation, on the other hand, involves gathering and analyzing data throughout the product's lifecycle to provide scientific evidence that the process consistently produces high-quality products. Process validation encompasses a series of activities conducted in three stages, spanning the product and process lifecycle.

Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.



Process Validation Flowchart

Types of Process Validation

The guidelines on general principles of process validation mentions four types of validation:

a. Prospective Validation
b. Retrospective Validation
c. Concurrent Validation
d. Revalidation

a. Prospective validation (or premarket validation)

Prospective validation is a validation approach that involves gathering documented evidence before the implementation of a process to demonstrate that the system functions as intended according to pre-established protocols.

b. Retrospective validation

Retrospective validation is a validation approach that utilizes historical data from facilities, processes, and process controls to provide documentary evidence that the process is functioning as intended. It confirms that the process has been consistently producing the expected results based on the analysis of past data.

Retrospective validation is done for facilities, processes, and process controls in operation by using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do.

c. Concurrent validation

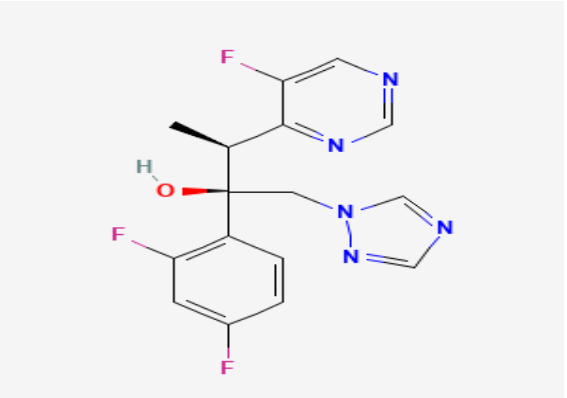
Concurrent validation is an approach used to gather documented evidence that a facility and its processes are performing as intended. It relies on real-time monitoring of critical processing steps and testing of the end product during actual production. The goal is to demonstrate that the manufacturing process is under control and consistently producing products that meet the desired specifications.

d. Revalidation

Revalidation refers to the process of repeating the original validation activities, either in full or in part, to ensure that the validated status of the plant, equipment, manufacturing processes, and computer systems is maintained. It may involve conducting an investigative review of existing performance data to assess the continued effectiveness and reliability of the validated processes. Revalidation is important to ensure ongoing compliance and to identify any changes or updates needed to maintain the validated state.

2.DRUG PROFILE

Voriconazole is an FDA-approved antifungal medication used to treat certain fungal infections, including esophageal candidiasis and invasive candidiasis. It acts by selectively inhibiting a specific enzyme involved in fungal cell membrane production, leading to fungal cell lysis. It is commonly used in the treatment of opportunistic infections associated with HIV.



Chemical StructureDepiction

IUPAC Name---(2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol

Molecular Formula---$C_{16}H_{14}F_3N_5O$

CLINICAL PHARMACOLOGY

Mechanism of action

Voriconazole, like other azole agents, works by inhibiting the cytochrome P450-dependent 14α-lanosterol demethylation, a crucial step in the synthesis of ergosterol, the main component of fungal cell membranes. While it exhibits fungistatic (inhibiting fungal growth) effects for yeasts, it can be fungicidal (causing fungal cell death) for certain filamentous organisms. This may be attributed to its stronger affinity for lanosterol 14α-demethylase in molds, allowing for a more complete interruption of ergosterol synthesis and subsequent cell death.

Pharmacodynamics

Pharmacodynamics refers to the relationship between drug exposure and its effects. Voriconazole exhibits high efficacy against most Candida species, including C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei. However, some strains of C. glabrata and C. krusei may develop resistance to all available azole antifungals. In susceptibility testing against filamentous fungi using macro- and microdilution methods, voriconazole demonstrates strong activity against A. fumigatus, with over 95% of tested isolates being inhibited at concentrations below 0.5 µg/ml.

Pharmacokinetics

Voriconazole exhibits non-linear pharmacokinetics, and its dose-response relationship shows wide interpatient variability. The therapeutic index is narrow, and serum concentrations are significantly influenced by various drug-drug interactions. It can be administered orally or intravenously.

After oral administration, voriconazole is rapidly absorbed within 2 hours, with over 90% oral bioavailability. Gastric pH does not affect absorption, but food delays absorption and reduces bioavailability by 22%. Therefore, it is recommended to take voriconazole on an empty stomach. Steady-state concentrations are reached after 5-7 days of multiple oral administrations, but a loading dose can reduce the time to steady-state to 1-2 days. Studies have shown non-linear pharmacokinetics, with maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) increasing disproportionately with dose, indicating saturation of its metabolism.

Voriconazole is a major substrate for the CYP2C19 isoenzyme, and genetic polymorphisms can lead to significant differences in plasma concentrations and clinical outcomes. Poor metabolizers and extensive metabolizers may exhibit different plasma concentrations despite identical dosing schedules, and low trough concentrations have been associated with poor clinical results. Plasma protein binding of voriconazole is 58%, and it is distributed widely into tissues with a volume of distribution of approximately 4.6 L/kg.

Since voriconazole is primarily eliminated by metabolism, its non-linear pharmacokinetics may be due to saturation of its metabolism with respect to dose. The variability in plasma concentrations and exposure depends on the genotype of hepatic CYP enzymes, particularly CYP2C19. Homozygous extensive metabolizers have lower exposure than heterozygous extensive or poor metabolizers. Poor metabolizers can have up to four times higher serum voriconazole concentrations than extensive metabolizers. However, no dosage adjustments are currently recommended based on these observations.

The CYP2C19 genotype, along with gender and age, contributes to significant variability in clearance and AUC of voriconazole.

Drug interactions

Co-administration of voriconazole with drugs that affect CYP2C19 activity can have significant effects on voriconazole plasma concentrations. Drugs such as rifampin, rifabutin, phenytoin, carbamazepine, and long-acting barbiturates can reduce voriconazole serum concentrations. Conversely, the levels of rifabutin and phenytoin may be increased when taken with voriconazole, necessitating monitoring of their serum levels.

Voriconazole can also impact the metabolism of other drugs that are metabolized by CYP enzymes, potentially leading to clinically relevant toxicity if the therapeutic index of those drugs is narrow. Co-medication with sirolimus and ergot alkaloids is contraindicated due to potential adverse effects. When voriconazole is used in combination with drugs like cyclosporine and tacrolimus, which are subject to CYP metabolism, monitoring of serum concentrations is necessary as voriconazole can increase their levels. This monitoring is also crucial for HMG-CoA reductase inhibitors (statins), sulfonylureas, vinca alkaloids, calcium channel antagonists, and benzodiazepines when used concomitantly with voriconazole.

4. AIMS AND OBJECTIVES

AIM: CONCURRENT PROCESS VALIDATION OF VORICONAZOLE TABLETS IP 200 MG

OBJECTIVES: The objective of this concurrent process validation of manufacturing process is to generate documented evidence that the method of manufacturing VORICONAZOLE TABLETS 200 MG produces acceptable quality product. The results obtained should indicate that the process adheres to predetermined specifications under typical operating conditions, and in some cases, under worst-case conditions.

The purpose of process validation of VORICONAZOLE TABLETS 200 MG is to establish scientific documented evidence which provides a high degree of assurance that the processes used to manufacture VORICONAZOLE TABLETS 200 MG is capable of consistently producing safe and effective product that meets the established specifications.

To perform Process validation **VORICONAZOLE 200 (Batch size: 25,000 Tablets)**. Concurrent validation of tablet manufacturing process includes major manufacturing steps like dry-mixing, kneading/wet mixing, drying, dry screening lubrication and compression of three successive batches of **VORICONAZOLE 200 MG.**

NOVELTY: The novelty of my research topic is due to the low amount of excipients used in the tablet to make it a stable product. Also, the in-process parameters shall be represented statistically which has not been used to validate the concurrent process validation of Voriconazole tablet till date.

4. RESEARCH METHODOLOGY

a. Concurrent process validation of Voriconazole Tablets IP shall be executed and each step shall beevaluated to determine the critical parameters that may affect the quality of finished product.

b. All the equipment, production facility, analytical method shall be pre-validated.

c. The underlying standard operating procedures, analytical method and batch manufacturing record shall be

predefined.

d.Three consecutive production batches shall be taken for concurrent process validation.

e.Critical processes and their variables are identified in the whole process and the corresponding test points are correlated.

f. The processing parameters and values of the evaluation parameter are generated from actual processing and analysis of the materials, intermediate and bulk as well as finished product as listed under critical parameter identification and acceptance criteria.

g.Extensive sampling at different stages of the validation batches shall be done as per the approved protocol and sampling plan and shall be documented.

h.All required critical parameters and values of validation test points shall be recorded in individual data record form.

i. Deviations to the procedures must be recorded on the data record forms.

j. Samples shall be analyzed as listed in the test points according to a validated analytical procedure.

k.Comprehensive documentation of the batches under validation shall be done.

l. All the test results obtained shall be attached for reference.

m. All data shall be correlated with respect to acceptance criteria and a conclusion shall be drawn if the processes described with their allowed variation are suitable for achieving the product quality with consistency.

Table 1: Batch composition and formula

S. No.	Ingredients	Category	Std.	Mg/Tab	Std. Qty. (Kg)
1.	Voriconazole	Active Pharmaceutical Ingredient	IP	200.0	5.000
2.	Cross Car. Sodium	Disintegrant	IP	15.00	0.375
3.	MCCP-101	Diluent	IP	63.20	1.580
4.	PVPK-30	Binder	IP	6.000	0.150
5.	IPA	Solvent	IP	-	3.0 Lts.
For Lubrication					
6.	Aerosil	Glidant	IP	1.400	0.035
7.	Magnesium Stearate	Lubricant	IP	1.400	0.035
8.	Sodium starch glycolate	Super Disintegrant	IP	13.00	0.325
For Coating					
9.	White Instacoat solution (IC-S-223)	Coating Material	INH	13.60	0.340
10.	Quinoline Yellow lake	Colourant	INH	0.720	0.018
11.	Indigo carmine lake	Colourant	INH	0.720	0.018
12.	IPA	Solvent	IP	-	2.6 Lts.
13.	Methylene chloride	Solvent	USP	-	3.9 Lts.

CRITICAL PROCESS PARAMETER

Following critical stages required to be validated to provide a high degree of assurance for the manufacturing of tablets.

S. No.	Stage	Parameters
1.	Sifting	Sieve Size
		Speed of machine
2.	Dry Mixing	RPM of mixer blade
		Load size
		Total time of mixing
		Uniform mixing by Assay analysis
3.	Wet mixing	RPM
		Load size
		Binder addition time
		Mixing time after binder addition /Total granulation time
		Uniformity of granulated mass (Visual Checking)
4.	Drying	Dryer outlet temperature
		Dryer inlet temperature
		Drying load
		Total drying time
		Weight of the dried granules
5.	Lubrication	Load size
		Speed of equipment (RPM)
		Total time of mixing
		Assay - (individual sample)
6.	Compression	Temperature of area
		Humidity of area
		Machine Details
		Weight variation of 20 tablets
		Average weight of tablet
		Disintegration time
		Friability
		Thickness
		Hardness
		Assay
7.	Coating	% Wt. gain
		Disintegration
		Thickness
		Hardness
8.	Packaging	Forming roller temperature
		Forming roller pressure
		Sealing roller temperature
		Sealing roller Pressure
		Speed of machine
		Assay

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