



Review Article

Cleaning validation in analytical development: Current challenges and future prospectives

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ABSTRACT

Cleaning validation is a prominent and ideal practice which is employed in industrial aspects to provide utmost shielding to develop drug products, so that a cleaning practice removes the particulate matters, chemicals, as well as the contaminant pathogens reside in active ingredients of drug product in a piece of apparatus, which are produced or being manufactured. The cleaning validation is established as the pre-eminent process that ensures the efficiency, safety, consistency of pharmaceutical equipment and manufactured product of assured quality. The utmost cleaning practice during manufacturing of drug substances affords the appropriate operator safety measures, organized calibration, description and routine monitoring of equipments, Sampling procedures, acceptance criteria's and detection limits of analytical methods. This also lead to systematic data analysis for estimating of probable contagions in product batches builds up. Abortive cleaning may lead to adulterated product that may be originated from preceding batches, clean-up agents or other superfluous materials produced during methodology. Hence to avoid the harmful contamination, sources, safety measures clean-in-practice is highly recommended as per regulatory and stability point of view. The present review intensifies the current challenges, basic mechanisms and future implication of cleaning validation in various analytical development firms and research organizations.

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1. Introduction

Cleaning validation is most essential procedure for an integrated documented authentication in the pharmaceutical industry to obtain homogenous safe product development. The key intent of the cleaning validation is to diminish the fractious infection of drug substances and manufactured products by additional explicit drug products where more than one products being manufactured with wide-ranging properties and also adulteration of drug products with new APIs such as instinctive compounds.¹ So it is quite essential to verify and frequently validate the hygienic and cleaning procedures to make assured safety, effectiveness,

quality of the subsequent batches of drug substances and regulatory requirements in API artifact, excipient residues or product development. Pharmaceutical giant's biotech and food manufacturing industries have every time validating subsequent validation protocols of their cleaning process in order to ensure compliance with regulation of cGMP system. Reducing equipment downtime has the potential to impact the efficiency and economics of pharmaceutical production and it quite beneficial for patient safety concern.² The utmost is advantages of cleaning validation are compliance with Code of federal regulations (CFR), detection and rectification of impending problems, before unsuspected troubles, which could compromise the safety and effectiveness- faster remedy of drug products.²⁻⁴ This brief review intensifies the current information about

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the impact of cleaning validation during development processes in pharmaceutical, biotech firms and food beverage industries along with its future prospective.

2. Scope and Challenges of Cleaning Validation in CIP Systems

2.1. Scope and approaches of cleaning systems

During CIP systems, a comprehensive validation scheme or proposals supposed to be pursued which contains: Plan, Do, Check, Act (PDCA) methodology for obtaining ultimate results. The predetermined goal of cleaning validation is to establish and undertaken the dispensation or management of dealing apparatus should be sanitized and washed off time-after-time and, it is employed with cleaned of product, chemicals, microorganisms, as well as allergens, to an adequate intensity, to stop direct cross-contamination of hazards between the developed drug products. The EHEDG guidelines which based on the concept of “Cleaning validation in the Food Industry- General Principles” are a brilliant resource to exploit when monitoring the CIP validation project charter.⁴⁻⁶

2.2. Challenges and adaptabilities of cleaning validation

A strong graphical projection or plan will take account of an assignment or typical Charter which defines the goals of mission and in-details actions, risks to accomplish those targets.^{5,6} A list of adequate machineries are preferred for examination and collection of data for uniform performance decisive factor, metrics, deliverables which will be considered at each stages of following parameters like qualification of equipments, evaluation of hazards, sampling process, analytical techniques, procedures for soiling, CVP, cleaning validation report and its procedures etc.^{3,4} In execution of data's section: Data is collected, according to fixed collection of methods, guidelines (in addition to health and safety) timeframe, as described in the project charter.^{5,6} In checking criteria's: the collected data is compiled and is compared with sequential past records and also against performance and measurement criteria's. Any deficiencies can be addressed and retested prior to the CIP system can be validated. The cleaning validation master plan including policy components, diverse corrective and preventive actions are highly needed to facilitate and congregate the requisite standards. Ultimately these PDAC acceptance limit, including its rationale, specialized cleaning validation protocols and adapted techniques are enormously recommended for monitoring, absolute verification, and change control/revalidation performance.⁶ Now a day's diverse CIP professionals are recommended in pharmaceuticals, biotech, and food industries that employ the rapid arrangement of data collections, comprehensive analysis of master plans, through efficient cleaning

protocols. This methodology can emphasize about several zones for improvements in drug safety, environmental impact and satisfies level of “OEE”. Eventually a documented report ought to be created once the CIP system has been productively and successfully validated as per the recommended FDA and ICH Q9 guidelines (Risk-MaPP baseline guide) which assign a science based limits for APIs.^{7,8}

3. Purpose, Types and Mechanism of Cleaning Validation

3.1. Purpose of cleaning validation

The main purpose and importance of cleaning validation is to establish the efficiency and steadiness of clean-up in a specified pharmaceutical production equipment to avoid cross contamination and adulteration of drug substances and products with other active ingredients like unintended compounds or microbiological contamination, leads to be prevented. The FDA recently posted their new Guidelines to Process Validation. Its rationale and nearly all of its elements are directly applicable to cleaning validation.⁹

3.2. Types of cleaning validation

Similarly, the cleaning validation basically categorized in to three types i.e Batch to batch cleaning, product to product cleaning, and periodic through cleaning. An successful clean in practice (CIP) might delivers standard confirmation that, the sanitizing methods employed inside a facility every time regulates the maximum allowable carryover (MAC) through dosage limits of product (together with impurities and reside intermediates), cleaning agents and extraneous material into succeeding invention to a level that is below the predetermined levels. Generally there are two basic types of sampling that are established. The most enviable is the direct method of sampling of the exterior of the apparatus; another selective method is the employ of rinse-sampling. The prime most process of sampling includes swabbing or rinsing or may different alternative techniques of interest like direct extraction pathways for determination of soluble and insoluble residues.^{9,10} Their detail applications of types of sampling methods associated with effective cleaning validations is demonstrated in Table 1. As the AMV having utmost sensitive to detect the contaminants or residuals based upon the limits of detection. The residual limits may be ascertained based upon the therapeutically or physiological activity of API. Validation of cleaning Procedures of API should be relied upon solubility as well as strength, toxicity and stability potential. Some additional types of cleaning validations are also enlisted like ultrasonic cleansing are the specific tools which runs by ultrasonic cleaners performed by revealing load items like surgical instruments to the waves of elevated frequency in a fluid (liquid) cleaning medium.^{10,11}

Table 1: Types of sampling methods used in effective cleaning validation

S.No.	Various Sampling Methods	Merits	Shortcomings	Significance
1.	Swab Sampling	<ol style="list-style-type: none"> 1. Dissolve and substantially remove the sample. 2. Adaptability to widespread variation of surfaces. 3. Cost effective and extensively available. 4. Might permit sampling of a defined area. 5. Valid to active, microbial, and cleaning agent residues. 	<ol style="list-style-type: none"> 1. An Invasive method that may introduce fibers. 2. Results may be technique dependent. 3. Swab material and design may inhibit recovery and specificity of the method. 4. Evaluation of large, complex and hard to reach areas difficult 	<p>It usually requires materials which are absorptive & to physically wipe the surface and recover the analyte. Because the need to physically wipe the surface was the favoured method that is readily accessible to human hand or arm.</p>
2.	Rinse Sampling	<ol style="list-style-type: none"> 1. Adjustable to on-line monitoring 2. Easy for illustration 3. Non-intrusive and Less technique dependent than swabs 4. Appropriate for actives, cleaning agents and excipients 5. Allows sampling of a large surface area 	<ol style="list-style-type: none"> 1. Limited information about actual surface cleanliness in some cases. 2. May lower test sensitivity. 3. Residues may not be homogeneously distributed. 4. Inability to detect location of residues. 5. Rinse volume is critical to ensure accurate elucidation of Results. 6. Might be problematic to precisely define and regulate the areas sampled, therefore usually used for rinsing a whole piece of apparatus, such as vessel. 	<p>Rinse sampling does not work mechanical action on the surface and the sample is composed as a final rinse or rinse applied explicitly for collecting a validation sample.</p>
3.	Placebo Sampling	<ol style="list-style-type: none"> 1. Placebo contacts the same surfaces as the product 2. Applicable for hard-to-reach surfaces 3. Requires no additional sampling steps 	<ol style="list-style-type: none"> 1. Difficult to determine recovery (contaminants may not be evenly distributed in the placebo) 2. Lowers analytical specificity and inhibits detect ability. 3. Takes longer and adds expense since equipment must be cleaned after the placebo run. 4. Placebos must be appropriate for each potential product. 	<p>Placebo is documented as both potential cleaning methods and potential sampling techniques. Placebo material comprises of all typical excipients but not the active ingredient. And the placebo batches were passed through a same line so that it will have opportunity to scrub of the clean system.</p>
4.	Direct Sampling	<p>The gain of using these techniques is that sampling and investigation will be taking place in one step and there will be no real forfeiture of sampling system.</p>	<p>The contaminant might not be soluble or may be materially occluded in the equipment.</p>	<p>It is completed by using FTIR or photoelectron emission methods. By employing these techniques, specific spectra obtained from residue remaining on the surface will unswervingly quantify the quality of the surface.</p>

3.3. Mechanism of cleaning validation

The basic cleaning Mechanism mostly includes the process like Dissolution (adding up Alkaline or acidic solvents, aqueous, non-aqueous solvents or a combination of both aqueous and non-aqueous solvents due to the solubility characteristics of the materials) in order to can enhance dissolution rate.^{9,10} Uniform brushing, in-depth scrubbing and applications of pressurized water to eradicate particulates, Instead of this other useful mechanisms includes detergency by the applications of surfactants, wetting agents, solubilizers, emulsifiers, dispersants. Chemical-redox reactions involving reduction followed by hydrolysis.^{11–13}

4. Multivariate Applications of Cleaning Validation in Various Fields

The concept leads to avoid numerous severe troubles and also functional in related studies like packaging component cleaning validation according to regulatory basis. In numerous conditions the similar apparatus might be utilized for dealing out diverse drug products. So in order to avoid cross infection of the following pharmaceutical product, adequate cleaning procedures are essential, and its importance is summarized.¹⁴ The applications of CV is observed and quite useful for Govt. regulations and its authorities, food, beverage, healthcare research labs, business organizations, to obtain high assurance of product quality, integrity, batches integrity, minimization of costs quality, fewer down time, product batch failures and can function efficiently.^{14,15} The schematic diagram elucidating various approaches of cleaning validations is depicted in Figure 1.

4.1. Applications of CV in analytical research and development

The major applications of Cleaning validation can be observed in Analytical developments in Healthcare and Pharma Industries, During AMV, the accuracy study of the method can be performed by using different 10cm²dimension using categochees integrity, reusing of apparatus or equipments, rise of plates like glass, stainless still, PEG, rubber, asbestos, granite are used in especially in FMCG industries. By the cleaning validation method can be developed using various AQbD software's like Design Experts, Fusion Product development, Minitab through Analytical QbD approach.^{16,17} As the 21st century quality scheme by USFDA, the conception of Quality by Design (QbD) has taken gigantic significance in attaining the preferred quality with safer robust product and sound science quality risk management.^{18–20} This can also be developed by using various sophisticated analytical instruments like (HPLC, UPLC, UFLC)^{21–25} and hyphenated techniques (LC-MS, GC-MS, ICP-MS,

ICP-OES etc.).^{26–30} The reagents and solvents like: IPA, Water, IPA 70%, (Ethanol 70%), (0.02 N NaOH), 0.2 N HCl, 0.02N HNO₃, Ethyl acetate, water surfactants SLS, SDS of manufacturing and fillings. Among all the reagents and solvents water is the most advantageous as, it is common and practical solvent non-toxic, non-expensive, does not leave residues, and among all it is eco-friendly. Other chelants solvents includes (acidic EDTA, bases like NaOH, KOH), Acid-Glycolic acid, citric acid, oxidants NaOCl, H₂O₂ etc. The USFDA specified and addresses the expects firms to have authorized written-based SOPs signifying the cleaning process used for various pieces of equipment's.^{26–31}

5. Conclusion

As per current regulatory prerequisite, it is quite essential to have efficient cleaning program in manufacturing of dosage forms and types of equipments used for experimental analysis in research laboratories. In several conditions, it has been noticed that, the similar machinery can be utilized for handing out miscellaneous products. Conversely, the basic reason is to make the products produced that should not be unadulterated and contamination free as the clean-in-practice can establish a documented verification by a strong guarantee that one can constantly sanitized the method or equipment's to predestined and adequate limits. This review critically focused towards all needful aspects, assigned with various significant approaches of cleaning validation like its route mechanism, cleaning and sampling procedures, needful solvents, equipments, and the basic elements involved in cleaning validation.

6. Current and Future Prospectives

In today's scenario, rapid and robust analytics methodology is highly preferred for pharmaceutical products by analytical developed which states the steps of cleaning validation for enhancement of safer and quality product development. The essence of two significant approaches i.e. decisions have to be based on sound scientific knowledge and during assessment tools of quality risk management (QRM) have to be used. Current trends in determining a realistic and secure founding of a science-based maximum allowable carryover (MAC) assessment of an APIs, that has been stirring, as the innovative recommendation entitled, Risk-based manufacture of pharmaceutical products" (so-called Risk-MAPP) was issued by the ICH stability guidelines which encloses also the philosophy of QRM. Recent advancements of cleaning validation also signifies the product-lifecycle approach described as process validation as per FDA concern. This is intended to help in the development of compliant, effective, and efficient cleaning validation processes and programs following a structured lifecycle approach. Successful cleaning validation is not

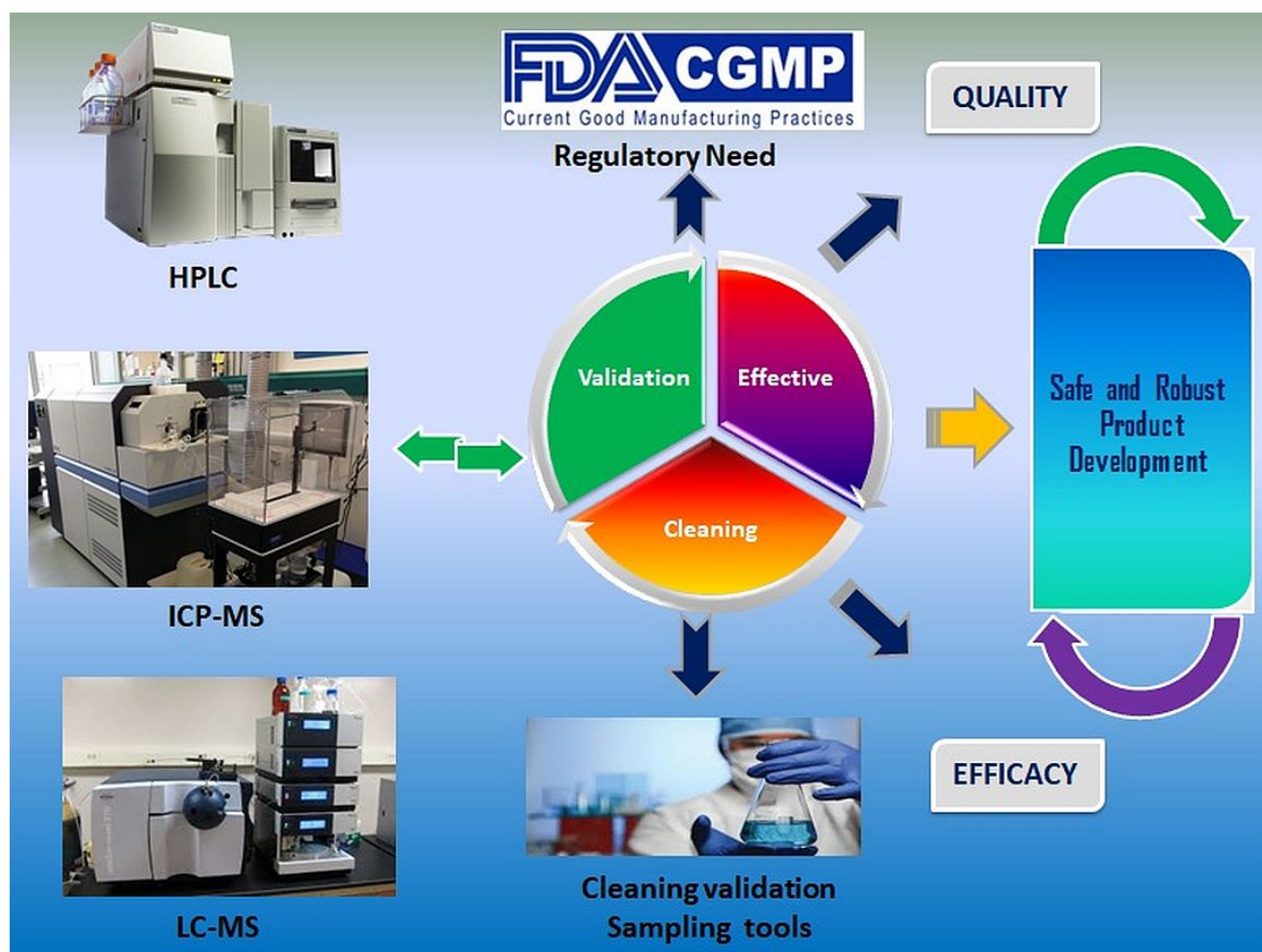


Fig. 1: Schematic diagram indicating various approaches of cleaning validation

only a regulatory liability for industrialized firms and research based organizations, but also it makes a first-rate sound business sense, by stopping batch failures of the cleaning systems that in turn effect in financial losses counting materials, misplaced timings, manpower, as well as the cost of investigations and documentation allied with these failures.

7. List of Abbreviations

CIP: Clean in practice; CV: Cleaning Validation; EHEDG: European Hygienic Engineering and Design Group; CVP: Cleaning validation protocol; OEE: Overall Equipment Effectiveness; FDA: Food and Drug administration; AMV: Analytical Method Validation; IPA: Isopropyl alcohol; ICP-MS: Inductively coupled plasma mass spectrometry; LC-MS: Liquid chromatography mass spectroscopy; GC-MS: Gas chromatography mass spectroscopy; PEG: Poly ethelene Glycol; SLS: Sodium Lauryl Sulfate; SDS: Sodium dodecyl Sulfate; MAC: Maximum allowable Carryover.

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9. Conflicts of Interest

Authors have no conflicts(s) of interest.

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References

1. Pandharmise PN, Shahzad N, Kamble A, Bhagat MP. Cleaning validation for oral solid dosage form and its Importance in Pharma Industry. *Res J Pharm Technol.* 2011;4(9):1449–54.

2. Ghosh A, Dey S. Overview of Cleaning Validation in Pharmaceutical Industry. *Int J Pharma Qual Assuran.* 2010;2(2):26–30.
3. Maurya S, Goyal D, Verma C. Cleaning Validation in Pharmaceutical Industry- An Overview. *PharmTut.* 2016;4(9):14–20.
4. Health products and food branch inspectorate guidance document cleaning validation guidelines guide-0028; 2008.
5. Sakthivel LP, Prakash STNK. Cleaning Validation and its Importance in Pharmaceutical Industry. *Pharm Times.* 2010;42(7):21–5.
6. Available from: <https://diversey.com/en/blog/validation-challenge-cip-cleaningprotocols#:~:text=How%20to%20Validate%20your%20CIP.>
7. FDA Guide to Inspections of Validation of Cleaning Processes. Food and Drug Administration; 1993. Available from: <https://www.gmp-compliance.org/guidemgr/files/1-2-16.pdf>.
8. ISPE Baseline® Pharmaceutical Engineering Guide, Vol. 7 – Risk-Based Manufacture of Pharmaceutical Products, International Society for Pharmaceutical Engineering (ISPE), First Edition, September 2010. Available from: www.ispe.org.
9. Guidance for Industry Process Validation: General Principles and Practices, January 2011.
10. Available from: <https://www.sciencedirect.com/topics/chemistry/ultrasonic-cleaning>.
11. Galatowitsch S. The Importance of Cleaning Validation. *Cleanrooms.* 2000;14(6):19–22.
12. Economic Control of Quality of Manufactured Product. In: Guidance for Industry Process Validation: General Principles and Practices. D. Van Nostrand Company; 1931.
13. Orchard T. Specification Setting: Setting Acceptance Criteria from Statistics of the Data. *BioPharm Int.* 2006;19(11):40–5.
14. Walsh A. “Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part I,” *Pharmaceutical Engineering*; 2011. Available from: www.ispe.org.
15. Fredrick R. The Basic Facts of Cleaning Validation. Canada: Pharmainfo.net; 2004. Available from: <http://www.pharmainfo.net/reviews/basic-facts-cleaning-validation>.
16. Chitra K, Murthy N. A Review Article on Cleaning Validation. *Int J Pharm Sci Res.* 2013;4(9):3317–44.
17. Jena BR, Panda SP, Umasankar K, Swain S, Rao GSNK, Damayanthi D, et al. Applications of QbD-based software’s in Analytical Research and Development. *Curr Pharm Anal.* 2020;16(1). doi:10.2174/1573412916666200108155853.
18. Swain S, Parhi R, Jena BR, Babu SM. Quality by Design: Concept to Applications. *Curr Drug Discov Technol.* 2019;16(3):240–50.
19. Singh B. Quality by Design (QbD) for holistic Pharma Excellence and Regulatory Compliance. *Pharm Times.* 2014;46(08):26–33.
20. Swain S, Jena BR, Madugula D, Beg S. Application of Quality by Design Paradigms for Development of Solid Dosage Forms. *Pharm Qualby Desig: Princip and Appl.* 2019;p. 109–130.
21. Sahu PK, Ramiseti NR, Cecchi T, Swain S, Patro CS, Panda J. An overview of experimental designs in HPLC method development and validation. *J Pharm Biomed Anal.* 2018;147(147):590–611.
22. Jena BR, Babu SM, Pradhan DP, Swain S. UPLC Analytical Method Development and Validation for the Simultaneous Estimation of Paracetamol and Caffeine Capsules Dosages Form. *Pharm Regul Affairs: Open Access.* 2017;06(01):1–9.
23. Aubry AF, Tattersall P, Ruan J. Development of Stability Indicating Methods. In: K HB, editor. Handbook of Stability Testing in Pharmaceutical Development. Springer; 2009.
24. Beg S, Kohli K, Swain S, Hasnain MS. Development and validation of RP-HPLC method for quantitation of amoxicillin trihydrate in bulk and pharmaceutical formulations using box-behnken experimental design. *J Liquid Chromatography Relat Technol.* 2012;35(3):393–406.
25. Pradhan DP, Annapurna MM. Stability indicating LC-TQ-ESI-MS method for the quantification of Racecadotril in presence of its degradants. *Res J Pharm Technol.* 2019;12(7):3437–43.
26. Kumar SV, Rudresha G, Gurav S, Zainuddin M, Dewang P, Kethiri RR. Validated RP-HPLC/UV method for the quantitation of abiraterone in rat plasma and its application to a pharmacokinetic study in rats. *Biomed Chromatography.* 2013;27(2):203–7.
27. Pradhan DP, Annapurna MM. Study of forced degradation behavior of fluorometholone by reversed-phase high performance liquid chromatography. *Int J Green, Pharm.* 2018;12(3):675–9.
28. Rao RN, Talluri MVNK. An overview of recent applications of inductively coupled plasma-mass spectrometry (ICP-MS) in determination of inorganic impurities in drugs and pharmaceuticals. *J Pharma Biomed Anal.* 2007;43(1):1–13.
29. Fischer L, Zipfel B, Koellensperger G, Kovac J, Bilz S, Kunkel A. Flow injection combined with ICP-MS for accurate high throughput analysis of elemental impurities in pharmaceutical products according to USP <232>/<233>. *J Pharm Biomed Anal.* 2014;95:121–9.
30. Chauhan A, Goyal MK, Chauhan P. GC-MS Technique and its Analytical Applications in Science and Technology. *J Anal Bioanal Tech.* 2014;5(6):1–5.
31. Annapurna MM, Baswani R, Pradhan DP. New Stability Indicating RP-UFLC Method for the Determination of Flucytosine -An Anti-Fungal Agent. *Acta Sci Pharm Sci.* 2019;(3):38–46.

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