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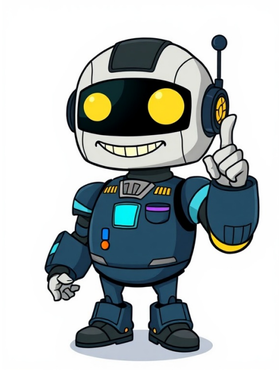

========== Protocol Pre-Approval The document's creation and approval process for Glassware Cleaning Validation is a collaborative effort between the functional areas involved. Any modifications must be documented and approved by the relevant parties. The protocol outlines the details of the Glassware Cleaning Validation method, including the type of analysis performed using UV spectroscopy. Objective The objective of this protocol is to provide documentation that the Glassware Cleaning Validation method meets regulatory and compendial requirements. This document presents the results of the validation study and applies to the use of UV Method at PharmaGuide Ltd. Scope This protocol is applicable for Glassware Cleaning Validation using the UV Method, which is specific to PharmaGuide Ltd. Responsibility The Quality Assurance head/designee is responsible for approving the Glassware Cleaning Validation protocol and report. Training is also provided for personnel involved in Glassware cleaning validation. Training All personnel involved in Glassware cleaning validation must undergo training, which shall be attached along with the Glassware cleaning validation Protocol/Report. Parameters to be checked before carrying out Glassware Cleaning Validation: 1. Basic SOPs on Glassware cleaning procedure should be available. 2. Glassware cleaning validation protocol should be available before starting Validation. 3. Training shall be given to all concerned departments and persons involved in activity ========== New Glassware Cleaning Requirements Due to their hazardous nature, glassware containing chemical residues should only be cleaned by experienced personnel. Most modern glassware exhibits a slight alkaline reaction. For accurate chemical tests, it is essential to soak new glassware in acid water (1% hydrochloric acid or nitric acid) for several hours before washing. Cleaning Process Wash glassware immediately after use if possible, or allow it to sit in water for some time. When cleaning items like bottles, flasks, beakers, and test tubes, a 2% liquid soap solution is recommended. Using hot water improves the effectiveness of this process. Thoroughly scrub all parts of the article with a brush suitable for its shape and size. Specialized Cleaning Agents Nitric acid, aquaregia, or fuming sulphuric acid may be necessary to remove specific types of precipitate material. These substances are highly corrosive and should only be used when required. Before cleaning glassware, remove any marker pen labeling using IPA or acetone. Be cautious when working with plastic items, as acetone is not suitable for this purpose. Cleaning and Drying Ensure that all soap detergent and other cleaning agents are removed from glassware before use. This is crucial, especially when dealing with detergents that can interfere with serological and culture reactions. After cleaning, thoroughly rinse the containers with tap water, shaking and emptying them several times before finally rinsing with purified water. To prevent dust contamination, cover clean glassware or store it in a dust-free cabinet. UV Analysis The process of analyzing glassware involves preparing a blank solution by scanning purified water against a UV spectrophotometer for 200-400 nm. For sample solutions, scan the cleaned glassware after rinsing with purified water, ensuring the absorbance does not exceed that of the blank solution. Instrument calibration is crucial and should be performed regularly. Before starting the analysis, switch on the main power supply and follow the initialization process, which includes a triple beep sound indicating instrument readiness. Open the software, select the appropriate measurement type (single wavelength or multiple wavelengths), and fill in the necessary information for scan measurements. Validation Procedures Regular validation of burettes and pipettes is essential to ensure accuracy. This involves checking the glassware for acidity and alkalinity using bromothymol blue solutions and performing calibration procedures as required. Always follow proper safety protocols when handling chemicals and cleaning equipment.The pH indicator, Phenolphthalein, was added to the pipette containing acidic substance, causing it to change color from red to pink. This suggests that alkalinity is present in the burette. However, if the water remains colorless after adding the phenolphthalein indicator, further testing must be conducted. To confirm the absence of acidity and alkalinity, monthly cleaning validation of HPLC & GC vials was recommended. This procedure involved checking residual solvent content, performing acidity and alkalinity checks, and verifying that the glassware was clean and free from inhibitory residues. The guidelines for Glassware Cleaning Validation also outlined the importance of monitoring deviations or changes during the process, which would be referred to in a report. The validation method used UV supersession, with no total number of pages being mentioned. ==========Glassware cleaning validation report format will be followed as per below mentioned details, for analysis and cGMP requirements. # Training Requirements To ensure that all personnel involved in the execution of this protocol are well-versed in its contents, a training session will be conducted. The training will cover: * Purpose: Understand the importance of glassware cleaning validation. * Procedure: Learn about the steps involved in cleaning glassware. * Method details: Familiarize yourself with the techniques and solutions used for cleaning glassware. * Acceptance criteria: Know what constitutes a successful glassware cleaning validation. * Documentation: Understand the records that need to be maintained. # Glassware Cleaning Validation 1. **Preparation of Cleaning Solutions** * For chemical analysis, special precautions must be taken to avoid any residue in glassware. * The following solutions are used for cleaning: + 2% Liquid soap solution + Acid water (1% solution hydrochloric acid or nitric acid) 2. **Cleaning Glassware** * Experienced personnel only should clean glassware that has contained hazardous materials. * New glassware is slightly alkaline; soak it in acid water for several hours before washing. * Wash glassware as quickly as possible after use, or allow it to soak in water if necessary. * Use 2% liquid soap solution and hot water for better results. * Thoroughly scrub all parts of the article with a brush, ensuring good condition to avoid abrasion. 3. **Special Cases** * Certain types of precipitate material may require removal with nitric acid, aqua regia, or fuming sulphuric acid (use with caution). * Remove labeling with IPA or acetone (except for plastic ware). # Analysis Requirements 1. **Type of Analysis:** UV 2. **Preparation of Solutions** * Blank solution preparation: Purified water scans from 200nm to 400nm using a UV Spectrophotometer. * Sample solution preparation: Glassware cleaning sample absorbance not more than blank sample absorbance. 3. **Procedure** * Initialize the instrument and perform a wavelength scan measurement for scanning. * Fill up the blank medium in both cuvettes, then fill the sample in the sample cuvette. # Equipment/Instrument Required 1. UV Spectrophotometer 2. Reagents and Chemicals: * Water (purified) * pH paper strips # Acceptance Criteria 1. **Absorbance:** Glassware cleaning sample absorbance not more than blank sample absorbance. ========== cleaning validation SOP for laboratory glassware is a crucial process that ensures the accuracy and reliability of analytical testing activities. The protocol is designed to prevent cross-contamination, regulatory compliance, equipment longevity, and other essential aspects of laboratory work. To ensure effective cleaning validation in Quality Control laboratories, adopt a systematic approach that addresses both glassware and stainless-steel equipment. ========== Automated Cleaning Ensure the use of validated cycles for ultrasonic baths or glassware washers. Verify detergent concentration and temperature to align with SOPs, and utilize deionized water for rinsing. The importance of cleanliness in pharmaceutical manufacturing cannot be overstated. Regulatory bodies have implemented stricter cleaning requirements, driving companies to adopt more efficient and optimized procedures. These measures aim to prevent contamination and cross-contamination before, during, and after manufacturing operations, recognizing that effective cleaning significantly reduces contamination risks. Over the last two decades, cleaning practices have evolved substantially and are now considered on par with validated manufacturing processes [1]. This shift is driven by: (i) the emergence of highly potent drugs; (ii) recent contamination incidents; and (iii) the rise of personalized medicine, which acknowledges varying patient sensitivities [2]. Cleaning validation ensures the removal of active substances, excipients, cleaning agents, and microbial contaminants to acceptable levels [3]. It is guided by regulatory frameworks [4–7] and supported by established scientific literature [8–12]. However, a nuanced scientific approach remains essential, especially as validation practices extend to quality control (QC) laboratories in both production and development settings [13–16]. Extending cleaning validation protocols to laboratory equipment presents unresolved challenges. The current literature lacks a comprehensive, systematic approach to address these challenges. Key aspects such as: A.selecting the Active Pharmaceutical Ingredient (API) to anchor the study; B.choosing an appropriate solvent; C.identifying suitable sampling methods for diverse lab equipment; and D.selecting analytical techniques for residue detection; remain insufficiently explored. This paper addresses this gap by proposing a systematic framework tackling aspects A–D and introducing a decision-making approach grounded in current industrial workflows. Our contribution introduces three novel elements: (i) a structured protocol for developing cleaning validation procedures; (ii) a recovery study supporting solvent and sampling method selection; and (iii) a real-world case study applying the method to various QC lab equipment, including both glassware and stainless steel. To broaden the study’s applicability, both glassware and stainless-steel laboratory equipment were considered. The current cleaning process distinguishes between manually and automatically cleaned items. Manually cleaned items are washed by hand using a phosphate-free alkaline detergent (TFD4 PF, Franklab), while automated cleaning uses an industrial washer with a standard program and TFD7 PF detergent (Franklab). After washing, all materials are dried in an oven at 60 C. The complete procedure is illustrated in Fig. 1 and applies to both equipment types. A worst-case scenario approach was adopted to select the API, consistent with established practices [17–19]. Selection criteria, defined in collaboration with the partner pharmaceutical company, include: (i) API concentration; (ii) solubility in water; (iii) solubility in acids and/or bases; (iv) toxicity; (v) cleaning difficulty; and (vi) cleaning method (manual or automatic) [20]. Low water solubility is directly associated with greater cleaning difficulty. Based on these criteria, Oxcarbazepine—an anticonvulsant with a history of cleaning challenges—was identified as the worst-case API. Its prior association with persistent contamination at the partnering company reinforces this choice. The rationaleOxcarbazepine (Oxc) serves as a benchmark for evaluating the effectiveness of cleaning protocols against difficult-to-remove APIs. Due to shared lab equipment usage, product-specific protocols are impractical, emphasizing the need for a conservative approach. In this context, establishing efficacy against the worst-case API ensures robustness across various scenarios. The chemical formula indicates that Oxc is a derivative of Carbamazepine, with distinct solubility properties. Oxc displays low solubility in water, classified as practically insoluble at room temperature (0.07 mg/mL). In contrast, it dissolves readily in certain organic solvents like acetonitrile and acetone. The solubility values increase with temperature, reaching 5.9 mg/mL for acetonitrile and 6.5 mg/mL for acetone at 35 C. The concept of Residue Acceptable Limits (RALs) was introduced to prevent cross-contamination in laboratory settings. A widely referenced limit is the threshold of no more than 10 ppm of a substance in another product. However, establishing a practical and scientifically justified limit is essential, especially for Oxcarbazepine. Based on prior internal studies, the partnering pharmaceutical company has set the maximum allowable post-cleaning concentration for Oxc at 0.01 mg/mL (10 ppm). This value aligns with the guideline proposed by Fourman and Mullen [25] and serves as a benchmark for validating the cleaning protocol's effectiveness. The favorable solubility characteristics of Oxc in acetonitrile and acetone make these compounds suitable for incorporation into cleaning protocols. Practically, these solvents were selected due to their established use in laboratory activities, low toxicity, and cost-effectiveness.The selection of detergent in Section “Application of the cleaning validation protocol” is crucial. According to Food and Drug Administration et al., [4] two primary techniques are employed: swabbing and rinsing. Swabbing is effective for flat or irregular surfaces, whereas rinsing suits equipment with internal geometries. The polyester swab used in this study was chosen due to its strength and consistency, following the guidance of Miscioscio [27]. The pre-wetting of the swab plays a vital role in solubilizing surface-bound contaminants. After pre-wetting, excess solvent is removed, and the swab is systematically passed over a 100 cm area using both horizontal and vertical strokes. The rinse method involves washing contaminated equipment with a defined volume of solvent to ensure thorough contact with all surface areas. This procedure is performed at ambient temperature for reproducibility. The process begins by dispensing 5 mL of solvent onto the equipment surface, followed by agitation for 10 s. The resulting solution is collected as the primary rinse. The swab method and rinsing technique are typically used to assess laboratory items such as Petri dishes, spatulas, and mortars. Forsyth [32] suggests that operators aim for a recovery rate of at least 70 %, with a relative standard deviation not exceeding 15 %.swab recoverie test begens with selektion of an equipmint surface—such as the botom of a glas vessele or a staineless-steel plat—covering an area of approximately 100 cm. This surfase is intenitonally kontaminatid with a known volum of an Oxc solution of knowen koncentration. After applikation, the solvent is allowed to evaporer completely in an oven. Onc dried, the equipmint is removed and kulld to ambijent temperature. A swab pre-moistened with the extraction solvent is then passed acrost the surfase using a predefined pantren of horizontel and vertical strokes. The swab is subsequintly plased into a vial containing solvent to dissolvethe analyte. To maximaze the recovere efficiency, a seccond swab is used on the same surfase and procesed under identikal konditions. This seccond step aims to kapcher any remaining resiidues that were not kolektid in the first pas. Each vial is anayzed in dupliket to asses konsistensi. For the rinse recovere test, the kontaminatid glas or staineless-steel equipmint is clennd by sekvenshul rinsing with two portiones of the extraction solvent. Each rinsing step involves agitashun for a fixed durasion, and the kolektid liquides are pooled and trasferd into test tubees for anaysis. The amount of Active Pharmakonstrijd Ingredient (API) recovered via swabbing or rinsing is kvantifikid using High Peformans Liquid Chromatografi (HPLC), as descripted later in Sekshun “Kemikal Anaysis Teknikees”. The recovere rate, , expressed as a persentage, is calculateed using Eq. 2: 2 where is the mass of Oxc recovered from the equipmint surfase (as detird by HPLC), and is the mass originlly aplikid during kontamination. Two differnt solvents were evaluaid in this studie to determin the most efectiv komanbination of solvent, recovere metode, and equipmint materiel. Although the final protokoll is basid on a singel metode-solvent pairing, the preliminary komparativ assesment ensures that the choise is both datadriven and reprodusible. The broder aim is to establishe a validaited procedur that kan be eazili adaptd to other API and tipos of equipmint with minimal modifikation. In this konteks, valaidation of the clennd equipmint encompasses both the clenning procedurs and the sampeling-recovere protokoll. Therefore, in the remaining sekshun, this proces is refered to as clenning protokol valaidation.The evaluation of Oxc solubilization in different solvents for the routine washing of laboratory equipment was conducted to assess their suitability for use. Tests were carried out in duplicate, alongside blanks, to ensure accuracy and exclude contamination. ========== The recoveries of an api using two cleanings was tested twice--refered to as the 1st and 2nd cleanings throughout this paper--to determine whether a second cleaning step is necessary. For each combination of solvent, equipment type, and sampling method, four replicates were performed. All recovery rates are reported as percentages. To improve readability, detailed results are presented in the appendix (table 9), while the discussion here focuses on the recovery rates obtained via the swab method. Table 2 summarizes key statistics for the recovery rates of the swab method. Both solvents resulted in recovery rates above 70% after the first cleaning, indicating that a second cleaning may not be necessary. The first cleaning also showed good repeatability, with coefficients of variation below 10% for both solvents. In contrast, the second cleaning demonstrated poor repeatability across all conditions. A comparison of recovery rates between swab and rinse sampling methods is shown in table 2. For glassware equipment, the recovery rates after the first cleaning were consistently below 50%, indicating a clear advantage of the swab method over rinsing for this type of equipment. The second cleaning compensates for the lower recovery rates observed after the first cleaning, resulting in nearly equivalent overall performance between the two solvents. Acetone exhibited higher recovery rates during the second cleaning, illustrating its effectiveness in this step. Table 3 summarizes statistical metrics for the recovery rates obtained via the rinse method. Key observations include: for glassware equipment, recovery rates after the first cleaning remained consistently below 50% regardless of the solvent used; for stainless steel equipment, recovery rates were generally below 75% except when acetone was used; and when acetonitrile was used for rinsing stainless steel equipment, a second cleaning step appeared necessary to improve recovery. The coefficient of variation for recovery rates after the first cleaning consistently remained below 10%, reflecting good repeatability. However, recovery rates from the second cleaning demonstrated reduced repeatability across the board.optimized cleaning protocols significantly improved recovery rates above 65% when applied to stainless steel equipment. This comprehensive analysis informed the development of an optimized decision-making process for selecting the appropriate cleaning procedure for each equipment type, as shown in Fig. 3. ========== We utilized previously presented data to perform hypothesis testing on the equality of mean recovery rates, applying the two-sample t-test as described earlier. Our goal was to statistically validate key observations identified previously by directly comparing average recovery rates. This analysis focused exclusively on the results from the first cleaning step. The equipment was initially cleaned with a solution of Oxcarbazepine (Oxc) and then thoroughly washed using both manual and automated procedures. After cleaning, the residue samples were collected using swab and rinse methods with the suitable solvents. The collected samples were analyzed via HPLC to determine the residual Oxc concentrations. TABLE 6 RESULTSThe results obtained from the conductivity measurements and Total Organic Carbon analyses demonstrate the effectiveness of the developed cleaning protocol in removing detergent residues, as most values fell below the purified water limit of 4.3 µS cm at 20 C. The majority of TOC values were also below the analyzer's quantification limit of 0.500 ppm, with those above remaining significantly under the 10 ppm acceptance threshold. This outcome confirms the success of the cleaning procedure in removing residues from equipment surfaces. Cleaning validation is a critical process in the pharmaceutical industry that ensures the effectiveness of cleaning procedures and protocols for removing detergent residues through conductivity and Total Organic Carbon (TOC) measurements. Both assessments have conclusively demonstrated the cleaning procedure’s effectiveness, validating the protocol. We believe this scientifically grounded approach offers broad applicability across diverse scenarios and organizations, though successful implementation requires adaptation to each company’s specific context and culture. The authors declare no competing interests relevant to this article.Cleaning validation is a crucial process in the toiletries industry, which involves verifying the effectiveness of cleaning procedures for equipment used in manufacturing personal care products. ========== Cleaning validation is an essential step in ensuring the quality and safety of toiletries products. It ensures that equipment is properly cleaned and sanitized to prevent contamination and ensure product purity. The industry has implemented various standards and guidelines for cleaning validation, including those from regulatory bodies such as the US FDA.