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A REVIEW ON CLEANING VALIDATION SAMPLING TECHNIQUES

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ABSTRACT

Pharmaceutical industries are vital segment of healthcare system. Manufactures of products which are life-saving, life maintaining drugs. Not to fail its client by releasing substandard or adulterated drugs. Quality product should be maintained throughout its product lifecycle. It is essential to validate and maintain all the critical process parameters within the limit as per specification. So it is essential to establish adequate equipment cleaning procedures to prevent cross contamination due to remnants of product residues. In Cleaning Validation, Sampling is Very crucial thing for any sample. Mainly three types of techniques are there like Swab, Rinse & Visual.

KEYWORDS: Cleaning Validation, Procedure, Swab, Rinse, Visual.

INTRODUCTION

Cleaning Validation is documented evidence which gives a high degree of assurance that cleaning procedure should consistently clean a system or a piece of equipment to predetermine and acceptance limits. Cleaning validation is required to verify the effectiveness of cleaning procedures and to ensure no risks are associated with cross contamination of active ingredients or detergent/sanitizer.[1-3] Equipment cleaning validation procedures are mainly used in pharmaceutical industries to prevent contamination of drug products; hence it is critically important as per federal and other standard regulations. The most important benefit of conducting validation study is identification and correction of potential problems that are previously unsuspected, which may compromise with quality of subsequent batches of drug product. The basic need of quality assurance that product produced must meet the quality requirements; i.e. Safety, Identity, Strength, Purity and Quality.[4, 5]

There are different levels or degrees of cleanliness required in pharmaceutical operations and naturally the specifications for each of the cleaning will differ substantially. Cleaning validation procedures are carried out in order to ensure that product residues are within acceptable limits after the cleaning process. The product residues which are in highly diluted state after rinsing procedure. This makes it difficult to find appropriate analytical methods that are sensitive enough to detect the product residues. It is advantageous that analytical method selected to be simple, accurate and give results quickly.[6, 7]

Pharmaceutical products and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, cleaning agents, microorganisms or by other material (e.g. air-borne particles, dust, lubricants, intermediates, auxiliaries). In many cases, the same equipment may be used for processing different products. To avoid cross contamination of the pharmaceutical product, adequate cleaning procedure must be strictly followed and validated. This applies equally to the manufacture of pharmaceutical products and active pharmaceutical ingredients (APIs). In any case, cleaning process has to be designed such a way thatcontamination is reduced to an acceptable level.[3]

The first step in designing a cleaning validation study is to define the key elements-products, equipment, manufacturing processes, cleaning procedures, acceptance limits, sampling and testing procedures, personnel and responsibilities. The next step includes designing the cleaning validation process, generating the protocol and conducting the study.[8] The cleaning of "difficult to reach "surface is one of the most important considerations in equipment cleaningvalidation. Equipment cleaning validation in an API facility is extremely important as cross contamination is one of the pharmaceutical dosage forms, will multiply the problem. Therefore, it is important to do a step-by-step evaluation of API process to determine the most practical and efficient way to monitor the effectiveness of the cleaning process. It is necessary to validate cleaning procedure for the reasons like:(1) it is regulatory requirement in ActivePharmaceutical Ingredient product manufacture. (2) It is prime customer requirement since it ensures the purity and safety of the product. (3) It also assures the

quality of the process through an internal control and compliance. Once the cleaning procedure for a particular piece of equipment (for a particular product following a specific manufacturing process) is validated, it should consistently produce the same results.

TYPES OF CLEANING PROCEDURE

Product Change over from one batch to next batch of same product/potency and of similar product with ascending potency with same colour. Cleaning procedures involves removal of powder of previous product by dry cleaning procedure by using vacuum or lint free cloth.[6]

For changeover of products with different API / colour, descending potency, after maintenance equipment, after production of several batches of same product and when next product batch is not known. Here the cleaning procedure involves removal previous product residues by dry cleaning procedure and then with wet cleaning procedure using water as cleaning solvent.[6] Cleaning is like any other critical process that requires validation. However, it is generally not well understood or studied. It is essential that adequate cleaning procedures should be established and validated.[9] The selection of cleaning method is depends upon the solubility and difficulty of cleaning of active ingredient. The calculations of product residue limit are based on potency, toxicity and stability of active ingredient.

The selection of cleaning method is depends upon the solubility and difficulty of cleaning of active ingredient. The calculations of product residue limit are based on potency, toxicity and stability of active ingredient. The ability to successfully clean a piece of equipment is closely related to the solubility of materials being removed in washes and stages of cleaning. Materials which are soluble freely in water can be rapidly reduced in concentration through repetitive dilution of the surface with additional washes. Materials which are poorly soluble are most likelyremoved from the surfaces by the force of wash and rinse spray against the equipmentsurface. The ability to remove the relatively insoluble materials can be enhanced by the introduction of surfactant, co-solvents etc to the cleaning process. The basic mechanisms involved in the removing the residues and contaminants from the equipment are mechanical action, dissolution, detergency and chemical reaction, so the cleaning procedure should be validated.[10, 11, 3]

Now-a-days pharmaceutical industries are increasingly using the multipurpose equipment and automated clean-in-place procedures; it has become more important to establish evidence that cleaning procedure is effective. FDA has placed an increased emphasis on the cleanliness of the equipment to minimise the risk of cross contamination and adulteration of drug products made subsequently using the same equipment.FDA" s July 1993 "Guide to Inspections, Validation of Cleaning processes requires companies to have "written general procedures on how cleaning processes will be validated and these procedures" should address issues such as sampling procedures, analytical methods to be used, including the sensitivity of those methods.[12]

Validation of cleaning processes should be based on a worst-case scenario including: challenge of the cleaning process to show that the challenge soil can be recovered in sufficient quantity or demonstrate log removal to ensure that the cleaning process is indeed removing the soil to the required level and the use of reduced cleaning parameters such as overloading of contaminants, over drying of equipment surfaces, minimal concentration of cleaning agents, and/or minimum contact time of detergents. At least three (3) consecutive applications of the cleaning procedure.

Should be performed and shown to be successful in order to prove that the method is validated. Equipment which is similar in design and function may be grouped and a worst case can be established for validation.[13]

SAMPLING TECHNIQUES

In developing the sampling plan for a validation study, it makes scientific sense to incorporate an understanding of the acceptance criteria and the limitations of the sampling method relative to the surface to be sampled. The two methods of sampling generally employed are swab and / or rinse sampling. (If neither or these methods are shown be a scientifically sound method for testing in a specific instance then an alternative is to consider testing the next Product.) The selection of either of these techniques must be consistent with sound scientific judgment and must support the objective of the study, which is to demonstrate that the amount of residual material in the equipment has been reduced to acceptable levels.[14]

EACH METHOD IS DESCRIBED IN BRIEF BELOW

1. SWAB

SWABBING[14]

In a typical pharmaceutical manufacturing environment, cleaning might be performed by using 70% isopropyl

alcohol (IPA) and/or other chemicals, detergents and sanitizing agents in order to remove residues from the previous batch run. The areas thus cleaned must now be sampled adequately and appropriately in order to validate the cleaning protocol.

While the FDA guidance indicates a preference for the more direct swabbing method, more recent communication from the International Conference on Harmonisation (ICH) ICH Q7A5 states that sampling methods need to be comprehensive enough to quantitate both soluble and insoluble residues that are left behind on the surfaces after cleaning. The exact protocols prescribed will necessarily vary depending on the nature of the products, residues and surfaces. These protocols must be tailored to the needs of each environment.

THE SWABBING PROCEDURE – CONSIDERATIONS[14]

The swab to be used for sampling is typically pre-wetted with water or another appropriate solvent in order to remove residues from the surface. Squeezing the sides of the swab against the inside of the vial upon pre-wetting prior to sampling removes excess solvent. This is important because excess solvent can itself serve as a source of residues leading to variable results. There is a direct, physical interaction between the swab, the solvent and the residues to be removed; therefore, the choice of swab is critical to the effectiveness of the sampling process. The swab used must offer ultra-low particulates and fibers, high absorbency and minimal extractable interferences. Polyester swabs are specially processed to meet the stringent requirements associated with cleaning validation protocols.

The physical nature of the swabbing process implies that significant levels of operator training be conducted prior to implementation of cleaning validation protocols. This training should serve to minimize the subjectivity that is inherent to such sampling activity. The recommended directions and motions used in actual swabbing of an area as and should be detailed in the training to ensure the highest levels of consistency. Alternate swab sampling patterns may certainly be used if they would help maximize percent recovery.

The swabbing pattern used is critical to ensure an accurate and reproducible collection of residues. A typical sampling pattern employing two swabs.

1. The first side of the first swab is swiped horizontally ten times.
2. The swab head is flipped over and the second side is swiped vertically ten timesover the same surface.
3. The swab is deposited in the vial.
4. The first side of the second swab is swiped diagonally upwards ten times.
5. The swab is flipped over and the second side is swiped diagonally downward ten times.
6. The second swab head is deposited in the vial.[15]

Swab sampling does not cover the entire equipment surface area therefore sites must be chosen with care. It is important that, as a minimum, the swab sites represents worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface area. This calculation makes it possible to make a worst case determination of potential carryover into subsequent product.

- Due to the nature of this method which employs physical forces as well as chemical forces it may be necessary to perform sampling technique evaluation.
- Swabbing efficiency (% recovery) for the swabbing method must be determined.
- It is necessary to ensure that extractible of the swab do not interfere with the sampling method.
- Using this technique it is possible to sample insoluble residues due to the physical action associated it.
- Swabbing technique involves the use of a swabbing material, often saturated with solvent, to physically sample the surfaces.[3]

Advantages

· Dissolves and physically removes sample
· Adaptable to a wide variety of surfaces
· Economical and widely available
· May allow sampling of a defined area
· Applicable to active, microbial and cleaning agent residues[16, 3]

2. RINSE

Rinse samples allow sampling of a large surface area. In addition, inaccessible areas of equipment that cannot be routinely disassembled can be evaluated. However, consideration should be given to the solubility of the contaminant.[18]

Rinse Sampling involves passing a known volume of solution over a large area and analyzing the recovery solution.

- The solvent rinse occurs after cleaning has been completed
- This method is not as direct as swabbing but will cover the entire surface area (and parts inaccessible to swabs)
- It is important to ensure chosen solvent has appropriate recovery for residues being quantified
- This method allows much greater ease of sampling than swabbing
- A reduced no of samples are required to generate a carryover figure.[16,3]
- Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and mixing involved. The solvent used should be selected based on the solubility of the active ingredients and should

either simulate a subsequent batch of product or at least provide adequate solubility. A disadvantage of rinse samples to that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot". In the evaluation of cleaning a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean: one looks at the pot.

- **Testing Methods[19]**

The basic requirements of the analytical methods should have the following criteria.

1) Testing method should have the ability to detect target substances at levels consistent with the acceptance criteria.

2) Testing method should have the ability to detect target substances in the presence of other materials that may also be present in the sample.

3) The testing analytical method should include a calculation to convert the amount of residue detected in the sample to 100%if the recovery data generated indicates a recovery outsides the allowed range. Selection of analytical techniques it mainly depends on a variety of factors. The most important factor is to determine the specifications or parameters to be measured. The limit should always be established prior to the selection of the analytical tool.

Sampling from rinses is the most commonly used technique for evaluation of cleanliness. It has become popular because of its ease, the only control required is solvent used and rinsing and contact/mixing. In the rinse sample, volume of rinse solvent is important. In the equipment designed to hold liquid, either the volume of rinse solvent should be sufficient to ensure contact with all product contact surface or method of introduction of solvent should be such that solvent make contact with entire product contact surface. For such equipment which cannot hold solvent, it must be ensured that solvent makes contact with product contact surface for sufficient time to dissolve any residual material. The best way in such cases is to rinse the equipment several times and collect the rinse/solvent and then to collect sample for analysis. However, the volume used each time must be known to draw meaningful conclusion. Unused solvent should be used as control sample. Rinse samples allow sampling of a large surface area and of inaccessible systems or ones that cannot be routinely disassembled. However consideration should be given to the fact that the residue or contaminant may be insoluble or may be physically occluded in the equipment. A direct measurement of the residue or contaminant in the relevant solvent should be made when rinse samples are used to validate the cleaning process. Indirect testing such as conductivity and TOC testing may be of some value for routine monitoring once a cleaning process has been validated. This could be applicable to reactors or centrifuge and piping between such large equipment can be sampled only using rinse solution samples.[20]

Advantages

Adaptable to on-line monitoring, Easy to sample, Non-intrusive, Less technique dependent than swabs. Applicable for actives, cleaning agents and excipients.[16,3]

3. VISUAL CLEANING METHOD

It is important to use visual inspection in addition to analytical methodology to ensure the cleaning process is acceptable. The study involves finding out criteria for visual cleanliness limit for selected drug by applying known amount of drug on SS plate before taking swab samples for chemical analysis.

The use of visual inspection as a criterion for equipment cleanliness has always been a component of cleaning validation programs. Mendenhall proposed the use of only visual examination to determine equipment cleanliness as long ago as 1989. He concluded that visible cleanliness criteria were more rigid than quantitative calculations and clearly adequate. The US Food and Drug Administration limited the use of visually clean criterion between lots of the same product.

A visible-residue limit (VRL) currently is used in a clinical pilot plant for the introduction of new compounds (4, 5) in cases for which the VRL is lower than the acceptable-residue limit (ARL). TheARL is the amount of a formulation component that can be carried over to the next formulation with no pharmacological or adulteration concerns. The initial use of an active pharmaceutical ingredient (API) in the facility is followed by cleaning and a visual inspection against the previously determined VRL. Visually clean equipment means the current cleaning procedure is effective and the new API is not a new worst case that would require cleaning validation.[17]

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