Spray Coverage Testing

Jennifer Carlson

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"Cleaning Compliance Forum" discusses scientific principles, strategies, and approaches associated with cleaning that are useful to practitioners in compliance and validation. We intend this column to be a valuable resource for daily work applications. The key objective for this column: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Jenna Carlson at carlson.jenna@gene.com or to managing editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:

- Coverage testing should be performed as part of equipment qualification for all process-contacting equipment utilizing spray devices for cleaning
- Coverage testing is used to verify that all process-contacting surfaces are wetted by cleaning liquids and to identify any potential blind spots or hard-to-clean locations on the equipment
- Locations on equipment that are not adequately cleaned are identified through riboflavin fluorescence testing
- Procedures should be in place to prevent or look for clogging of spray coverage devices over time that would potentially affect the spray pattern
- Coverage testing is a regulatory expectation.

INTRODUCTION

In order for process equipment surfaces to be cleaned, they must be able to be contacted with cleaning liquid. Spray devices are an efficient means of delivering cleaning solution to a surface. It is much more efficient to clean a large vessel using spray devices than to fill it completely with liquid and clean by a soak method. Also, by spraying liquid up along the top head of a vessel, the sidewalls and other internal components are cleaned by the resulting turbulent falling film of solution. This turbulent falling film provides a more thorough cleaning of surfaces than the relatively quiescent flow of solution in a fully flooded and mixed tank. In these

ways, utilizing spray devices is a more effective and efficient means of cleaning.

Spray coverage testing is performed on equipment that is cleaned using a spray device or devices (e.g., balls, nozzles, etc.). Spray coverage testing provides assurance that spray devices used during cleaning for a particular piece of equipment are able to reach and rinse all interior process contacting surfaces. Spray coverage testing identifies any potential hard-to-clean or inadequately cleaned locations (blind spots) on the equipment. Riboflavin fluorescence is used to identify blind spots on tanks. If blind spots are identified during spray coverage testing, a corrective action should be performed to ensure that the blind spot is cleaned. In addition, spray coverage testing results help provide scientific evidence to support grouping of equipment for cleaning validation activities.

REGULATORY REQUIREMENTS

There are no specific regulatory requirements that require spray coverage testing. US Code of Federal Regulations (1) and Eudralex Volume 4 Part II (2) both specify equipment should be of appropriate design to facilitate cleaning. One part of demonstrating this is through spray coverage testing.

In addition, both the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) (3) and Health Canada (4) specify "critical areas (i.e., those hardest to clean) should be identified, particularly in large systems that employ semi-automatic or fully-automatic clean-in-place (CIP) systems." Spray coverage testing enables identification of blind spots for the equipment spray devices to clean by an automated cleaning cycle.

An important aspect of grouping of equipment is demonstrating that the "equipment is similar in design and function" (3, 4). One part of demonstrating that equipment is of similar design to support grouping for cleaning validation is through spray coverage testing.

REGULATORY EXPECTATIONS

When spray balls or nozzles are used to deliver cleaning agent to equipment for the purposes of cleaning, health agencies expect to see documentation of spray coverage testing.

The US Food and Drug Administration is known to give FDA-483 observations for not having completed spray coverage testing. An example and observation of not having spray coverage testing from a FDA-483 is as follows:

> "Documentation of sprayball coverage for processing tanks is not found in cleaning validation studies or I/OQ studies for these processing tanks" (5).

A 2004 FDA warning letter (6) included two separate mentions of inadequate spray ball coverage:

> "Your firm failed to establish and follow written procedures to assure the cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b) and 600.11(b)]. For example, cleaning validation for the clean-in-place (CIP) process vessel [redacted] which is utilized in the aseptic formulation of trivalent bulk influenza vaccine, did not include an assessment of the spray ball coverage for the vessel. The spray ball is used for cleaning product contact equipment."

The lack of spray coverage testing is mentioned again later in the warning letter as follows:

> "In addition, the cleaning validation did not include an assessment of the spray ball coverage for the tanks" (6).

IMPLICATIONS FOR COMPLIANCE

For equipment that is cleaned-in-place (CIP) by automated cleaning systems, documentation of spray coverage should be performed as part of equipment qualification for all process-contacting equipment. In addition, procedures should be in place to prevent or look for clogging of spray coverage devices. Obstruction of spray openings over an extended time period could potentially affect the spray pattern. Clogging of a spray ball could also affect the ability of the cleaning cycle to deliver effective cleaning.

SPRAY COVERAGE TESTING

Qualification of equipment containing a spray device must include identification and documentation of the spray device including its proper orientation, alignment, and coverage results. Spray coverage test should assure complete coverage of internal surfaces of equipment. If spray coverage testing demonstrates that equipment has blind spots that would not be contacted by cleaning liquid introduced by any other means (i.e., direct flow of cleaning solution into a vessel via a port on that vessel), the company should document remediation activities to correct the blind spot and assure that cleaning of the blind spot will be successful.

Testing should be performed for each tank and spray ball configuration. If a change has occurred to the tank configuration or the spray ball, the test should be performed again as part of change control or revalidation.

EXAMPLE PROCEDURE FOR SPRAY COVERAGE TESTING

Equipment being tested must be cleaned and verified to be visually free of any residue that may fluoresce and give a false positive when inspected by a UV light source. Ensure that hard-to-see areas (e.g., bottom of impellers, dip tubes, and ports) are verified. Record any initial inspection observations.

Application of Riboflavin to Tanks

The following steps should be taken in the application of riboflavin to tanks for cleaning.

Apply a 0.2g/L solution of riboflavin to the interior surfaces of each tank. Verify that complete coverage is attained using a UV light source. Dextrose (20g/L) solution may be used to help the riboflavin bind to the tank surface, if needed. Riboflavin solution is typically used for coverage testing. Other chemicals may also be used as long as they allow determination of coverage. Other chemicals used include uranin and flourescein.

Confirm that the riboflavin fluoresces by using a UV lamp source. This is accomplished by applying a small amount of riboflavin solution to a stainless steel surface (i.e., stainless steel coupon) and fluorescence is verified.

Wearing gloves is required during application of riboflavin on equipment surfaces that are being qualified. Oils from hands may cause riboflavin to abnormally adhere to surfaces and may result in a false positive.

Shake the riboflavin solution prior to use. Settling may occur while solution is idle.

Apply a fine mist of riboflavin solution on required equipment surfaces to create uniform surface coverage. Avoid over-application or a solid stream. With a solid stream setting, the riboflavin will tend to form larger droplets and will be less likely to adhere to the surface in a uniform manner. A fine mist of riboflavin liquid is preferred when spraying equipment surfaces. Likewise, if riboflavin is over-applied, droplets will tend to pool together and drip down, preventing the riboflavin solution from uniformly covering equipment surfaces.

Verify required surface(s) has complete and uniform riboflavin coverage by using a UV light source. Ensure hard-to-reach areas have been uniformly covered with riboflavin. Document inspection results.

Ensure that the spray ball has been verified to be free of any foreign objects prior to use in testing.

Equipment Coverage Testing

The following steps should be taken when spray-coverage cleaning equipment.

Ensure that equipment is properly set up for cleaning per applicable procedure.

Record rinse flow rate and pressure, or pump speed, and rinse time (or flow total) set points. Compare to actual cleaning parameters and document.

Perform coverage testing utilizing a water rinse that is equivalent to the shortest phase of the cleaning cycle. Verify the equipment is drained after testing is complete.

Change and inspect gloves and gowning prior to inspection to prevent any contamination from garments. Wipe down all equipment that may enter the equipment being tested prior to inspection in order to prevent false positives. If possible, dim the room lighting.

Once equipment is accessible for inspection, search for areas of pooling or drips that may contain riboflavin by using available UV light. If there is riboflavin residue in equipment, it will fluoresce.

Inspect all surfaces under qualification with UV light. It is important to inspect the hard-to-reach areas. Use mirrors to assist in inspection, if necessary.

In some cases, equipment surfaces that are under qualification may become dry prior to inspection. If surface is dry during inspection, a spray bottle containing water should be used to check for illumination—riboflavin does not illuminate when dry.

Lightly spray water mist on the dry surface and check for riboflavin illumination by using available UV light. Avoid excessive application of water to reduce the chances of dripping or dilution.

The interior surface of the vessel must show no evidence of residual riboflavin after the partial (worst-case) cleaning cycle. Document inspection results. If riboflavin is apparent on equipment surface(s) during testing, initiate an investigation and deviation.

GROUPING FOR COVERAGE TESTING

One important consideration for grouping of equipment for cleaning validation is the cleanability of process-contacting surfaces (hard-to-clean areas). Spray coverage testing is one way to determine if equipment has hard-to-clean areas or if similar equipment has the same hard-to-clean areas. It is difficult to justify grouping for spray coverage testing. If spray devices are shown to be of consistent design with the same spray pattern, then it should be possible to justify grouping of spray devices for use in cleaning equipment of the same design.

CONCLUSIONS

Spray coverage testing assures that spray devices used for cleaning of a particular piece of equipment are able to reach and rinse all interior (process-contacting) surfaces. While spray coverage testing is not specifically identified as a requirement by the regulations, it is a regulatory expectation.

REFERENCES

1. FDA, 21 CFR 210, Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding Of Drugs: General, April 1, 2008 (revised).
2. EC, *Rules Governing Medicinal Products in the European Community. Volume IV, Good Manufacturing Practices for Medicinal Products*, October 2005.
3. PIC/S, *Recommendations on Cleaning Validation*, Document PI 006-1. Pharmaceutical Inspection Cooperation Scheme, Geneva, Switzerland, August 3, 2001.
4. Health Canada, *Cleaning Validation Guidelines* (GUIDE-0028), Health Canada, January 1, 2008.
5. FDA, FDA-483 issued to Evans Vaccines, a Division of Chiron, Liverpool UK, October 10-15, 2004, http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/ucm166572.htm
6. FDA, FDA Warning Letter issued to Chiron Corporation, December 9, 2004, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2004/ucm146700.htm

GENERAL REFERENCES

LeBlanc, Destin A., *Validated Cleaning Technologies for Pharmaceutical Manufacturing*, Interpharm/ CRC Press, 2000.

Verghese, George and Paul Lopolito, "Cleaning Engineering and Equipment Design," *Cleaning and Cleaning Validation for the Pharmaceutical and Medical Device Industry*, Volume 1. Paul L. Pluta, ed., PDA and Davis Healthcare International Publishing, 2009. **GXP**

ARTICLE ACRONYM LISTING

CIP	Clean-in-Place
FDA	US Food and Drug Administration
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-Operation Scheme
UV	Ultraviolet

ABOUT THE AUTHOR

Jenna Carlson is a senior technical manager in Genentech's Corporate Quality System and Support, Validation department. She is responsible for developing and overseeing governance activities for cleaning validation, including the corporate requirements and procedures. She has more than 11 years experience focusing on validation and quality assurance. She may be reached by e-mail at carlson.jenna@gene.com.