

DEVELOPING AND VALIDATING ANALYTICAL METHODS FOR CLEANING VERIFICATION

In an operation where equipment is used for multiple products, the prevention of cross-contamination is critical. The selection, development and validation of analytical methods to verify that equipment has been adequately cleaned are important elements of the overall cleaning strategy.

Analysing samples to confirm the effectiveness of equipment cleaning is an important aspect of the cleaning process in the pharmaceutical industry. In many operations, it is not economically feasible to dedicate equipment to the processing of individual products. Analytical evaluation against prescribed limits ensures that product carryover does not occur and minimizes the risk of cross-contamination. Even in those operations where equipment can be dedicated, the assessment of cleaning effectiveness mitigates the potential for build-up of impurities, which can jeopardize product quality.

Selecting an Analytical Technique

Prior to beginning the method development process, we need to consider what the method needs to achieve. Questions that need to be asked include

- Which materials are to be analysed for?
- What levels will we need to detect?
- Will we need a method that is specific to the materials in question (for example, an HPLC method) or will a nonspecific method (for example, a pH determination) be adequate to meet our needs?
- How long will the testing take and how much will it cost?

Materials

Frequently, the materials to be tested for provide a good indicator of the appropriate methods to be used. The removal of the API can be evaluated by using ultraviolet (UV) scans or by high performance liquid chromatography (HPLC). Using a chemical spot-test or inductively coupled plasma (ICP) can ensure that all residual metal catalysts are removed. The removal of organic solvents could be demonstrated with gas chromatography (GC). The absence of residual cleaning agents — in particular, detergents — could be demonstrated with chromatography or a total solids test. In certain operations, when residual water cannot be tolerated, Karl Fischer may be used. For techniques used during drug product operations, it may be necessary to demonstrate the absence of inactive excipients to ensure

that the next product is unaffected. We may also consider the reduction of bioburden or endotoxin load and the possible need to sterilize the equipment.

Levels

It is also important to consider detection and quantitation limits, as well as the level of tolerated residue. Certain chromatographic techniques may be adequate for limits in the part-per-million range whereas total organic carbon (TOC) can be used in the part-per-billion range.

Method

The choice of specific methods versus nonspecific methods should be taken into consideration. In practice, both methods have their advantages; but if we are trying to demonstrate that the equipment is free of acid, either from processing or from the cleaning procedure, the nonspecific method pH is the appropriate technique.

For APIs and their precursors, we have developed specific methods usually using HPLC. Fortunately, many active compounds have chromophores that can be detected by UV. When the compound of interest does not lend itself to UV, mass spectroscopy, refractive index or evaporative light scattering detection may be necessary. It may also be possible to form a derivative of the active compound to produce a new compound that can be detected by UV. Occasionally, we have developed methods to quantitate the active compound and its precursors using the same HPLC conditions. Such methods provide a wealth of valuable information in relatively little time.

Time and Cost

Finally, some thought needs to be given to the duration of the analysis and the cost of conducting it. Although we regard this as subordinate to the science, we do not want to develop methods that use exotic HPLC columns or expensive reagents, or take an extraordinarily long time to complete. A 60-min run-time to release the drug may be appropriate; in practice, we try to test cleaning samples with injections that run for no longer than 15 min, if possible.

More than one technique may be applied in a given cleaning campaign; for example, a reactor used in chemical synthesis. HPLC can be used to confirm the absence of

Material to test for	Method to use
Active pharmaceuticals	HPLC, UV, TOC, LCMS
Metal catalysts	ICP, AA, Spot-test
Solvents	GC, GC/MS, TOC
Acids, bases	pH
Water	Karl Fisher

Table I

active chemicals and TOC can be employed to confirm the absence of undesirable residual solvents. The recording of a pH can demonstrate that residual acids or bases have been neutralized or washed out. Finally, Karl Fischer can confirm that the equipment is dry.

Method Development

In practice, the development of analytical methods for drug release testing is often completed before scientists develop methods to evaluate cleaning samples, so this is usually a good place to start. There is one particularly important difference, however; the method for drug testing will be demonstrated to be valid in a range around the nominal test sample concentration, usually on the order of mg/mL. A cleaning method, on the other hand, will need to be sufficiently sensitive to detect and quantitate levels on the order of mg/L or three orders of magnitude more sensitive.

Furthermore, the method used for the drug release testing may use reagents or have testing conditions that are appropriate for drug release, but less so for the testing of cleaning samples. For example, many HPLC methods use acetonitrile in relatively small volumes. Cleaning and sampling of cleaned equipment would use substantially larger volumes that would be quite undesirable if there were a worldwide shortage of acetonitrile, as was the case 2 years ago.

In developing methods and the cleaning procedure itself, it is useful to evaluate the solubility of the materials to be tested for. If the compound is insufficiently soluble, the method will be difficult to validate because the results will be inconsistent. Be sure that the method is appropriate for the solvent used to collect the sample; for example, TOC would be inappropriate for the detection of API in an acetone rinse wherein acetone is more than 60% carbon. A good and experienced analyst can work with process development or operations to develop methods appropriate for evaluation of cleaning samples. Some suggestions are listed in Table I.

Method Validation

There are two excellent and widely referenced guides for Validation of Analytical Methods: USP General Chapter <1225>, "Validation of Compendial Procedures," and The International Conference on Harmonization (ICH) Guidance Q2.^{1,2} These references provide useful direction for characteristics to be evaluated and for a methodology to conduct these evaluations. Both provide direction

for the evaluation of specificity, range and linearity, accuracy, precision, detection limit, quantitation limit and "robustness."

These are extremely useful references, but they address method validation for drugs and drug substances, not for cleaning samples. Furthermore, while the ICH document is "guidance," other approaches may be acceptable if they are scientifically rational and appropriately justified. In practice, we follow the ICH Guidance when validating cleaning methods. It is easier to defend this approach to regulatory inspectors and auditors than it is to defend a novel approach to validation.

In light of the fact that these references are for drugs and drug substances, there is one aspect of cleaning method validation that must also be addressed: cleaning swab recovery. A rigorous cleaning policy will include equipment sampling using swabs. Swabs are a necessity in areas that are "hard to clean" and/or "hard to see." An important aspect of the development and validation process is the determination of the amount of material a swab will remove and release into the sample test medium. We take a known amount of compound and place it on a coupon of similar material as the equipment to be cleaned, such as glass or stainless steel. We then swab the coupon, soak the swab in the testing medium and conduct the analysis. To calculate the average, we calculate the percent detected relative to the known amount placed on the coupon and replicate this experiment at least three times with a low and a high concentration. Achieving as high a recovery as possible provides more accurate cleaning calculations. Sometimes, however, the compounds are not co-operative and we accept a recovery as low as 30%. Once the methods have been developed and validated and the swab recovery has been determined, cleaning verification and validation can proceed.

Cleaning Verification and Validation

Regulatory bodies (and client auditors) expect cleaning procedures to be validated to "establish documented evidence that provides a high degree of assurance that a specific process will consistently meet its pre-determined specifications." Prior to a pre-approval inspection, we conduct the cleaning process and subsequent testing, and prepare a report to meet this obligation. After validation and the processing campaign are complete, we perform analytical verification that the cleaning process continues to perform as expected, even if the cleaning process has been validated.

Conclusion

Cleaning and analytical verification to confirm the success of the cleaning process are critical steps in the manufacturing cycle for pharmaceutical products. We have provided a framework and suggested points to consider in the design of an effective programme to ensure patient safety and regulatory compliance in a multi-use pharmaceutical facility. **Pharma**

Table I: Suggested analytical methods.

References

1. *The United States Pharmacopeia*, 34th Revision, General Chapter <1225>, The US Pharmacopeial Convention (Rockville, MD, USA) 2011.
2. *The International Conference on Harmonisation Tripartite Guideline*, "Validation of Analytical Procedures: Text and Methodology Q2(R1)," Adopted July 1995 (Part A) and October 1997 (Part B).

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