Using Visible Residue Limits for Introducing New Compounds into a Pharmaceutical Research Facility

Richard J. Forsyth* and Vincent Van Nostrand

AUTHORS

An increasing number of new compounds are being introduced into pharmaceutical pilot plants. The knowledge base for these compounds regarding their toxicities, physical handling, and cleaning is limited. The authors examine various approaches for addressing the cleaning validation of new compounds and discuss the role of determining appropriate visible residue limits.

Richard Forsyth is a senior manager and Vincent Van Nostrand is a staff chemist, both in Pharmaceutical R&D, Merck & Co., Inc., WP78-210, West Point, PA 19486, tel. 215.652.7462, fax 215.652.2835, richard_forsyth@merck.com.

*To whom all correspondence should be addressed.

Introducing new compounds into a pharmaceutical manufacturing facility can pose ongoing challenges to a facility's cleaning validation program. Some discussions have described how a cleaning validation program can be conducted (1–2). Several programs have used a worst-case approach to validating a cleaning program (3–8). Approaches for determining the worst-case soil have included evaluating which residue was the last to rinse from the manufacturing vessel (3), using a product grouping strategy (4–6), assessing the relative toxicological properties of the formulation components (7), and relying on the practical cleaning experience of the formulators and equipment cleaners (8).

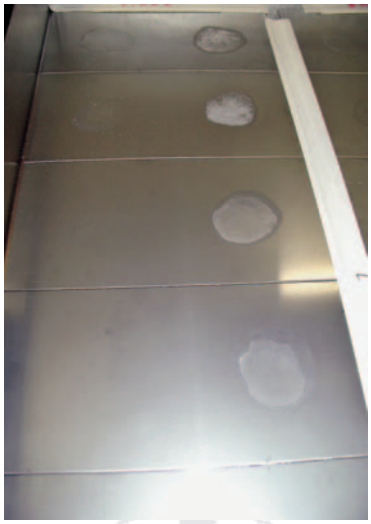
Once a worst-case soil has been validated, however, introducing a new compound requires determining whether this compound is a new worst case. This task is accomplished through a cleaning verification procedure of the new compound or an assessment to justify why it is not a new worst case.

In a manufacturing facility, the number of new compounds entering the facility is limited. Therefore, it might be appropriate, and certainly prudent, to validate each new compound as it is introduced into a facility. The time and resources necessary to validate a new compound can be substantial and, if on the critical path, could slow down a program and result in a substantial loss in revenue. To minimize this possibility, cleaning validation should be addressed as part of the technology transfer into the manufacturing facility. A cleaning process for the compound should be addressed at the pilot-plant stage. Cleaning transfer to the manufacturing facility then could be conducted during batch scale-up. This practice would still require the resources to validate the cleaning of the new compound but would not affect the product timeline adversely.

Introducing a new compound in a research pilot-plant environment is a more challenging and complex task. The number of new compounds entering a pilot plant each year is much greater than the number of new compounds entering a production facility. The resources required to fully validate each new compound would have a significant adverse effect on the pilot plant's ability to operate. The necessary equipment hold times would slow early-phase formulation development at a time when there is ongoing emphasis on shorter timelines during the development process.

Drug development is an evolving process in which clinical and safety data that determine the market dose are generated. Physical properties of the compound and the stability of early-phase formulations affect the final market formulation. As the compound goes through scale-up during development, manufacturing equipment capacities increase. The type of equipment also can change. Evolving formulations make cleaning validation in the pilot plant even more challenging.

The vast majority of new compounds entering a pilot plant are in the early phases of development. The knowledge base for these compounds regarding toxicity, analytical testing, physical handling, and cleaning is limited. Toxicity data based on animal studies are not fully developed. Analytical test methods are typically limited to the bulk material, and compound degradates have not been characterized. The physical handling of the new compound in the pilot plant is developed during the introductory formulations. The effectiveness of the current cleaning procedure for the new compound is unknown. A method to evaluate the cleaning of new compounds is needed until a full evaluation that is based on a completely developed formulation and cleaning procedure is possible.



AUTHORS

Figure 1: Representative residues on stainless steel.

New compounds

Although novel pharmaceutical formulations contain a number of compounds, the active pharmaceutical ingredient (API) is generally considered the new compound. By definition, the API has the greatest pharmacologic effect and has been considered the subject of greatest concern during cleaning processes. Formulation excipients are generally regarded as safe and/or have higher safety margins. In practice, however, the excipients may be more difficult to clean than the API. Therefore, it would seem appropriate to evaluate new excipients as well as new APIs, because both are introduced in the pilot plant.

The resources to validate or evaluate the introduction of every new compound—both API and excipient—in a pilot plant would be significant. The benefits of validating new compounds have to be balanced against the cost for the pilot plant and analytical laboratories.

The options for evaluating new compounds in the pilot plant are limited. Either special batches are manufactured for the cleaning studies or cleaning studies are built around the clinical manufacturing schedule. Because of the supply of a new compound is often limited, producing special batches is not a viable option. More options exist in the analytical testing laboratory (4, 9). Testing methods range from selective, highly sensitive instrumental methods to general methods that are not as sensitive. Method development costs and resource requirements typically are directly related to the method's sensitivity. To ensure that new compounds are cleaned effectively in the pilot plant, various testing methods were studied.

Methodology

Although a wide range of testing methodologies can be used for new compounds, these methods can be categorized as being either instrumental or physical. Instrumental methods have greater selectivity and sensitivity. They require more development time and can affect timelines. Physical methods are not as selective or sensitive, but they can be implemented relatively quickly.

The optimum testing method for new compounds would attain the necessary selectivity and sensitivity to ensure that manufacturing equipment can be adequately cleaned without adversely affecting pilot-plant operations.

Instrumental methods

HPLC-UV. Validating each new compound for cleaning using high performance liquid chromatography (HPLC) coupled with UV detection (HPLC–UV) is probably the most comprehensive methodology for introducing new APIs into a pilot plant. A well-developed method provides selectivity for both the API and the degradates. Sensitivity is at the parts-per-billion (ppb) level, which is well below any cleaning limit. Several cleaning validation programs successfully use HPLC to analyze cleaning swab samples (10–12). Preliminary information about an HPLC method typically is available either from the bulk API manufacturer or from ongoing formulation methods development.

The drawbacks of HPLC include validation work and the availability of methods. Because methods validation is required before cleaning samples are tested, the analytical laboratory would have a direct, critical effect on the use and availability of pilot-plant manufacturing equipment. The resources required to validate an analytical method for every new API could be considerable, and most drugs do not progress to new drug application approval. In addition, the availability of HPLC testing methods for new excipients would be limited. If methods were available, they would require validation for cleaning samples.

HPLC–MS. Using HPLC in tandem with mass spectrometry (MS) offers several advantages over HPLC–UV alone. MS conditions are available from the characterization studies on the API bulk material. Methods development time and individual-sample injections are generally shorter than those for an HPLC-UV assay. The HPLC method selectivity and the mass spectrometric analysis separate the API from its degradates. For a typical MS analysis, methods can be as sensitive as HPLC or better, and newer instruments have the potential to provide superior sensitivity. The cost for this instrumentation can seem excessive unless the instrument is used frequently enough to justify the monetary investment.

Other limitations of MS include method ruggedness and lack of information about excipients. In our laboratory, the ruggedness of simple, nonbuffered methods has been an issue, which can lead to further time-intensive development activities. Finally, the application of MS to excipients has not been explored extensively.

TOC. Total organic carbon (TOC) testing offers a universal, nonselective detector for organic compounds. Various TOC instruments have detection sensitivities at the ppb level. Because of these characteristics, TOC offers a distinct advantage for biopharmaceutical cleaning (13, 14), where formulation components are not individually characterized. Because of the nonselective method used in each TOC analyzer, methods development is performed once.

The shortcomings of TOC are its inapplicability to many excipients, its requirement for water solubility, and the sometimes unreliability of the instruments. Because TOC is limited to organic compounds, it is inadequate for many excipients such as those used for tablet coatings and certain buffering agents. In addition, the compound must be water-soluble, which limits the application of TOC analysis for any API that is water-insoluble. Finally, without a good preventative maintenance and calibration schedule, TOC analyzers may malfunction, providing erroneous data for numerous analyses, which costs time and money for repairs.

In addition to the instrumental alternatives, there are several physical testing methods to evaluate the cleaning of new compounds in the pilot plant.

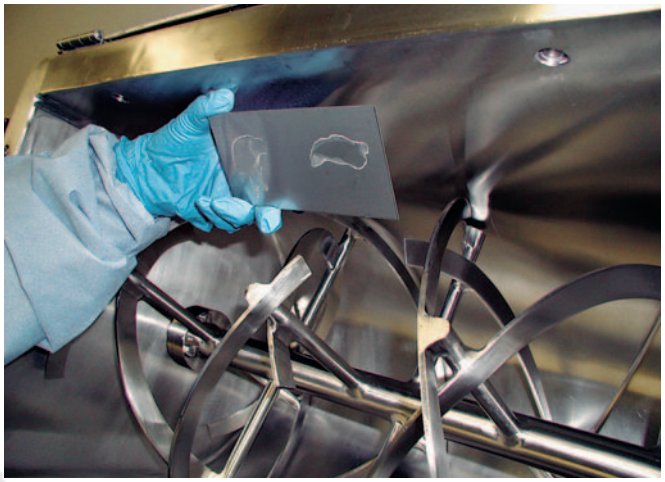
Physical methods

Cleanability studies. Bench-scale cleanability studies can evaluate the relative cleanability of a new soil and assess the need to revalidate the cleaning cycle (15). This is accomplished by comparing the cleanability of the new soil with that of the existing worst-case soil. If the new soil is easier to clean than the existing worst-case soil, validation is not necessary. In these studies, a solution or suspension of the new compound is spotted on a coupon representative of the manufacturing equipment (*e.g.,* stainless steel) and allowed to dry. The coupon is then submerged or repeatedly dipped in a solution of detergent for a specified length of time. The spot and/or the solution are assayed to determine how much of the compound has been removed.

This technique can be applied more easily in a manufacturing environment, where the final formulation composition is already determined, than in a pilot plant, where the formulation may change. The potential benefit of cleanability studies in a pilot plant is limited because the formulation is under development. Performing a cleanability study solely on an API or an excipient is probably not a sufficient indication of the pilot plant's ability to clean a new compound because excipients may be more difficult to clean or may interfere with the cleaning of the active.

Solubility. The solubility of an API is routinely determined during development studies. Solubilities of APIs are determined in organic solvents and aqueous solvents of varying pH or in the detergents used by the pilot plant. Aqueous solubility should provide an indication of the relative ease of cleaning an API. The solubility of excipients typically is not determined before use in a pilot plant, but information about excipient solubility should be available in the literature.

Many APIs and excipients are not water soluble. Therefore, much like TOC testing, using solubility as a criterion for predicting the cleanability of a new compound has limited applicability. There is also no validation or even verification of cleaning in the pilot plant using this approach alone.



AUTHORS

Figure 2: Equipment inspection using spotted plates.

Visible residue limit. A visible residue limit also provides a universal, nonselective cleaning assessment. Sensitivity has been observed to below the 1-$\mu g/cm^2$ level (16). The majority of APIs tested were below 2 $\mu g/cm^2$. Visible residue limits can be established for APIs, excipients, and formulations, making this technique the most versatile option for residual detection (16). A visible residue limit can be established quickly, and the process consumes only small amounts of a new compound, which is often in limited supply.

To establish a visible residue limit, a solution or suspension is prepared, and aliquots of the sample in concentrations around the acceptable residue limit are spotted onto coupons of material representative of the manufacturing equipment (typically stainless steel). The spots are dried under nitrogen to minimize the possibility for oxidation during drying, which could alter the appearance of the dried residue (see Figure 1). The coupons are then taken into the pilot plant and compared with the cleaned equipment to verify the removal of the new compound (see Figure 2). The hold time for the coupons should be minimized to preserve the appearance and integrity of the spots. Coupons can be prepared shortly before comparison with the equipment, or electronic images clearly showing the spots can be documented and stored.

Discussion

The purpose of any cleaning validation program is to ensure that cleaning procedures are adequate to prevent cross-contamination from one batch to the next and to ensure the safety and efficacy of manufactured supplies. When new compounds are introduced into the program, an evaluation against the existing cleaning procedures is required to determine whether further cleaning validation studies are necessary. A visible residue limit is a viable method to determine equipment cleanliness, provided that the assessment is conducted under controlled circumstances (*e.g.,* lighting, viewing distance), and that the visible residue limit is lower than the acceptable residue limit (2, 8) for the compound.

The scope for using a visible residue limit must be controlled for it to be viable. Different APIs and excipients have different visible residue limits, either individually or combined in a formulation. Visible residue limits have been quantitatively determined for APIs and excipients in our facility (16).

More important, inspectors perceive cleanliness differently. One inspector may determine that a piece of equipment is clean, whereas another inspector may conclude that the same piece of equipment is still soiled (16, 17). Using a completely subjective visual evaluation assessment would be problematic. As a result, soiled equipment could be put back into production or clean equipment could be recleaned unnecessarily. The former situation jeopardizes the purity of subsequent formulations, and the latter wastes resources and ties up manufacturing equipment. A trained inspector using spotted coupons as a reference makes the process more quantitative and less subjective.

Ideally, the visible residue limit would be determined for an entire formulation because excipients are often harder to clean than APIs, or there could be interactions between the excipients and API during the manufacturing or cleaning processes. However, formulation development is dynamic in the pilot plant. The excipients in the formulation, as well as the ratio of API to excipient, will most likely be refined during the development process. Therefore a formulation-based approach is not practical for the introduction of new compounds into a pilot plant.

This lack of formulation information is not a concern even if the visible residue limit of one or more of the formulation excipients is higher than that of the API. An adulteration limit is applied to the API and any other potent component of the formulation. An adulteration limit is not appropriate for excipients that are generally regarded as safe. Historically, it was considered satisfactory for excipients to be visibly cleaned from the manufacturing equipment. The visible residue limits of excipients that are generally regarded as safe are only important in relation to how they could influence the visual cleanliness assessment of the API after cleaning.

Because an API typically is the most potent compound in the formulation, its visible residue limit is used as a limit for cleanliness. In most cases, the visible residue limit is below the acceptable residue limit. For highly potent compounds, the reverse may be true. Calculation of the acceptable residue limit can be determined using toxicity data (2, 8). The acceptable residue limit should routinely be determined and compared with the visible residue limit. Only if the visible residue limit is lower, should it be used as an acceptance criterion for cleanliness.

The most suitable time to implement using the visible residue limit is the first time a new compound is used in the pilot plant. The first use of a new compound, however, might not be representative of the future use of the compound. For example, the first use could be a dry-filled capsule, but later formulations might be film-coated tablets. During formulation scale-up, different types of manufacturing equipment are sometimes necessary to provide a uniform formulation. Therefore, it would be prudent to monitor the visible residue limit for new compounds whenever a major change is made in the manufacturing process.

Using a visible residue limit to address the introduction of new compounds into a pharmaceutical research pilot-plant facility addresses subjectivity (17) in the cleaning evaluation. The development time and resources required are limited. The implementation of a visible residue limit program for introducing new compounds balances the need for quantitative cleaning determination against the costs of delaying product development timelines, of keeping manufacturing equipment tied up during testing, and of expending resources for programs that will not be successfully brought to market.

References

1. FDA, "Guide to Inspection of Validation of Cleaning Processes" (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, July 1993).
2. G.L. Fourman and M.V. Mullen, "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," *Pharm. Technol.* **17** (4), 54–60 (1993).
3. D.A. LeBlanc, D.D. Danforth, and J.M. Smith, "Cleaning Technology for Pharmaceutical Manufacturing," *Pharm. Technol.* **17** (10), 118–124 (1993).
4. K.M. Jenkins and A. J. Vanderwielen, "Cleaning Validation: An Overall Perspective," *Pharm. Technol.* **18** (4), 60–73 (1994).
5. H.L. Avallone, "Drug Substance Manufacturing and Control," *Pharm. Eng.* **9** (2), 37–57 (1989).
6. M. Montalvo and A. Hewing, "How to Develop an Effective and Successful Cleaning Validation Program," *J. Val. Technol.* **10** (1) 62–82 (2003).
7. D.W. Mendenhall, "Cleaning Validation," *Drug Dev. Ind. Pharm.* **15** (13), 2105–2114 (1989).
8. R.J. Forsyth and D. Haynes, "Cleaning Validation in a Pharmaceutical Research Facility," *Pharm. Technol.* **22** (9), 104–112 (1998).
9. PhRMA Quality Committee, "PhRMA Guidelines for the Validation of Cleaning Procedures for Bulk Pharmaceutical Chemicals," *Pharm. Technol.* **21** (9), 56–73 (1997).
10. A.O. Zeller, "Cleaning Validation and Residue Limits: A Contribution to Current Discussions," *Pharm. Technol.* **17** (10) 70–80 (1993).
11. W.K. Gavlik, L. A. Ohlmeier, and H. J. Kaiser, "Analytical Strategies for Cleaning Agent Residue Determination," *Pharm. Technol.* **19** (3), 136–144 (1995).
12. J.A. Shea *et al.,* "Validation of Cleaning Procedures for Highly Potent Drugs. I. Losoxantrone," *Pharm.Dev. Technol.* **1** (1), 69–75 (1996).
13. R. Baffi *et. al.,* "A Total Organic Carbon Analysis Method for Validating Cleaning Between Products in Biopharmaceutical Manufacturing," *J. Paren. Sci. Technol.* **45** (1), 13–19 (1991).
14. K.M. Jenkins *et al.,* "Application of Total Organic Carbon Analysis to Cleaning Validation," *PDA J. Pharm. Sci. Technol.* **50** (1), 6–15 (1996).
15. R. Sharnez *et al.,* "In Situ Monitoring of Soil Dissolution Dynamics: A Rapid and Simple Method for Determining Worst-case Soils for Cleaning Validation," *PDA J. Pharm. Sci. Technol.,* **58** (4), 203–214 (2004).
16. R.J. Forsyth, V. Van Nostrand, and G. Martin, "Visible Residue Limit and its Application in a Pharmaceutical Research Facility," *Pharm. Technol.* **28** (10), 58–72 (2004).
17. D.A. LeBlanc, " 'Visually Clean' as a Sole Acceptance Criteria for Cleaning Validation Protocols," *PDA J. Pharm. Sci. Technol.* **56** (1), 31–36 (2002). **PT**