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CLEANING VALIDATION

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INTRODUCTION

The subject of cleaning validation is an important but very sensitive issue to the industry. We have long recognized the importance of cleanliness in our business to avoid potentially dangerous cross contamination. Development of methods to adequately clean equipment and facilities has therefore always been an important part of how we operate and goes hand in hand with the development of the manufacturing process for any new drug product. The relatively recent formalization of a systematic approach to proving the effectiveness of all our processes, including cleaning methods, under the collective term "validation" does not therefore introduce a totally unknown concept--although its practical implementation is a significant economic and resource issue. There is a tendency in such formalized systems to enforce a uniform approach even though what has been done for many years has proven completely adequate. The danger therefore of giving such a talk, especially to the extent one "suggests" possible methods and procedures, is that this may then become some sort of benchmark by which all of the industry is judged. I do not believe there is a single "right" way for all firms--let alone for all products and/or processes--to validate their cleaning procedures. It is therefore explicitly not my intent to set such standards or even imply there is a best way to do it. Sufficient flexibility in how cleaning validation is approached needs to be maintained to allow individual firms to adopt methods and rationales which fit the

unique circumstances of their products, processes, facilities and historical practices--there are a wide variety of acceptable ways to accomplish the requisite proof that a cleaning method "does what it is intended to do." As with other laudable efforts to improve the quality of our industry's products, it is I believe wise to moderate our enthusiasm with a useful Midwest axiom: "If it ain't broke, don't fix it." The pharmaceutical industry in the Western world has an exemplary record for consistently producing quality drugs. While we should and are constantly striving to improve that record, imposition of rigid procedures which do not acknowledge the acceptability of existing alternatives accomplishes nothing but increasing the cost for the ultimate recipient of these efforts, the consumer.

While the subject of this meeting is primarily the development of new drugs, I do not see any significant differences between the fundamental approaches one takes for a new drug versus an established drug product. The sole exception to this might be in the safety factor one imposes when establishing limits--for a compound of relatively unknown toxicity this factor may need to be larger and/or the use of dedicated equipment may need to be considered until additional experience and safety data is accumulated which allows reduction of these precautionary measures. I therefore don't plan to focus this discussion on new drugs since I feel the concepts and issues are the same.

What I plan to do in this talk is to review some of the more difficult issues which firms will need to address in assessing and documenting the adequacy of their cleaning procedures for new or existing products and compounds. As I believe you will see, there are a number of complex issues which must be addressed and practical compromises which must be made to evolve a workable cleaning validation program.

ESTABLISHMENT OF LIMITS/DETERMINATION OF CONFORMANCE

These two issues are inseparably intertwined since a limit is only meaningful in the context of detection capability. This is at the

heart of the conflict between modern technical capabilities and antiquated legal concepts of purity (or adulteration).

Adulteration

The following is taken from the Food Drug & Cosmetic Act and is the legal basis for regulatory requirements that our facilities and equipment be clean: "A drug...shall be deemed to be adulterated...if it consists...in part of any filthy, putrid or decomposed substance...if it has been prepared, packed or held under unsanitary conditions whereby it may have been contaminated by filth, or whereby it may have been rendered injurious to health...or if...its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health..." A literal interpretation of this law could be (and perhaps has been in the past when analytical capabilities were not routinely able to challenge it) interpreted to mean that no measurable residuals are allowed.

De Minimis

A conflicting concept dictated by the increasingly sophisticated analytical technology is commonly referred to as de minimis. This concept recognizes that below a certain level, incidental residual agents/chemicals/drugs, etc. (i.e., "residuals") have no measurable biological effect even though they still may be analytically detectable (i.e., chemical exceeds biological detectability). This concept has been the focus of recent controversy in the food industry (e.g., methylene chloride residues in instant coffee, listing of dyes as food additives) and continues to be vigorously challenged by health consumer groups using the Delaney clause. Its applicability in the drug field is largely untested but can be anticipated to be at least equally controversial. In either case, de minimis can be considered an attempt to give legal recognition to physical reality.

Analytical Method

Selection of the analytical method will determine the residual's detectability. For the most part, if one is willing to pay enough, residues can be found at any level (i.e., nothing in

the universe is truly clean); hence to comply with a rigidly interpreted concept of what constitutes an adulterated product (i.e., must have no detectable residuals present), we must set our analytical method to detect potential residues only to the level independently determined as being meaningful from a safety risk standpoint.

Criteria For Limits

Two extreme positions of how to do this illustrate the difficulties in the task. Perhaps the most satisfying from a scientific perspective would be to approach this task quantitatively: (a) establish in collaboration with tox and medical authorities an effect threshold (will be dictated by the lowest dose at which toxicity or therapeutic effects are expected from the residual material on a chronic or acute basis); (b) superimpose an appropriate safety factor (e.g., 10X or 100X); (c) for each piece of equipment/contact surface involved calculate what level of residual could be tolerated if it found its way into the smallest batch size/maximum dose combination of any product made in that piece of equipment. Alternatively, one could use a very pragmatic approach: visual cleanliness. While the latter may sound far too unsophisticated and non-quantitative, in our experience quantitative calculations have almost universally yielded tolerable levels of residuals which were readily apparent visually, i.e., the visual cleanliness criteria was more rigid and clearly adequate. Clearly, however, for extremely potent or toxic substance, calculated tolerable residuals may be well below visual detectability. Hence, common sense and judicious use of quantitative methods when appropriate are called for depending on the nature of the possible residuals involved.

Dilution Assumptions

A critical consideration in establishing limits is the assumptions one makes about the dilution the residual will experience before it finds its way into a product subsequently manufactured in the same equipment. An often made assumption for batch processing equipment is that the residuals will be uniformly

diluted by the product subsequently made in that equipment. Given the focus on content uniformity in such processes, this would seem quite reasonable in most cases. For continuous or unit processing equipment (e.g., a tablet press), residuals cannot be reasonably assumed to be diluted by the entire batch, but rather progressively thru a relatively small portion of the subsequently manufactured batch. This might seem to dictate more stringent limits for such equipment; however, such equipment also generally has much less exposed surface area per batch which tends to more than counterbalance this concern. Hence, in a practical sense, a single residuals limit for a given type of product contact material based on a homogeneous dilution assumption would seem reasonable and conservatively supportable.

Pockets of Residuals

One issue that is frequently confused with the previously discussed dilution assumptions is the potential for pockets of residual product to collect in poorly accessible components of certain kinds of processing equipment. This problem is further compounded since these pockets of material are usually not well exposed to the bulk material flow (i.e., the reason for the pocket forming there in the first place). One has to therefore consider the potential for such pockets of residuals to break loose at an inopportune time (e.g., late in the processing step) and hence to be carried on to the next step in a relatively undiluted state. To try to accommodate this potential by modifying limits is not a workable option since such events are by definition unpredictable, i.e., there is no intent to allow such pockets to exist. Rather, the potential for such less accessible areas must be addressed and accommodated in development of a validated cleaning procedure, including appropriate training and rigorous compliance to the cleaning procedure which may call for disassembly and/or special intensive cleaning of equipment parts which have this potential.

WHICH RESIDUALS SHOULD BE MONITORED/VALIDATED

Relatively few drug products contain only a single component. In most cases a number of components are included in the drug

product accompanying one or more active ingredients. In addition, potential residues can be introduced in the cleaning process itself (e.g., detergents). In a practical cleaning validation program, one must therefore determine which of these components should be monitored for their presence after cleaning. This could include not only the active ingredients but also their degradation products, preservatives, excipients which may have some safety or cosmetic (e.g., dyes) liabilities of their own and the cleaning agents themselves. I don't intend to exhaustively review the issues involved in making such determinations. However, as with other aspects of validating a thorough yet practical cleaning program, judgements should be made with a recognition of the relative safety liabilities and technical risks of the various residues which may be present. Both the industry and the regulatory agencies could, I believe, readily agree that it is of no practical value to undertake analysis of all such potential residuals; the issue then is developing a sound basis for which residues are selected for monitoring to establish the effectiveness of the cleaning method.

USE OF MODELS

In all but the simplest circumstances (e.g., dedicated equipment), it is a practical necessity to limit the amount of testing as the possible combinations of equipment and products approaches an unwieldy if not infinite number. To validate each combination is neither cost effective nor a judicious use of often scarce technical resources. Hence, rational judgements need to be made on what compounds or pieces of processing equipment can reasonably be used to represent others.

Model Compounds/Products

There are several potential bases for selecting an active compound as being representative of other compounds or products which are cleaned from equipment using similar methods. These may include the compound's solubility, structural similarity, similar sorption/desorption isotherm behavior, similar dosage form matrix,

similar potencies and degree of cleaning difficulty. A frequently invoked rationale is that of a "worst case" situation: a compound or product is selected which can be argued to be the most difficult to clean; demonstration that it can be effectively cleaned using the cleaning method being validated can then be considered to encompass the less difficult compounds or products being cleaned using the same method.

Model Equipment/Materials

A very similar approach may be useful in limiting the number and type of equipment requiring full testing to establish a validated cleaning program. The majority of processing equipment in the pharmaceutical industry is stainless steel; we therefore most often deal with a common contact material. Furthermore, similarities in design, shape, size, functional purpose and/or processing stage may allow extrapolation of data to cover several pieces of equipment which utilize the same basic cleaning procedure. Again, worst case arguments may be usefully employed to limit testing to pieces of equipment which are particularly difficult to clean.

SAMPLING METHODS

There are several valid approaches to obtaining samples for residual testing after the proposed cleaning method has been employed. Their use will vary depending on the circumstances.

Swab Samples

This method uses swabbing of a defined surface area with an appropriate solvent in which the residual is soluble. The exhaustiveness to which the swabbing should be carried out will often be determined in independent studies which demonstrate the swabbing procedure's ability to recover sorbed residues from the contact material. Once the residue content of the swab solvent is determined, the total amount of residual material contained in the piece of equipment being tested can be back calculated based on its known total contact area. This method is quite straightforward but does require the development of an appropriate solvent and swabbing method. It is this author's view that this method will also tend to conservatively overstate the actual recoverable residues since

in most cases the solvent utilized will be far more efficient in recovering the residual material than the subsequently manufactured product would desorb during the process.

Rinse Samples

Analysis of a final rinse for residual levels is another useful method. It is particularly appropriate when the subsequent product being made in that piece of equipment is one utilizing the same solvent (e.g., water). The volume of this final rinse is usually accurately determined such that the total amount of residuals in the piece of equipment can be back calculated from the amount found in the rinse sample aliquot. Advantages of this method are its simplicity and essentially non-existent analytical background.

Pseudo-Product Samples

Occasionally it may be useful to determine how much surface residuals are actually solvated or worn off by attrition into a representation of the subsequently manufactured product. This "pseudo-product" can be processed in the piece of equipment under essentially normal operating parameters to very accurately simulate the actual manufacturing process. Again, using the known dilution factors, the total residuals and their distribution in a defined batch size can then be easily back calculated from the assay values of the aliquot sample. While this method may seem to give the most accurate representation of the true amount of residuals which are recovered in a subsequently manufactured product, this procedure is inevitably much more complex from an analytical point of view and may therefore suffer significantly in terms of accuracy. Furthermore, the solvating power or abrasiveness of different formulations may vary widely and be difficult to predict (i.e., to identify a true worst case situation); therefore, multiple pseudo-formulations could be required to fully validate the cleaning method for a variety of subsequently manufactured products. This method is therefore not recommended except under extraordinary circumstances.

OTHER ISSUES

Dedicated vs. Multi-Use Equipment

In most situations involving dedicated equipment (or equipment used in a campaign of several successive batches of the same product) less stringent limits are appropriate compared with the standards which must be met when a different product is manufactured in the equipment. Individual circumstances (including elapsed time of the campaign and the microbial growth potential of the product matrix) will determine how often a more thorough cleaning will be required but it certainly seems reasonable to allow the production of several successive batches of the same product/formulation before a more rigorous cleaning approaching a product changeover standard would be required.

Clean-In-Place/Automated vs. Manual Cleaning Methods

From a validation standpoint, there is no fundamental difference between these options, neither being inherently superior to the other. In both cases, the cleaning method must be demonstrated to consistently yield the desired level of cleanliness. In the manual case, this usually will require more thorough operator training and appropriate supervision.

Microbial "Residues"

This issue is independent of cleaning validation in the author's view. Appropriate microbial standards for both sterile and non-sterile manufacturing facilities should be established, validated and monitored to assure consistent conformance in all product manufactured therein.

SUMMARY

I have tried to briefly review what I believe to be the critical issues in designing a cleaning validation program. There are no absolute answers to the questions raised--and certainly none are offered here. Different solutions to the same problems can be and are frequently found so long as they are all consistent with the end objective of establishing a meaningful and fully documented

cleaning validation program. As with most other interfaces of quality and manufacturing, the desire for highest quality products to meet the public's health needs must be weighed against the costs of achieving them. Sound technical judgements provide a realistic tempering medium to achieve both objectives.