What to do if you can't use or obtain samples of materials used in your manufacturing process for cleaning validation recovery studies.

Regulatory Expectations

It is a regulatory expectation (e.g. FDA, EU, Health Canada)[1],[2],[3] that the ability to recover chemical residues after cleaning and the efficacy of disinfectants used, be demonstrated for all materials used within the manufacturing process. These regulatory expectations are that studies are performed from every product-contact Material of Construction, regardless of how prevalent it is in the manufacturing process.

The FDA *Guide to Inspection of Validation of Cleaning Processes* [4] states that firms need to "show that contaminants can be recovered from the equipment surface and at what level…".

The EU Guidelines for GMP Annex 15 [5] states that "recovery should be shown to be possible from all materials used in the equipment with all sampling methods used".

The Health Canada [6] and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) [7] cleaning validation guidance's also require that residue recovery experiments be completed.

Performing the effectiveness of the disinfectants and chemical residue recovery on the actual equipment or within the actual cleanrooms themselves can take 6 – 12 weeks to perform and may require the closing down of the equipments or cleanrooms themselves for this length of time.

Instead, coupons (samples) of representative material of each or the equipments or cleanroom surfaces s are used and can be tested in the laboratory instead.

Consequences

Failure to consider all surfaces will, and have led to warning letters and FDA 483 notices being issued:

> *"All surfaces that are used in critical processing and manufacturing areas were not evaluated." (FDA Warning Letter January 29, 2013)*

It is also important to consider that the Materials of Construction (MOC) used in the testing not only fairly represent the manufacturing surfaces themselves, but that they represent the condition of the surfaces as well. It is not always possible to repair or replace damaged or worn surfaces but if such surfaces are to be kept in use for an extended period of time (e.g. until the next scheduled maintenance event), then damaged surfaces must also be represented in coupon studies.

> *"The stainless-steel coupons tested did not represent these damaged surfaces." (FDA Warning Letter May 25, 2011)".*

:"The coupons used ….. were not representative of the surfaces found in the ……. Areas" FDA Warning Letter January 29, 2013)

Cleanability

Measuring the effect of the "cleanability" of a residue from a surface depends on three main parameters - residue solubility, sampling method used to sample the surface and the material of construction. These three parameters are interrelated

1) Each residue has an inherent cleanability, which may be related to its solubility [8].

2) The swab material must be able to absorb sufficient residue and solvent to remove the residue from the equipment material surface. The swabbing technique should be standardized to minimize subjectivity.

3) Finally, the material of construction of the manufacturing equipment needs to be considered. The swab recovery of residue from each material of construction should normally be determined to accurately quantify residue levels and assess material cleanliness.

And so, if the same residue is used and sampled in the same way, then the residue sample recovery will depend on the material of construction.

Risk Based

However, sometimes it's just not possible to obtain coupons of some or all the materials used in process (I had a case recently where surfaces used to construct an old cleanroom where no longer available from the supplier and obtaining coupons would have meant cutting up parts of the existing cleanroom) – so what should you do?

The use of a risk based method may be the answer.

The International Conference on Harmonization's (ICH) guideline on risk management [9] clearly states that any risk methodologies should be based on scientific knowledge.

Two studies in the past have examined the effects of using groups of representative materials to test for cleaning validation recovery factors.

RJ Forsyth et al [10] have proposed a risk based approach where they state;

> "*The material of construction is a factor in the recovery of residue in cleaning validation. An analysis of existing recovery data showed that recovery factors for drug products on various materials of construction may be categorized into several groupings".*

This shows that materials can be "grouped" together by Identifying the physical characteristics of the materials and parameters that influence recovery-data results. This will allow the cleanability of a process to be assessed by selecting a representative material from each group.

In that article, data was collected on swab recovery studies from 16 Merck manufacturing sites, involving 1262 recovery factor values for 48 different substances (including actives and detergents). This involved 29 different MOC's. Based on statistical analysis the materials of construction were classified into groups with similar recovery factors.

Le Blank [11] tabulated these groups as;

Group	**MOC's in Group**
A	Nylacast Oilon Plastic, Perspex, Cast Iron (polished)
B	Glass, PTFE, Stainless Steel, Delrin, Silicone, HDPE, Brass, EPDM, Bronze, Nylon, Carbon Steel (plus 6 other various MOC's)
C	Plexiglass, Latex Rubber, Butyrate, PTFE / Latex Rubber
D	ABS Plastic, Aluminium
E	Neoprene, Butadiene-Acrylonitrile, Methacrylate

The grouping shows that for a given residue, essentially the same swab recovery would be obtained for any MOC in that group.
Forsyth et al proposed this analysis to simplify recovery studies on a scientific basis by using a given MOC in a group to represent the recovery value for any material in that group.

This being the case then a sample representative of the material in each group could be used if samples coupons of the actual material was not available.

A similar study by Pack Hofer [12] using s smaller number of samples but using two different actives (one with a low solubility and one with a high solubility), at several different spiked levels, and to see if there were any trends among MOCs produced a similar grouping:

Group	**MOC's in Group**
1	Stainless Steel 316L, Stainless Steel 304, Anodized Aluminium, Nickel, Polyamides, Teflon (PTFE), Acetal, Polycarbonates, Ertalyte
2	Cast Iron, Stainless Steel 420, Stainless Steel 630, Bronze
3	Type III Hard Anodized Aluminium

Conclusion

While it could be justifiable to simply use a representative material of construction coupon from each of the groups above if coupons from the actual materials of construction were unavailable, the justification for this approach would be strengthened if materials from some of these groups could be tested using specific facility or company residues and using the specific facility or company sampling techniques and be shown to be consistent with the groupings shown above, combining published results with actual results from that facility/company.

There are commercial companies that can supply suitable MOC coupons in most materials.

References

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