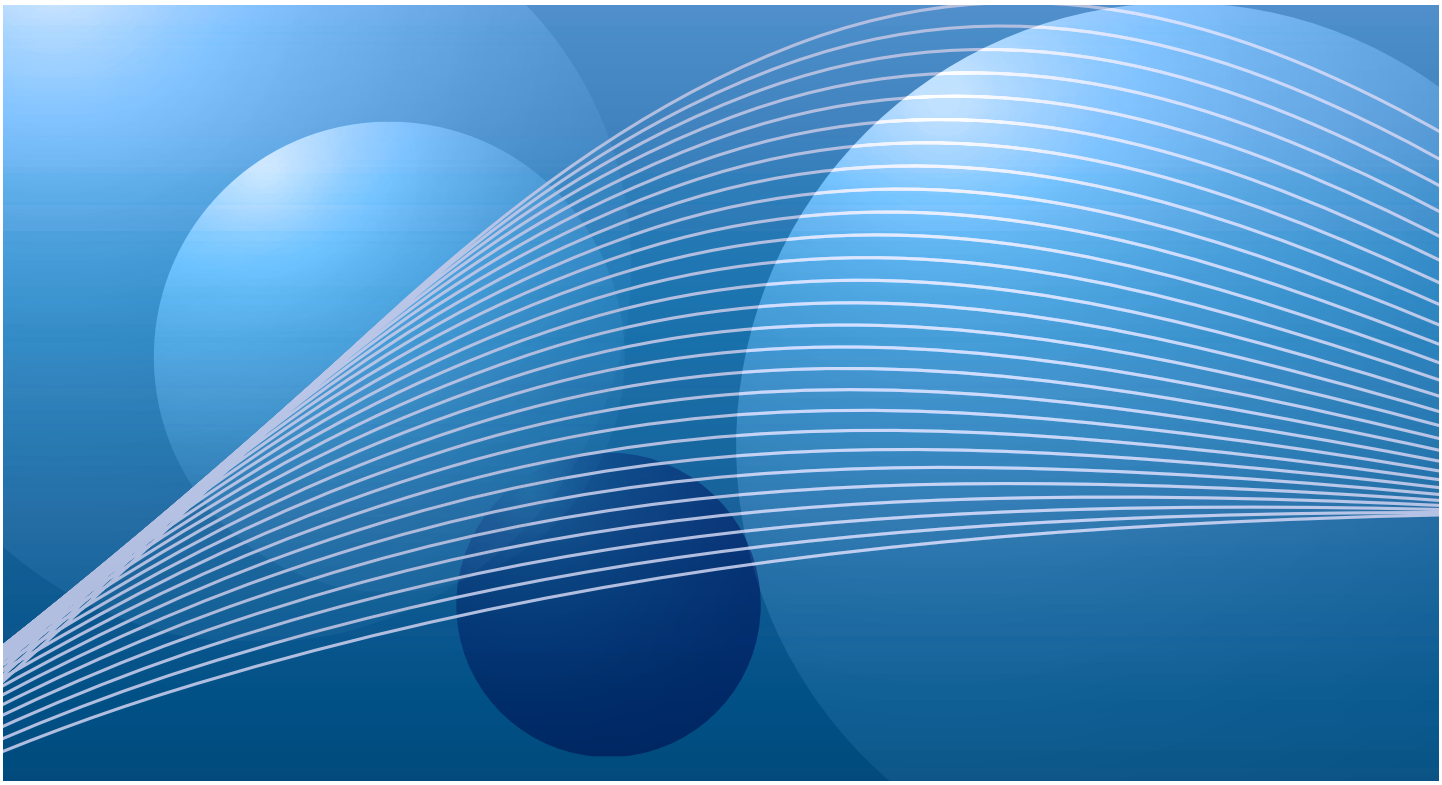

White Paper

Cleaning Validation

What do you need to consider to ensure a successful outcome?

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Abstract

The data used to determine the success of a cleaning validation is built upon both the effective evaluation of the manufacturing plant and the robustness of the validated analytical method. In order to ensure the safety of the consumer, there must be a high degree of confidence in the analytical results in order verify the absence of residues at the prescribed limits on the various equipment surfaces. This white paper discusses the over-arching strategy for performing a successful cleaning validation, with detail on some of the key factors to consider at both the manufacturing and analytical stages, highlighting many common pitfalls to avoid.

Contents

Introduction

Cross contamination must be avoided in the Pharmaceutical industry at all costs, successful cleaning validation ensures that patients are not put at risk due to cross contamination.

The process can be divided into a number of sections each of which must be fully understood and areas of concern addressed to ensure a successful outcome across the entire process. This spans both the manufacturing and subsequent analytical support.

The data used to confirm a positive/successful cleaning validation is underpinned by the results of validated analytical methods. It is essential that these results are truly representative as patient safety is based upon the absence of equipment residues.

So what are those areas of concern, what affects your ability to get a successful outcome and what do you need to consider when carrying out a Cleaning Validation exercise?

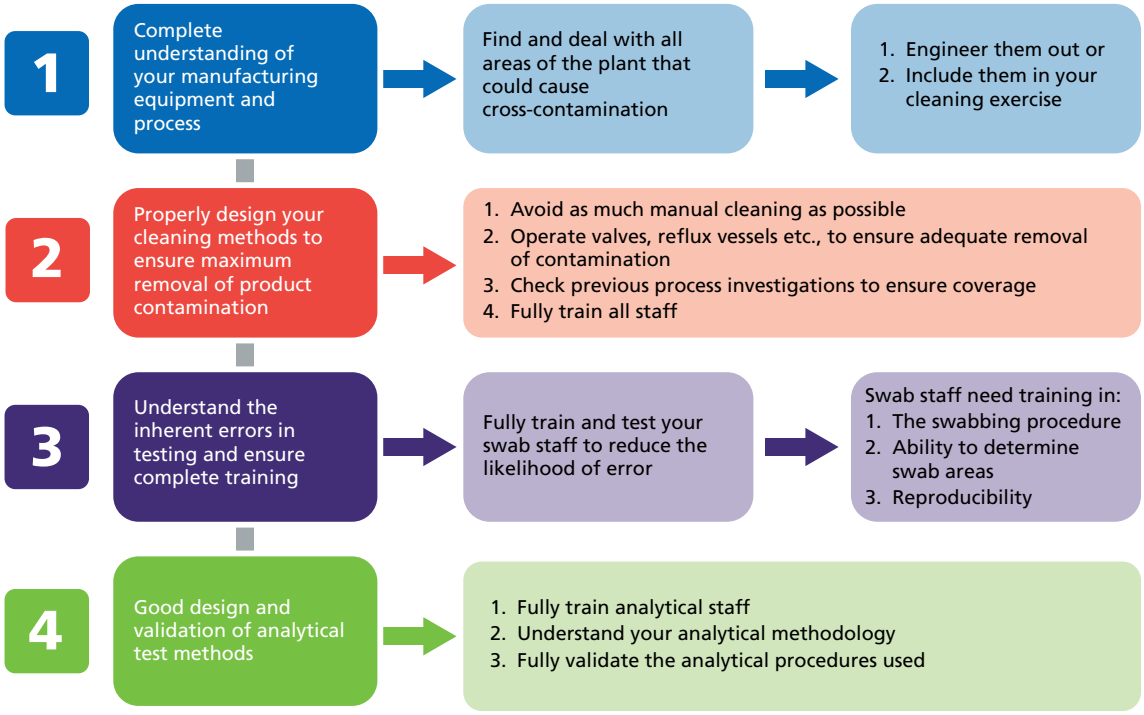
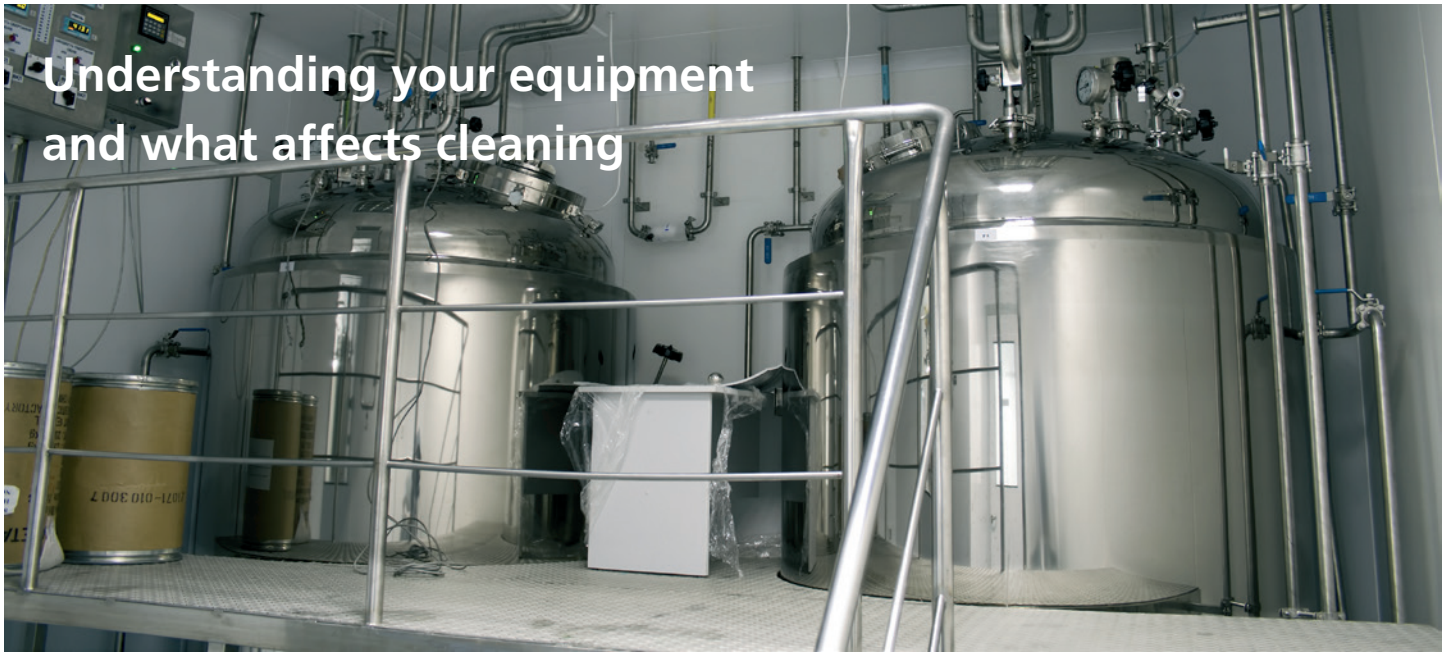


Figure 1. An overview of the areas to be considered to ensure success.



Understanding your equipment and what affects cleaning

Figure 2: Showing complex nature of a cleaning plant

A detailed study of all the equipment to be cleaned must be carried out by a qualified team to ensure the chosen cleaning method will be successful. This is colloquially known as "Walking the plant". It is important to understand what can affect your cleaning results and to either engineer out those areas of concern or include them in your cleaning procedure.

Areas of concern

All product contact pipe work should be thoroughly evaluated. The geometry of the pipe work can play a vital role in a successful outcome. Multiple bends, flanges, angles of pipework and dead ends, can all result in product retention and possible cross contamination. There are recorded cases in the industry of minor changes to pipework geometry resulting in cross contamination issues.
Remember – If you change the shape of a piece of pipework it may no longer clean as well.

Specific areas to be mindful of are:

1. **Service lines** – These are small bore lines and very difficult to clean. There have been a number of cases over the years where investigations into cross contamination issues have concluded that the service lines were at fault. Ensure that you have adequate safeguards in place (e.g. non return valves and filters) to ensure these lines do not get contaminated.
2. **Gaskets** – The microscopic nature of materials used to make gaskets result in product retention and possible swab failure. It is recognised that gaskets are necessary but a study should be carried out to ensure that there are not gaskets in the system that are no longer required and that all gaskets in the plant are in good condition to reduce the risks.
3. **Filter meshes** – These are designed to retain product and therefore can also result in cross contamination if not carefully cleaned.
4. **Valves** – Material can be drawn into valve housings and returned to the product stream at a later date resulting in cross contamination. All valves in the product stream should be investigated, a cross section dismantled and tested during validation to ensure that they do not present a risk to the outcome.
5. **Pumps and samplers** – These pieces of equipment are very difficult to clean successfully. It should be determined if they are really necessary. Can the geometry of the plant be altered to avoid their usage? If not they must be included in your cleaning exercise.
6. **Process investigations** – It is important that an understanding of what can go wrong in a process is obtained. Sometimes a process error at an earlier date can result in product being deposited in an area of the plant where it normally would not reach. This can then result in swab failures during cleaning or more critically Product contamination at a later date. E.g. Over-heating of a vessel can result in product being deposited in condenser return lines.
7. **Packaging lines** – It should be determined that there are no areas in the line where tablets could bounce and get stuck e.g. on the top of sensors etc. These may then fall off later into a different product and cause cross-contamination, patient injury or even death. Screens should be erected at these areas to ensure this cannot ever happen.

Remember – A good plant walk around, if performed thoroughly, with the right team, will not only reduce errors, but will also write most of your cleaning validation protocol. Swabbing points and plant break in lists can be decided during this investigation.

Design and control of cleaning methods

Good cleaning procedures are fundamental. A procedure that has been used for years may not necessarily be the best. A review of the methods should be carried out at validation to determine their suitability and effectiveness.

Procedures should include factors such as:

1. Operation of valves during cleaning
2. Filling pipework with solvent and allowing dissolution time
3. Refluxing solvent around system and through condenser return lines

Manual cleaning is very subjective. Two different operators may not necessarily clean to the same degree. In order to achieve reproducibility it is critical that all operators carry out the procedure in the same way. Very detailed procedures and training are required to ensure the successful outcome of a manual cleaning exercise. It is sometimes easier to alter plant layout so that Clean in Place (CIP) can be performed in place of manual cleaning, e.g. moving a pan filter from beside the vessel to the floor below can result in a double bonus. The pan filter can then be washed using a CIP procedure and the move also results in a loss of a pump and extra pipework. This sort of rearrangement should be considered as it reduces risks of error.

Ensure that:

- Written procedures will deal with the outcome of a process failure based on knowledge of what can go wrong in your process. Often what can go wrong in a process is more critical to the cleaning than what can go right.
- All process operators are fully trained and their records are up to date. Validation exercises have failed in the past, during audits, due to failure to ensure that operators' training records were complete and up to date.

Figure 3: Example of problematic plant areas

Issues with sampling and testing

A considerable proportion of the testing failures experienced in the industry are not related to the ability to clean the equipment or perform the analysis. They are solely related to the skills of the person taking the swabs. It is easy to write and train a procedure on how to carry out a swab test but it is a different thing being able to perform a test correctly and reproducibly. So what can be done to reduce this risk and help secure a successful validation outcome?

- A number of issues can be identified related to the swabbing procedure and these must all be addressed if success is to be guaranteed.
- Control of swab equipment – It is essential that all the equipment used to carry out a swab test is reliably controlled. It is extremely easy to contaminate a swab and put your whole cleaning validation exercise at risk of failure. The swab material, the solvent used, any disposable gloves etc. must be very carefully controlled to reduce the risk of possible false results.
- Test the ability of the operator to perform not only the swab procedure itself but also their skill in:
  - Being able to determine the correct area to be swabbed even when they cannot visually see where the task is being performed. Failure to swab the required area will result in either a failed swab or worse still, from a cross contamination viewpoint, a passed result which should really fail.
  - Their reproducibility in being able to repeat this exercise 4 times in exactly the same place.
  - It has been demonstrated that a swab taken using 4 wipes of the same area results in maximum recovery (>90%) from a given surface. However the ability to do this requires considerable skill and training.

All of the above require considerable skill and extensive training of the operator. However, techniques have been developed that will test these skills and give assurance that the final test results reflect the actual plant cleanliness and not the ability of the swab operator to perform the task.

Development and validation of analytical test methods

Alongside the product manufacture, the analytical method is of critical importance when assessing the cleanliness of pharmaceutical manufacturing equipment. In order to satisfy this requirement, it is key to ensure a high level of confidence in the generation of results derived through the use of the method. This, in turn, is underpinned by the development of a suitable, fit-for-purpose analytical method, designed not only to be specific to the analyte, but also able to ensure its ability to quantify at the prescribed residue limits.

On the subject of residue limits, this is very much a subject in its own right. The regulatory authorities do not set limits for specific products. The key factors to bear in mind when approaching this with respect to a given pharmaceutical product:

- Defined limits should be logical
- They should be practical and achievable (in terms of method sensitivity)
- Verifiable

An approach for limit setting should be identified early on since this will have a direct impact on the analytical test method and its ability to detect the analyte(s) at the required level.

Determining cleanliness can prove to be a very challenging task, with the aim being to measure trace residues (target analytes) on the surfaces. The residue must initially be extracted from a surface, recovered from the extraction matrix and then suitably quantified. Note that sampling is usually performed via direct methods (swabbing), however indirect strategies (such as rinse samples) may also be used, though the latter is not a preferred approach.

Very often, the starting point in the development of a cleaning method would be based upon a previously developed assay method. The main aspects to be borne in mind are (1) attainment of suitable sensitivity to quantify at the limits, (2) specificity (between the target analyte and other matrix components) and (3) a curtailed run time to allow the requisite high sample throughput that is generally needed when analysing swab samples.

In many respects, the requirements for validating cleaning methods are closely aligned with a standard assay, evaluating factors such as specificity, accuracy (recovery), linearity, sensitivity, precision, robustness and solution stability. However, one area that does require some time is the swabbing technique itself. A large part of the development procedure itself is focused upon deriving a swabbing procedure that allows acceptable recovery of API residues from the required surface types. Furthermore, the choice of swab surface used will be dictated by conducting a plant walk-around and subsequent risk assessment of the manufacturing plant and determination of the key 'risk' areas where residues are most likely to remain following manufacture.

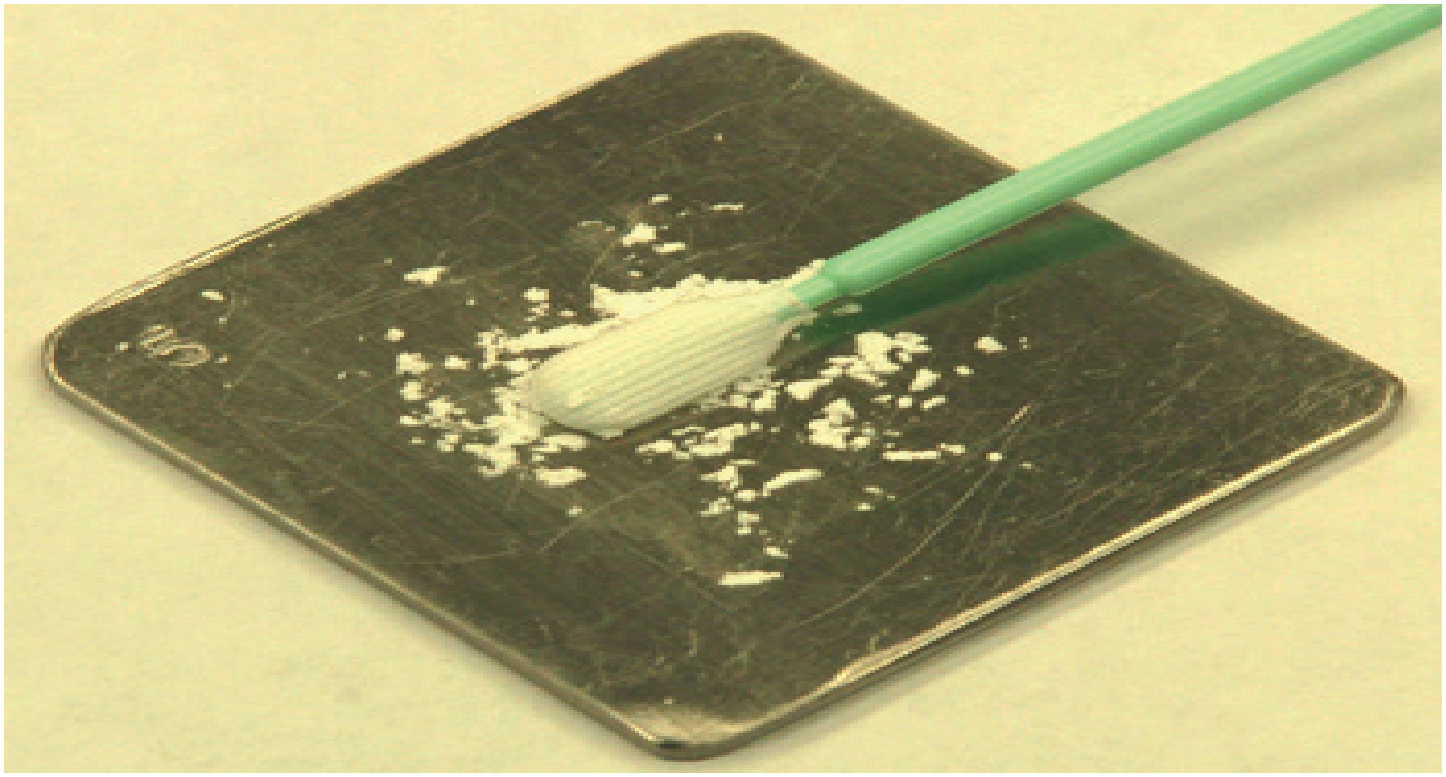


Figure 4: Swabbing of a stainless steel coupon

Swabbing

Often, insufficient time is invested in the actual swabbing regime, which can ultimately lead to a less than robust final method. Each of the surface types identified (discussed previously) should be spiked with the API (at the calculated residue limit) and experiments performed to demonstrate that acceptable recovery is repeatedly obtained. This can involve the evaluation of a number of different swabbing solvents and swab types together with optimisation of the actual swab technique. This, combined with the need to be able to repeatedly detect residues at very low levels, can contribute significantly towards the time required for successful method development and validation.

Figure 4: Example of different swab types

Recovery experiments essentially underpin all other validation parameters since the residue must be:

1. Successfully extracted from a surface
2. Recovered from the extraction matrix
3. Appropriately quantified

If the method is shown to have sufficient accuracy, then all of these parameters can be evaluated as a single entity. If inadequate results are obtained then each of the steps would need to be investigated individually to identify which of the component steps is responsible for the poor recovery, and allow screening of other solvents or swab material that may improve recovery. It should provide assurance that an analyte can be analysed in a matrix, which, for a finished product, would include excipients, impurities or perhaps solvents used in the manufacture of the actual API. If a cleaning agent is used, its composition should also be considered. An evaluation of specificity should first be conducted to ensure the absence of any interference between matrix components and the target analyte.

Another key factor to be considered throughout the development process is the stability of the analytical samples; that is, the ability of the active substance to degrade once in the extraction solvent. If appropriate expiry dates are not set, significant degradation could occur, leading to apparent low swab levels, which could actually be attributable to the instability of the active and not representative of the levels actually swabbed from the equipment surfaces – potentially giving a result that "passed" which should actually fail.

There is such an array of validation parameters that could be discussed, however this article cannot possibly do each of these justice. However, In terms of analytical method validation, there should be no unexpected surprises. All of the critical parameters to be assessed should be identified and evaluated prior to commencement of the formal validation. The method development should therefore be used to obtain the initial information to set the limits stipulated within a validation protocol and hence build in Quality by Design.

Conclusion

The over-arching principle when embarking on pharmaceutical cleaning validation is to ensure that the manufacturing and analytical aspects are conducted synergistically, with good communication between manufacturing and analytical teams. This will build solid foundations to ensure that the final analytical method is able to fully encompass the requirements of the cleaning process, and can reliably and consistently quantify the required residues at the calculated limits, hence ensuring the pharmaceutical product is safe for the consumer.

About the authors

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Technical Specialist

Steve has sixteen years' industry experience, having graduated in 2000 from Kingston University with a Bachelor's Degree in Pharmaceutical Science. He has spent his entire career to date working in the pharmaceutical sector and has gained all of his experience within a CRO environment, gaining exposure to a wide range of analytical techniques and product matrices. Steve's main area of expertise is Early Phase Development, Validation and Stability Testing of New Chemical Entities and Formulations mainly in Pre-clinical Development or Phases I and II.

Brian Hammond
Cleaning Validation
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Brian has forty six years' experience in the industry after graduating in 1970 from London University. His experience was initially in Analytical Development moving onto Quality Compliance and System Validation, followed by 21 years' experience in the training and consultancy arena. Brian's main area of expertise is in Cleaning Validation, he has been heavily involved in developing techniques, resolving issues and has been running very successful cleaning validation training courses for RSSL for many years.

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