Major Cleaning Periodic Monitoring Reduction in a Solid Dosage Pharmaceutical Plant

Héctor Martínez Zeno
Master of Engineering in Manufacturing Engineering
Rafael Nieves, PharmD.
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract — *Regulatory agencies expected that pharmaceutical industries must demonstrated with a high degree of assurance the effectiveness, consistency and reproducibility of the cleaning process in producing visually clean surfaces and reducing microbial levels, active ingredient and detergent residues to acceptable limits. Also, once the cleaning processes are validated, it is required to periodically assess to evaluate if the cleaning process maintained its validated state. An evaluation of the cleaning process for Pharmaceutical Company XYZ was performed. Using a risk based approach and groping strategies for active ingredient and equipment, the periodic monitoring exercise was reduced for more than 50%.*

Key Terms *– Cleaning Validation, Periodic Monitoring, Risk Based Approach, Worse Case Scenario.*

INTRODUCTION

The pharmaceutical industry is highly regulated by federal (Food and Drug Administrator [FDA]) and internationally agencies (European [EU] Medicines Agency). One parameter verified during an audit is equipment cleaning. Pharmaceutical industries must demonstrated with a high degree of assurance the effectiveness, consistency and reproducibility of the cleaning process in producing visually clean surfaces and reducing microbial levels, active ingredient and detergent residues to acceptable limits.

Once the cleaning procedures are validated, it should be monitored at appropriate intervals to ensure that these cleaning procedures are effective when used during routine production. An evaluation of equipment cleaning should be performed by performing visual inspection of the equipment surface. Once the visual inspection is completed samples for microbial growth, active ingredient and detergent residues should be collected from the equipment. Cleaning process effectiveness will be demonstrated by samples satisfactory results.

Manufacturing equipment can either be cleaned manually, automatic or semiautomatic. Manual cleaning is performed by an operator. Automatic cleaning can be CIP (Clean In Place) or COP (Clean Out of Place). CIP systems are installed in the equipment and no operator is required to perform the cleaning. COP systems are commonly used in the industry. Parts needed to be clean must be transferred to COP locations. An example of this system is a cabin washer.

For automatic cleaning procedures, the periodic monitoring exercise can be performed in longer intervals since there is no manual intervention. For manual cleaning, the agencies expectations are to be monitored annually. For the selected pharmaceutical industry, a solid dosage pharmaceutical industry, most of the cleaning processes are manual process. The expectation is to reduce the amount of periodic monitoring exercise using a scientific based approach.

Research Description

Based on the actual periodic monitoring approach, a total of forty nine (49) exercises are performed every year. Table 1 summarizes the samples collected as part of the forty nine (49) exercises.

The periodic monitoring process consisted of the following steps:

- Perform a manufacturing campaign.
- Clean the equipment.

- Perform a visual inspection.
- Collect the required samples (Microbiologic, Active Pharmaceutical Ingredient [API] and/or Detergent).

Once a periodic monitoring exercise sampling is performed, the manufacturing equipment is placed on hold until analytical results are obtained. Normally, the holding time is twenty four (24) hours.

Table 1
Periodic Monitoring Sampling

Sampling Type	Amount
Active Pharmaceutical Ingredient (API) Swabs	**74**
Detergent Swabs	**81**
Rodac (Microbiological Analysis)	**33**
API Rinse	**6**
Detergent Rinse	**6**
Micro Rinse	**12**
Total Sampling	**212**

Research Objectives

The purpose of this project is to reduce the amount of periodic monitoring exercise and sampling in more than twenty five percent (25%).

Research Contributions

Periodic monitoring exercise reduction will provided the following benefits:

- More equipment availability in the manufacturing area and in the Quality Control laboratory equipment High Performance Liquid Chromatography (HPLC) and Ultraviolet (UV).
- Cost reduction since fewer swabs and laboratory reagents will be used.
- Increase in man hours for technicians (In the manufacturing) since fewer exercises will be performed.

LITERATURE REVIEW

The pharmaceutical industry develops, produces, and markets drugs or pharmaceuticals licensed for use as medications. Pharmaceutical companies are allowed to deal in generic or brand medications and medical devices. They are subject to a variety of laws and regulations regarding the patenting, testing and ensuring safety and efficacy and marketing of drugs.

In the United States, new pharmaceutical products must be approved by the Food and Drug Administration (FDA) as being both safe and effective. Different countries have their own agencies that approved products for their corresponding markets. An agency like European Medicines Agency (EMA) certifies products for Europeans countries. Others countries like Australia, Turkey, Japan, Korea, Brazil, among others have similar regulatory agencies that approve drug products.

For FDA to require that equipment be clean prior to use is nothing new, the 1963 GMP Regulations (Part 133.4) stated as follows "Equipment shall be maintained in a clean and orderly manner." [1] A very similar section on equipment cleaning was included in the 1978 cGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust control systems. Also, historically speaking, FDA was more concerned about the contamination of nonpenicillin drug products with penicillins or the cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

One event which increased FDA awareness of the potential for cross contamination due to inadequate procedures was the 1988 recall of a finished drug product, Cholestyramine Resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides [1]. The cross-contamination in that case is believed to have been due to the reuse of recovered solvents. The recovered solvents had been contaminated because of a lack of control over the reuse of solvent drums.

Drums that had been used to store recovered solvents from a pesticide production process were later used to store recovered solvents used for the resin manufacturing process. The firm did not have adequate controls over these solvent drums, did not do adequate testing of drummed solvents, and did not have validated cleaning procedures for the drums.

Some shipments of this pesticide contaminated bulk pharmaceutical were supplied to a second facility at a different location for finishing. This resulted in the contamination of the bags used in that facility's fluid bed dryers with pesticide contamination. This in turn led to cross contamination of lots produced at that site, a site where no pesticides were normally produced.

FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer which manufactured potent steroid products as well as non-steroidal products using common equipment [1]. This firm was a multi-use bulk pharmaceutical facility. FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection and it was considered inadequate by FDA. One of the reasons it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from Thin-Layer Chromatography (TLC) tests on the rinse water, of the presence of residues of reaction byproducts and degradants from the previous process.

In terms of general approach for equipment cleaning, all agencies concur that pharmaceutical industries must provide documented evidence that the cleaning process consistently provides a high degree of assurance that after cleaning, potential contaminants, (active ingredient, detergent residues and bioburden) are reduced to acceptable levels from the equipment surfaces avoiding the contamination or adulteration of subsequent products to the extent that fitness for use would be compromised. Based on these requirements cleaning procedures are validated to assure efficiency. In order to validate a cleaning procedure, the following considerations may apply.

Detailed cleaning instructions must be written and operators carrying out cleaning procedures must be adequately and/or trained, monitored and periodically assessed. Cleaning procedures should contain sufficient details in order to enable manufacturing operators to clean each type of equipment in a reproducible and effective manner. Procedures must be specific on cleaning parameters such as water type (Purified water, water for operations, water for injection, etc.), rinsing time, scrubbing times, detergent concentration, water temperature, among others. If a detergent is required, cleaning instruction must demonstrate the removal of the detergent agent. Studies should be conducted to determine detergent selection. A scientific rationale most demonstrates detergent selection.

Cleaning procedures must have but not limited to the following: Responsibilities for cleaning activities, equipment and materials to be used, detail cleaning instructions, Equipment's disassembling and re-assembling instructions, clean equipment protection instructions, cleaning frequencies, among others.

Residues left in the equipment must be analyzed to determine if the cleaning procedure is effective. In order to determine cleaning procedures effectiveness, an effective test method, sampling and acceptance limit are required.

The analytical method used to detect active and detergent residues and microbial activity must be validated. Such validation method must consider and support the adequacy of using the methods for the analysis taking into consideration recovery studies (Detailing sampling material and solvent), detection and quantification capabilities among others. Analytical methods must be sufficiently sensitive to detect the established acceptable level of residues being tested; and may be specific or non-specific. For non-specific methods, all of the compound detected must be attributed to the residue being tested. Test results must be reported

by numerical values. Pass or fail results are not acceptable for cleaning validation. [2]

Sample collection locations from the manufacturing equipment should be identified following similar criteria.

- Equipment/equipment component gas significant surface area in contact with active ingredient/non active ingredient/detergent.
- Different surface material of equipment/ equipment component in contact with active ingredient/non active ingredient/detergent.
- Hard to get or to clean equipment/equipment component surface.
- Operators input during Standard Operation Procedure (SOP) evaluation.
- Large equipment/equipment component surface area in contact with active ingredient/non active ingredient/detergent. More than one location is taken for better representation.
- Area with significant product exposure.
- Point at the end of the cleaning circuit in which the water (Final Rinse) leaves the circuit.

With the identified sampling locations, a sampling technique must be implemented in order to collect a representative sample from the sampling locations. There are two general types of sampling that have been found acceptable. The most desirable is the direct method of sampling the surface of the equipment. Another method is the use of rinse solutions.

Direct Surface Sampling determines the type of sampling material used and its impact on the test data since the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with the analysis of samples. Therefore, early in the validation program, it is important to assure that the sampling medium and solvent (for extraction from the medium) are satisfactory and can be readily used.

Advantages of direct sampling are that areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "Dried Out" or are insoluble can be sampled by physical removal.

Rinse Samples have two advantages, a larger surface area may be sampled and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated.

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the “Dirty Pot”. In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

Regulatory agencies do not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. Is not adequate establish one specification due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. Residue limits rationale should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 PPM, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue.

Routine monitoring should be performed after every cleaning. Visual inspection of product contact must be inspected and documented after cleaning. For manual cleaning, the cleaning and visual inspection should be performed by a one person and the visual inspection must be verified by a second person. Visual inspection must be verified as acceptable prior to reuse the equipment.

Once the cleaning instructions have demonstrate with high degree of assurance that after cleaning, potential contaminants, (active ingredient, detergent residues and bioburden) are

reduced to acceptable levels from the equipment surfaces avoiding the contamination or adulteration of subsequent products to the extent that fitness for use would be compromised, a periodically monitoring plan must be performed.

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

Regulatory agencies do not have criteria for periodic monitoring. Pharmaceutical agencies must determine monitoring frequencies. For manual cleaning, it is recommended to perform periodic monitoring annually. For automatic cleaning, different approach should be used.

METHODOLOGY

In order to reduce the amount of periodic monitoring samples, the following strategies will be followed: Active Ingredient Worst Case Scenario and Equipment Grouping Strategy. Using these two strategies, cleaning validation exercise will be performed in the granulation equipment. Also, equipment classification will be performed based on the manufacturing process performed in order to minimize the microbial growth periodic monitoring. Risk based approach will be used for worse case scenarios determination and equipment classification.

Acceptability of a "Worst-Case Approach" for cleaning validation is included in regulatory documents: EU GMP Annex 15, 39 established the following: "For cleaning procedures and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilizing "Worst-Case" approach can be carried out which takes account of critical issues".

Cleaning procedures for products and processes which are very similar do not need to be individually validated. This could be dependent on what is common, equipment and surface area, or an environment involving all product-contact equipment. It is considered acceptable to select a representative range of similar products and processes. The physical similarities of the products, the formulation, the manner and quantity of use by the consumer, the nature of other product previously manufactured, the size of batch in comparison to previously manufactured product are critical issues that justify a validation program.

A representative product can be selected for cleaning validation (e.g., worst-case or bracketing). The policy states the following must be considered: Solubility in cleaning solutions, Potency, Toxicity, Stability, Difficulty to clean, Concentration of the API in the formulation, Excipients type and quantity in the formulation and Finished Products Water activities (Microbial). Considerations for worst case scenario are explained above.

- Solubility in cleaning solutions: Solubility in cleaning solutions is a key indicator of clean-ability. When a compound is more insoluble, the risk of not appropriately cleaning the equipment increases, so this will be used as a factor in the risk-based assessment to determine the "Worst-Case" compound. [3]
- Potency: As the compound becomes more potent, the manufactured dose becomes smaller. The cleaning limit is determined based on the smallest dose of the compound manufactured. This is not required to be used as a factor to determine the "Worst-Case" model compound, since the most stringent limit will be applied to cover the group of products which will be validated regardless of the smallest dose manufactured of the "Worst-Case" compound selected.
- Toxicity values (Acceptable Daily Intake, ADI) are considered in the cleaning limit. This is not required to be used as a factor to determine the "Worst-Case" model compound,

since the most stringent limit will be applied to cover the group of products. [4]

- Stability: Release testing for all XYZ products includes evaluation of related substances. This is not required to be used as a factor to determine the "Worst-Case" model compound, since all lots manufactured are tested for related substances.
- Difficulty of cleaning can be evaluated by operators' feedback from cleaning experience that a compound is difficult to clean. The manufacturing cleaning experiences will be used to determine Worst Case.
- Concentration of API in the formulation: Selecting a compound with the highest concentration of API provides a more robust challenge during the validation exercise by exposing the equipment to the highest concentration of API, so this will be used as a factor in the risk-based assessment to determine the "Worst-Case" compound.
- Excipient type and quantity in the formulation: Product formulations should be assessed for any potentially toxic excipients that should be considered in determining a "Worst-Case" compound. Insoluble excipients may directly impact the cleanability of a drug product. It is reasonable to consider the impact of excipients type and quantity when determining a worst-case compound based on the higher risk of adherence to the equipment surface; therefore, it will be used as factor in the risk-based assessment to determine the "Worst-Case" model compound.

To determine the "Worst-Case" compound, a risk priority index will be calculated for each compound using risk priority numbers which takes into account the factors of product solubility, active ingredient solubility, concentration of the API and excipients solubility and quantity in the formulation.

In terms of equipment grouping strategy, some equipment was considered functionally equivalent in terms of their design characteristic regardless of their different capacities. Equipment grouping involves items that are similar in every way (Design) except for size. Some equipment will be used as a worst scenario due to its size, hence their cleaning process is more difficult to perform and cleaning as well as rinsing times will be appropriate for the smallest. For similar equipment having same cleaning processes (Same procedure/ instructions), a grouping strategy will be used in which one equipment is selected as representative of the grouping established.

Active Ingredient Worst Case Scenario and Equipment Grouping Strategy will be documented and included as part of the site cleaning validation master plan. Document will be reviewed and approved by Technical Services, Manufacturing and Quality Assurance Departments.

RESULTS AND DISCUSSION

Pharmaceutical company XYZ is dedicated to the solid dosage manufacturing process. Products are manufactured in bulk and shipped to their assign packaging site. A total of six (6) products are manufactured in this site. The manufacturing area is divided in sections; Capsules, Tablets and High Volume Product. In the Capsule area, two (2) products are manufactured. In the Tablets area, three (3) products are manufactured and in the High Volume area, one (1) product is manufactured. For project purpose, products manufactured in the Tablets area will be identified as products A, B and C. Product manufactured in the Capsule area will be identified as products D and E and product manufactured in the High Volume area will be identified as product F. Product F is manufactured in capsules.

Tablets products (A, B and C) manufacturing process consisted of the following stages: dispensing, granulation (High Shear), drying, milling, blending, compression, coating and printing. Capsules products (D and E) manufacturing process consisted of the following stages: dispensing, milling, blending and encapsulation. The High volume area is dedicated

to the manufacturing process of product F. Product F manufacturing process consisted of the following stages: dispensing, solution preparation, coating and encapsulation.

Company XYZ quality standard established that all validated cleaning procedure must be periodically evaluated to assure a validated state. In addition, manual cleaning process must be annually evaluated. Most cleaning processes in company XYZ are manual. High volume area has automatic cleaning process for the Active tanks 1, excipients tanks 1, transfer lines and precision coating.

Cleaning validation in company XYZ were performed using the worst case product. Cleaning validations were divided in chemical validations (API and Detergent Removal) and microbial growth validation. Each cleaning validation exercise has a different worst case product. Since the periodic monitoring is a verification of the cleaning validation performed, multiple periodic monitoring has to be performed for the same equipment in order to verify the chemical and microbial validation requirements. Table 2 shows the total periodic monitoring sampling and runs per year.

Table 2
Total Periodic Monitoring Sampling and Runs per Year

Sampling Type	Previous Strategy			Amount of Run
	API	Detergent	Micro	
Swab	74	81	0	49
Rodac	0	0	33	
Rinse	6	6	12	

In order to reduce the amount of periodic monitoring per year, the following actions were performed.

- Establish one worse case product that can justified chemical (API and Detergent Agent Residues) and microbial growth.
- Perform a grouping strategy for the granulation and compression equipment. Activity required a validation exercise for both stages.
- For dedicated equipment, no API sampling is required. Only detergent residues (If applies) and microbial growth.
- No periodic monitoring will be performed for automatic cleaning because an in-line testing (Conductivity) is performed after every major cleaning.
- Product F has an inhibitory property that does not promote microbial growth. Based on this information, no microbial growth will be performed product F.
- Company XYZ manufacturing equipments were classified in two categories: Type 1 (Dry) and Type 2 (Wet).
    - Type 1 (Dry) equipment is one that has been exposed to processing conditions or materials for which the ability to clean is not likely impacted by total exposure time or idle exposure time. Examples of materials include dry powders and equipment which are dry at the end of processing.
    - Type 2 (Wet) equipment is one that has been exposed to processing conditions or materials for which the ability to clean is likely impacted by total exposure time or idle exposure time. Examples of materials include wet powders and equipment which are wet at the end of processing.

Based on the bioburden control strategy and the satisfactory results obtained for all cleaning validation exercise for microbiology sampling, it was determined that for Type 1 (Dry) equipments no microbiology monitoring exercise (Annually) will be performed. For Type 2 (Wet) equipments, microbiology monitoring exercise (Annually) will be performed.

Capsules Area Mixer was classified as Type 1 (Dry) equipment. This equipment is dedicated Capsules excipients mix. One of the excipients used in this mix is considered as a worst case since it promotes microbial worth. In addition, Mixer is considered a hard to clean equipment due to equipment design. Based on this information,

microbial annual periodic monitoring will be performed.

Precision Coater 2, Active Solution Tank 2 and solution lines were classified as Type 2 (Wet) equipment. These equipments are dedicated to Product F manufacturing process. Product F has microbial growth inhibitor properties. In addition, Product F Coating process is conducted using an Inlet Air Temperature between 85ºC to 95ºC with a product temperature between 40ºC to 50ºC. These conditions minimize the microbial growth during the manufacturing process. Based on this information, no microbial periodic monitoring will be performed for these equipments.

In order to establish a grouping strategy, an evaluation product Solubility in cleaning solutions, Potency, Toxicity, Stability, Difficulty to clean, Concentration of the API in the formulation, Excipients type and quantity in the formulation and Finished Products Water activities (Microbial) was performed. Depending on the product properties, a value was assigned based on the criticality of the parameters.

An evaluation of the Finished Products Water activities was performed. From this evaluation, it was concluded that the water activity for all product manufactured are below 0.6. If the water activity of the product is less than 0.600 aw, it can be expected that microorganisms do not proliferate. Low water activity prevents microbial growth. Water activity, aw, is a physical-chemical measurement that expresses the water vapor pressure above the test sample as a fraction of the water vapor pressure of pure water at the same temperature as the test sample. This measurement, determines how much water is free from physical and chemical bonds and thus available for migration, chemical reaction, use by microorganisms, or other activity. Based on this information, the water activity criterion was classified as a low risk and a risk priority index of one (1) was assigned. The worst case scenario determination using a risk based approach tool was completed. Product A was selected as the worst case scenario for the tablet manufacturing area and product D was selected as the worst case scenario for the capsule manufacturing area.

Equipment grouping strategy was used as part of the cleaning validation exercises performed in the granulation and compression suites. Since the granulation equipment was the same operational principle, same design and material of construction, a cleaning procedure was developed to clean both granulation suites. The only different between granulation suites was the equipment size. A cleaning procedure was validated using the worst case equipment (Granulation suite 2) and worse case product (Product A). Cleaning validation exercise was successful and demonstrated the removal of API, detergent agent and microbial growth. The same approach was used in the compression suites. Cleaning exercise obtained satisfactory results. [5]

A grouping strategy was also used in the High Volume area for the filler machine. A cleaning process was developed to clean all fillers. Coated pellets are encapsulated in this filler. Since the product is coated, active ingredient in contact with the equipment surface is negligible. Based on that, no cleaning agent was used during cleaning. Cleaning validation exercise obtained satisfactory results for API residues and microbial growth.

Using the information above, Risk Assessment for Company XYZ Cleaning Process, Risk Assessment for Cleaning Process from Microbial Standpoint and Risk Assessment Manually Clean Equipment used as part of Product F Process from Chemical Standpoint were performed. Table 3 shows the new total periodic monitoring sampling and runs per year.

Table 3
New Total Periodic Monitoring Sampling and Runs per Year

Sampling Type	New Strategy			Amount of Run
	API	Detergent	Micro	
Swab	26	43	0	18
Rodac	0	0	10	
Rinse	0	0	1	

Comparison was made between periodic monitoring sampling.. Based on the new strategy, a

61.8% reduction was observed in the total amount of samples collected in the periodic monitoring of company XYZ (Table 4). In addition, a reduction of 63.3% was observed in the total amount of periodic monitoring exercises. These reductions were obtained using a risk based approach with a scientific data base and grouping strategies for equipment and products.

Table 4
Periodic Monitoring Comparison After New Strategy Implemented

Sampling	Old Strategy	New Strategy	Variation	Percent (%)
API Swab	**74**	**26**	**48**	**64.9**
Detergent Agent Swabs	**81**	**43**	**38**	**46.9**
Microbial Rodac	**33**	**10**	**23**	**69.7**
API Rinse	**6**	**0**	**6**	**100.0**
Detergent Agent Rinse	**6**	**1**	**5**	**83.3**
Microbial Rinse	**12**	**1**	**11**	**91.7**
Total	**212**	**81**	**131**	**61.8**
Total Exercise	**49**	**18**	**31**	**63.3**

CONCLUSIONS

Project purpose was to reduce the amount of periodic monitoring exercise and sampling in more than fifty percent (50%). Using a risk based approach tool and the grouping strategies for active ingredients and equipment; it was able to achieve a 61.8% reduction in the amount of sampling collected during the periodic monitoring exercise performed at company XYZ. In addition, a reduction 63.3% was obtained for the total amount of exercise performed in a year basic (From 49 exercise to 18).

Periodic monitoring exercise and sampling were able to be reduced by performing cleaning validation exercise in the granulation, compression and filler equipment. Grouping strategies for equipment and active ingredient were used as part of the validation strategies for these equipments. Also, bioburden evaluation of all cleaning validation exercises were performed to assess which equipment will be monitored annually based on the manufacturing process performed and the product properties.

Based on the information gathered in this project, it can be concluded that the project purpose was successfully achieved and exceeded. Periodic monitoring new strategy was implemented in company XYZ.

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