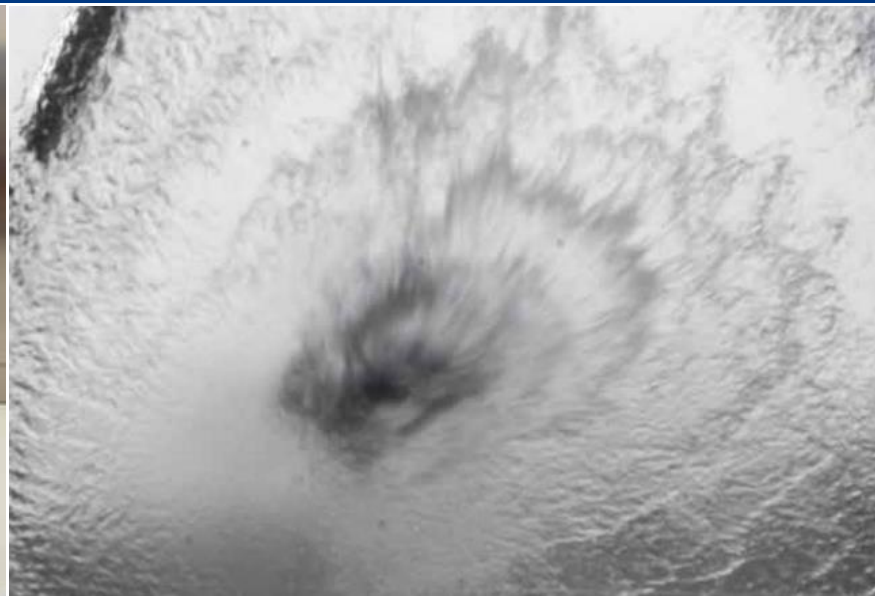


M-Line: mobile high pressure unit

IBCs Cleaning performance evaluation study in a solid manufacturing area



Introduction

IWT committed to execute an Atorvastatin removal test as worst case for a potential new client. The grounds for buying a new washing machine came from the failures registered during their own cleaning validation test as a result of the Atorvastatin introduction. In fact, Atorvastatin proved to be resistant to removal due to the high adhesion to the BIN walls, which are used for mixing, with a criticality around the top angles. An integrative test with dihydrate Azithromycin with sugar is requested.

Object

The object of this test is a performance evaluation study for the introduction of a new bin washing machine set for the bin automatic washing used in a Solid Manufacturing area.

The efficiency of the bin washing through the IWT mobile unit and the high-pressure is evaluated on the Bin by means of the following products:

- Atorvastatin blend
- Powder doxycycline for suspension

Purpose

The purpose is:

- to prove the efficiency of the bin washing through the mobile unit and the high-pressure M-Line. This machine will be installed in the Solid manufacturing area
- To verify that the correct removal of the active principle, the other ingredients and the detergent
- To ensure that the containment of the microbiologic load is below the acceptable limits established by client's protocol.

The following checks are executed – during and at the end of the cleaning phases:

- Visual inspection of the surfaces in contact with the product
- Biologic swabs of the surfaces in contact with the product for microbiological checks
- Chemical swabs of the surfaces in contact with the product for the active principle research
- Sample of the rising water for chemical analysis in order to check the removal of the detergent and the other ingredients
- Sample of the rising water for microbiologic control in order to check the containment of microbial load

Product formulation

Below a list of bins divided among customized Bins that handle only one active principle – and the multi-product Bins that handle more active principles.

EQUIPMENT	MULTI-PRODUCT vs DEDICATED	API
BIN 2200 LT	MULTI-PRODUCT	ATORVASTATIN
		AZITHROMYCIN
		DOXYCYCLINE
BIN 1200 LT	MULTI-PRODUCT	ATORVASTATIN
		AZITHROMYCIN
		SERTALINE
TANK 1700 LT	DEDICATED	(non-active) NA BLEND

The validation tests are performed with the Bin 2200 lt and the Bin 1200 lt. It is agreed not to carry out any trial on the 1700 lt S/S tank because it is used only to contain the inactive blend. This represents a less critical condition for the cleaning procedure.

To choose the most difficult products to remove, the following features for each product are considered by client as critical:

- The active principle percentage for the batch size
- Solubility in water of the active principle in room temperature
- Lethal dose (LD50) of the active principle
- Occupational Exposure Limit (OEL)
- Experience in the area of removing different processed products

Challenges

The following tests are planned:

EQUIPMENT	TEST	API	EVALUATION
BIN 2200 LT	TEST 1	DOXYCYCLINE	MILL DRAIN AREA
BIN 1200 LT	TEST 2	ATORVASTATIN	MILL DRAIN AREA

Based on the evaluation carried out during the client’s internal Validation Cleaning Project Plan, Atorvastatin is proved as the Worst-Case product.

Even in the microbiologic section, atorvastatin proves to be the worst-case in not having any bacteriostatic action, such as the Azithromycin. For this reason, a specific test is made on bin 1200 Lt with API Atorvastatin.

The Doxycycline power production process for suspension is not yet validated by client, therefore a Bin 2200 Lt with a Doxycycline blend is used with reduced 6Kg batch size.

Process Description

The Bin Washing Machine used for the performance evaluation study is an IWT M-line high pressure mobile washing machine. The machine allows an automatic washing cycle using purified water, provided by a piston pump with a payload of 40 Lt/min with high pressure (70bar) in order to optimize the process efficiency.

All the surfaces in contact with process fluids are made of stainless steel AISI 316L. The machine is equipped with a detergent dosing system and using a flowmeter it is possible to measure the quantity of detergent and the concentration used during the washing phase.

The equipment for the test is provided with a hydrokinetic lance that allows the entire internal Bin surface (approximately 1,5min) to be covered through the usage of 4 rotating nozzles that produce high pressure water jets.





DATA SHEET M-LINE	
DIMENSION (L x D x H)	1440x755x1250 mm
WEIGHT	<350 Kg
WATER PRESSURE	20÷80bar
WATER PAYLOAD	20-40 Lt/min
WATER TEMPERATURE	Max 90°C

For the automatic cleaning the following supplies are used:

- Tap water
- Purified water (PW)
- Detergent: solution P3Cosa Flux 33 (the detergent concentration is evaluated on site)
- Compressed air

In the following chart is reported the detergent P3Cosa Flux 33 data sheet:

DATA SHEET P3Cosa Flux 33	
DENSITY	1,34-1,38g/cm ³
SOLUTION USE	50 ml (1%)
% TOT ALKALINITY	23,25-24,49 %
WATER PAYLOAD	20-40 Lt/min
WATER TEMPERATURE	Max 90°C

Washing conditions and duration for each phase are confirmed during the performance evaluation study, based on monitored results during the cleaning process.

- **Prewashing** with tap water without heating up
- **Washing** with detergent COSA FLUX 33 to 1% diluted with cold tap water
- **Rinse** with PW water heated as previously set in the recipe
- **Drying**: it is made according to the drying Bin Washing recipe validated by the customer protocol

Analytic Plan

The Analytic Plan executed during the performance evaluation study is shown here below:

PROCESS PHASE	SAMPLES	TEST	LIMITS
Pre-washing	Rinse waters (chemical)	pH	5-7
		Conductivity	< 5ppm
	<i>At the end of pre-washing phase</i>	TOC	< 5ppm
Rinse	Rinse waters (chemical)	pH	5-7
	<i>Each 30'' from the beginning to the end of the rinse</i>	Conductivity	< 5ppm
		TOC	< 5ppm
	NA (chemical)	Visual inspection	Parts visible inspected are cleaned
	<i>At the end of the rinse phase</i>		
	Rinse waters (biologic)	Tot Microbial load	≤100CFU/ml
	<i>At the end of pre-washing phase</i>		
Swab (biologic)	<i>At the end of pre-washing phase</i>	Microbial count	≤50 CFU/swab
		Pathogens	Absent
	Swab (chemical)	Atorvastatin	< 0.026 mg/swab
<i>At the end of pre-washing phase</i>			

Acceptance Criteria

The cleaning procedure is considered effective if the following criteria are met every time:

- All the pieces are inspected and cleaned.

On the **Swabs**, the limits below must be respected:

- The maximum tolerated dose of each active principle for swab lower than **0,026 mg/swab**.
- The microbial load **<50 CFU/Swab**
- The **rinse water** must respect the following characteristics:
 - **Visually clear**
 - **pH between 5 and 7**
 - **Conductivity analysis**
 - **TOC < 5 ppm**
 - **Total microbial load of filtered water < 100 CFU/ml**
 - **Pathogens absence**

Test Report

Connections Details:

- Hot PW water supply ca 50°C
- Static pressure 2.7 bar
- Dynamic pressure 1.8 bar with machine at 100%
- Flow rate 40 Lt/min.

Material: AISI 316

Water temperature: 50°C

Inlet water pressure: 1.8 bar

Lance type: H930

Accessories used: //

Detergent used: P3 Cosa Flux 33

1° TEST on BIN 2200

Product to be cleaned: DOXYCYLINE

CYCLE:

	TIME	POWER	H ₂ O CONSUMPTION	PRESSURE	H ₂ O TEMP.
PRE-WASHING	60''	100%	37 l'	76 Bar	52° C
	VISUAL CHECK RESULT				
WASHING	60''	100%	37 l'	76 Bar	52° C
	VISUAL CHECK with sampling				
RINSE	360''	100%	37 l'	76 Bar	52° C
	ANALITIC CHECK with sampling				

Detergent concentration 0,1% P3 Cosa Flux 33

The long rinse time has the aim of sampling the water for the laboratory analysis in order to determine the needed time for a right rinse.

CONSIDERATIONS:

Cycle time: 480'' to be verified according to the laboratory analysis results

Total Time: 480'' - 8'

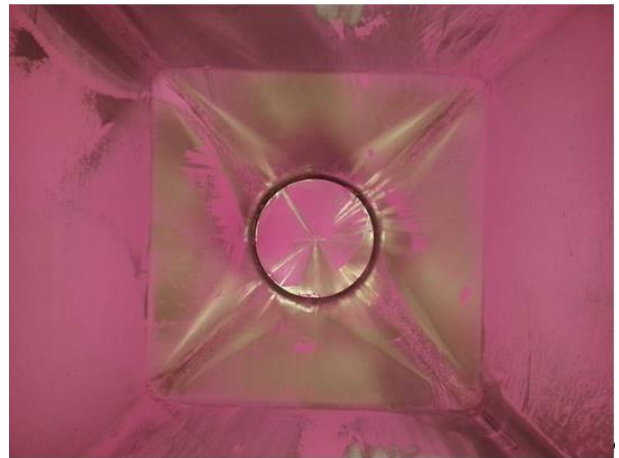
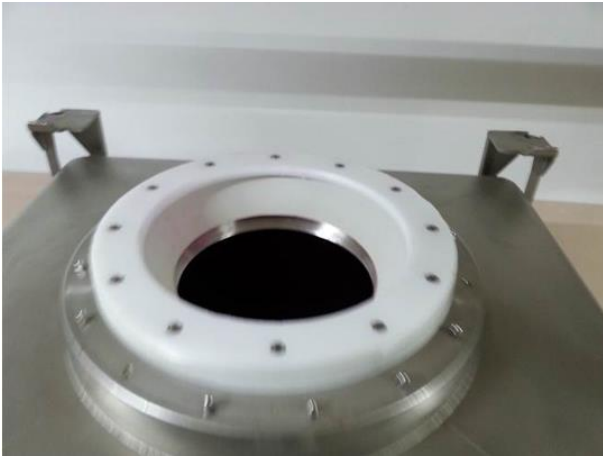
Water consumption: 296 Lt to be verified according to the laboratory tests.

Detergent consumption: 37ml

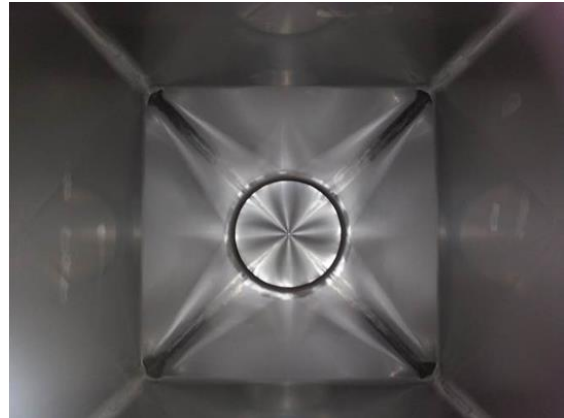
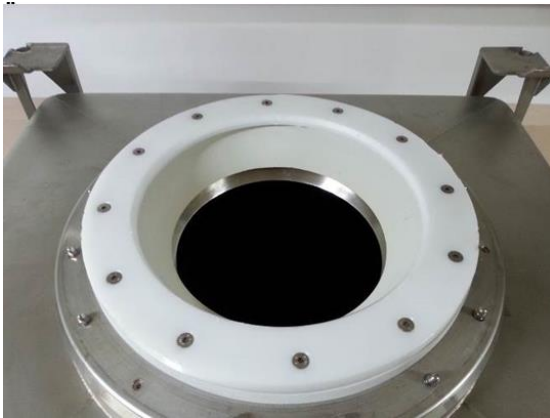
Estimated residue: absence of visible traces, to evaluate according to laboratory analysis

Execution: After the first 60'' of cycle there are still few visible product traces. Test proceed with 60'' washing phase with 0.1% detergent followed by the 360'' of rinse phase with the relative samplings.

Photos BEFORE the washing test



Photos AFTER the washing test



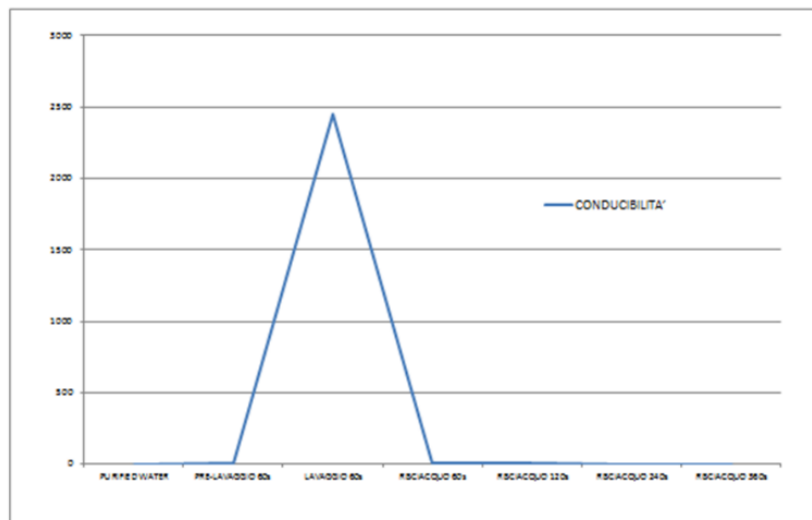
RESULTS:

The customer laboratory results

BIN 2200 lt – DOXYCYLINE / DETEREGENT: YES - Concentration: 0,1%

	TIME	VISIBLE CHECK (conform y/n)	CONDUCTIVITY (conform y/n)	pH (conform y/n)	TOC (conform y/n)	SWAB (conform y/n)	WATER CONSUMPTION (conform y/n)	DETERGENT CONSUMPTION (conform y/n)		
PRE-WASHING	60s	Non Compliant	na	na	na	na	36 Lt/min	na		
	na	Non Compliant	na	na	na	na		na		
WASHING	60s	na	na	na	na	na		36 Lt/min	70g	
	Na	na	na	na	na	na				
RINSE	120s	Na	Compliant	Compliant	Compliant	na			36 Lt/min	na
	240s	Na	Compliant	Compliant	Compliant	na				
	360s	Compliant	Compliant	Compliant	Compliant	na				

		TIME	CONDUCTIVITY	pH
WHITE	Purified water		0,76	6,1
PRE-WASHING	Pre-washing 60s	60s	3,95	6,29
	Pre-washing 120s	120s		
WASHING	Washing 60s	60s	2450	11,56
	Washing 120s	120s		
RINSE	Rinse 60s	60s	8,85	8,60
	Rinse 120s	120s	2,72	6,90
	Rinse 240s	240s	1,15	6,60
	Rinse 360s	360s	0,95	6,16



	TIME	CONDUCTIVITY	TOC
PRE-WASHING	60s	na	na
	na	na	na
WASHING	60s	na	na
	na	na	na
RINSE	120s	1,941µs	0,4298ppm
	240s	1,789µs	0,3061pm
	360s	1,481µs 4	0,552ppm

The result obtained from the test is considered compliant.

The rinse could be reduced to 240'' with a water saving of 74Lt for a total consumption equal to 222Lt.

2° TEST on BIN 1200

Product to be cleaned: ATORVASTATINA (Pure API)

CYCLE:

	TIME	POWER	H ₂ O CONSUMPTION	PRESSURE	H ₂ O TEMP.
PRE-WASHING 1	60''	100%	37 lt	76 Bar	52° C
	VISUAL CHECK RESULT – if there are any traces carry out the 2° pre-washing				
PRE-WASHING 2	60''	100%	37 lt	76 Bar	52° C
	VISUAL CHECK RESULT				
WASHING	120''	100%	37 lt	76 Bar	52° C
	ANALITIC Check with sampling				
RINSE	360''	100%	37 lt	76 Bar	52° C
	ANALITIC Check with sampling				

Detergent concentration 0,1% P3 Cosa Flux 33

The long rinse time has the aim of sampling the water for the laboratory analysis in order to determine the needed time for a right rinse.

CONSIDERATIONS:

Cycle time: 600'' to be verified according to the laboratory analysis results

Total Time: 600'' - 10'

Water consumption: 370 Lt to be verified according to the laboratory results

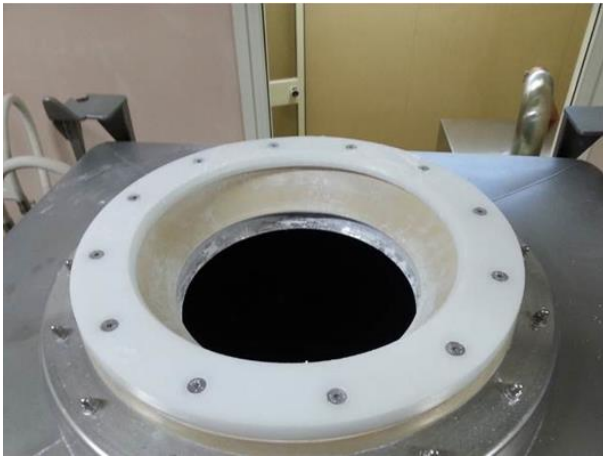
Detergent consumption: 74ml

Estimated residue: absence of visible traces, to evaluate according to laboratory analysis

Execution: After the first 60'' of cycle there are still visible products residues but also visible water jets traces, this means a high adhesion. After repetition of the 60'' pre-washing phase fewer but still visible residues can be observed. Process continue with 120'' wash with 0.1% detergent. Cycle concludes with 360'' rinse phase.

Suggestion: Evaluate different nozzle design (2'' surface covered) in order to guarantee closer water jets traces.

Photos BEFORE the washing test



Photos DURING the washing test

After the first pre-washing 60''



After the second pre-washing 120''



Photos AFTER the washing test



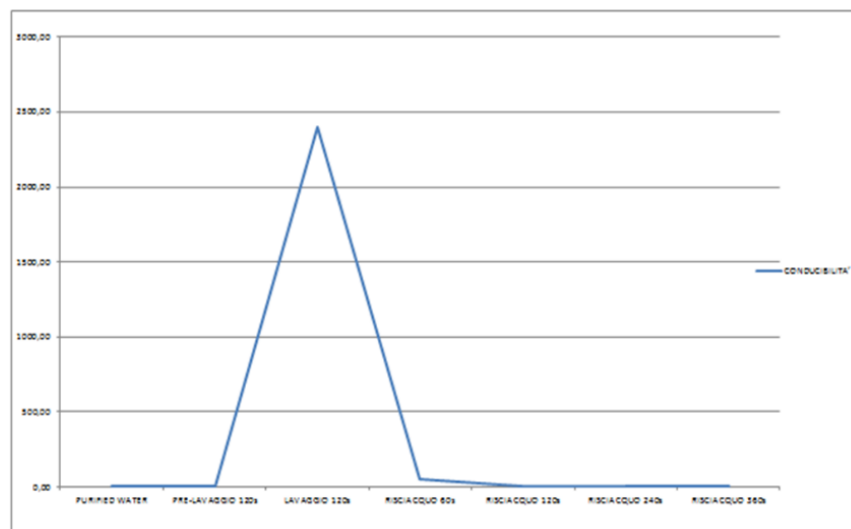
RESULTS:

The customer laboratory results

BIN 1200 lt – ATORVASTATIN / DETERGENT: YES – Concentration: 0,1%

	TIME	VISIBLE CHECK (conform y/n)	CONDUCTIVITY (conform y/n)	pH (conform y/n)	TOC (conform y/n)	SWAB (conform y/n)	WATER CONSUMPTION (conform y/n)	DETERGENT CONSUMPTION (conform y/n)
PRE-WASHING	60s	Non Compliant	na	na	na	na	36 Lt/min	na
	120s	Non Compliant	na	na	na	na		na
WASHING	60s	na	na	na	na	na		70g
	120s	na	na	na	na	na		na
RINSE	120s	na	Compliant	Compliant	Compliant	Compliant		na
	240s	na	Compliant	Compliant	Compliant	Compliant		na
	360s	Compliant	Compliant	Compliant	Compliant	Compliant	na	

		TIME	CONDUCTIVITY	pH
WHITE	Purified water		0,76	6,1
PRE-WASHING	Pre-washing 60s	60s		
	Pre-washing 120s	120s	6,33	6,08
WASHING	Washing 60s	60s		
	Washing 120s	120s	2400,00	11,47
RINSE	Rising 60s	60s	57,00	9,90
	Rinse 120s	120s	2,2	7,25
	Rinse 240s	240s	1,4	6,67
	Rinse 360s	360s	1,1	6,30



	TIME	CONDUCTIVITY	TOC
PRE-WASHING	60s	na	na
	120s	na	na
WASHING	60s	na	na
	120s	na	na
RINSE	120s	2,34μs	2,217ppm
	240s	2,25μs	2,169ppm
	360s	2,21μs 4	1,285ppm
	360s	2,21μs 4	1,285ppm

The result obtained from the test is considered compliant.

CONCLUSIONS:

The introduction of atorvastatin API in the client production line represented an issue due to its incompatibility with the existing cleaning procedures. The investment in the M-line system, thanks to its mobile design, can mitigate the collateral infrastructural costs and represents a simpler add-on to existing and running operations.

The cleaning procedure described above is considered effective, all pieces are perfectly clean after visual inspection and the customer's laboratory reports are exceeding the acceptance criteria. Even critical areas, such as the internal bin top corners achieved proper results.

The atorvastatin API, which was considered the worst-case scenario either from a removal and a microbiological point of view, can be successfully processed.

The introduction of the M-Line mobile high pressure washer brings to client a repeatable and validate method to automatize and standardize the cleaning operations in their solid manufacturing area.

The present cleaning evaluation study showed also potential improvements in processing times and reduced water and detergent consumptions.