Title: Out-of-limit TOC value measured on EM sample TANK_T22 (Purification Line 2).

Reference: PR3016700

Type of document: Investigation Report

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Executive summary:

This report documents the investigation related to the Out of Level (OoL) result (Out of Action level what is not more than (NMT) 500 ppb) for Total Organic Compound (TOC) of the EM cleaning sample Tank_T22 sampled in room R605 (Purification L2 Post Nano area) on 12 September 2022.

PR#	Description	Sample date	Discovery Date	Results
3016700	OOL TOC	12 September 2022	15 September 2022	505 ppb

The investigation performed in the frame of this event showed that:

- All other results, *i.e.* LAL, pH, conductivity and Bioburden, obtained for TANK_T22 taken on 12 September 2022 were satisfactory;
- The CIP cycle performed on T22 on 12 September 2022 was satisfactory;
- The final conductivity measured in-line for the CIP cycle of T22 performed on 12 September 2022 was satisfactory;
- NaOH 29% is the cleaning agent used for the CIP of T22 tank. No carbon in that composition;
- The TOC of WFI loops C102 and C104 was NMT 500 ppb;
- T22 tank as well as the CIP station 638-7 were operational and the integrity of these equipments was ensured during the EM sampling;
- The EM sampling was performed according to the standard operating procedures (within 48 hours after the CIP cycle) and no activities were reported between CIP and EM sampling;
- The QC laboratory testing analysis was satisfactory and no testing error was identified;
- No change impacting T22 and /or CIP station 638-7 were implemented in the period of 11 August 2022 (last satisfactory EM testing) till 21 September 2022 (re-test due to PR3016700);
- The revision of maintenance activities (11 August 2022 till 21 September 2022) demonstrated that no maintenance Work Order had impact on this OOL TOC;
- No other non-conformance events concerning T22 were reported;

No assignable root cause was identified in the investigation of PR3016700. Nonetheless, deviation PR3060455 has been opened on 14 October 2022 for an atypical trend in the occurrence OoL TOC observed for EM samples. This PR is still under investigation at the time.

Investigation of PR3016700 can be closed without additional action.

There is no quality impact (product nor process/system/equipment) of the OOL TOC value measured on EM sample of TANK_T22 taken on 12 September 2022 as concluded in the impact assessment (see Evaluation PR3016700 attached in TW8).

There is no additional raw material impact following the quarantine of TOC tube lot number 21277-4627 in PR3060455.

Immediate action after the discovery of OOL TOC result on 15 September 2022 was to perform EM re-testing for TOC. The re-test was performed on 21 September 2022 and the obtained TOC result (50 ppb) was satisfactory.

Table of contents

1. BACKGROUND

In the downstream manufacturing processes conducted at the Takeda Lessines facility, manufacturing process tanks are cleaned after each use with a Cleaning in Place (CIP) cycle. This cleaning must be performed within validated dirty hold time after use.

Current CIP sequence is as follows:

Figure 1. CIP cycle sequence

A CIP cycle CIP638-7 (used for T22) is considered as valid in routine production, if the final conductivity value measured in-line (at the CIP station) respected as required per SOP-013469. If the conductivity value is above this cut-off, a second CIP cycle is performed. As per Standard Operating Procedure (SOP) SOP-013469, an event record is issued if the final conductivity value measured in-line after the third CIP cycle is higher than 5.0 µS/cm.

As per SOP-026466, four (4) samples are taken on each manufacturing equipment (if used during the month) by an Environmental Monitoring (EM) laboratory operator. Those samples are: conductivity/pH, Total Organic Carbon (TOC), Limulus Amebocyte Lysate (LAL) and bioburden samples. Equipment (*i.e.* process tanks) used in routine manufacturing is therefore sampled once a month and tested for pH/conductivity & TOC at the Lessines Quality Control Laboratory (QC Lab). The current water pH and conductivity tests performed by Lessines QC Lab is described in SOP-026359 and TOC tests in SOP-015413.

2. DESCRIPTION OF THE EVENT

The details upon the Out of Limit (OOL) event initiated for T22 Tank due to routine Environmental Monitoring (EM) are as indicated in Table 1.

PR#	Description	Sample date	Discovery Date	Results
3016700	OOL TOC	12 September 2022	15 September 2022	505 ppb

Table 1 Event description

The Total Organic Carbon (TOC) testing was performed according to SOP-015413 and results did not meet the acceptance criteria as defined in SOP-048762 (NMT 500 ppb).

All others testing performed on EM samples, *i.e.* pH, conductivity, LAL and bioburden were within the specified limits (see Table 2).

Test	Unit	Result	Acceptance criteria
pH	-	5.6	5.0 – 7.0
Conductivity	*µS/cm*	1.1	*See SOP-026359*
TOC	*ppb*	**505**	≤ 500
LAL	*EU/ml*	0.005	≤ 0.25
Bioburden	*Cfu/10 ml*	0	< 1

Table 2 Results of testing performed on TANK_T22 samples taken on 12 September 2022 (ref.: NWA database).

The previous EM testing of TANK_T22 was performed on 11 August 2022 and all the results obtained were satisfactory.

The EM re-testing for TOC was performed on 21 September 2022. The TOC (50 ppb) result obtained was satisfactory.

T22 is a buffer tank in Purification L2 Post Nano area (R605), and is used during the manufacturing of Cuvitru to prepare the dialysis buffer and the NaCl buffer used to clean the UF605.

No lots were impacted by this event, as concluded in the impact assessment (see *Evaluation PR3016700* attached in TW8).

3. PURPOSE

The purpose of this report is to document the investigation associated to the out-of-limit TOC value measured on EM cleaning samples of tank T22 (TANK_T22) taken on 12 September 2022.

4. INVESTIGATION LEVEL

T22 is tested in a montly manner; the retrospective analysis is carried out over 730 days (+ 76 days for the shutdown periods included in the period to be analysed) what is from 28 June 2020 to 26 September 2022. The research criteria is OOL TOC on the sample TANK_T22.

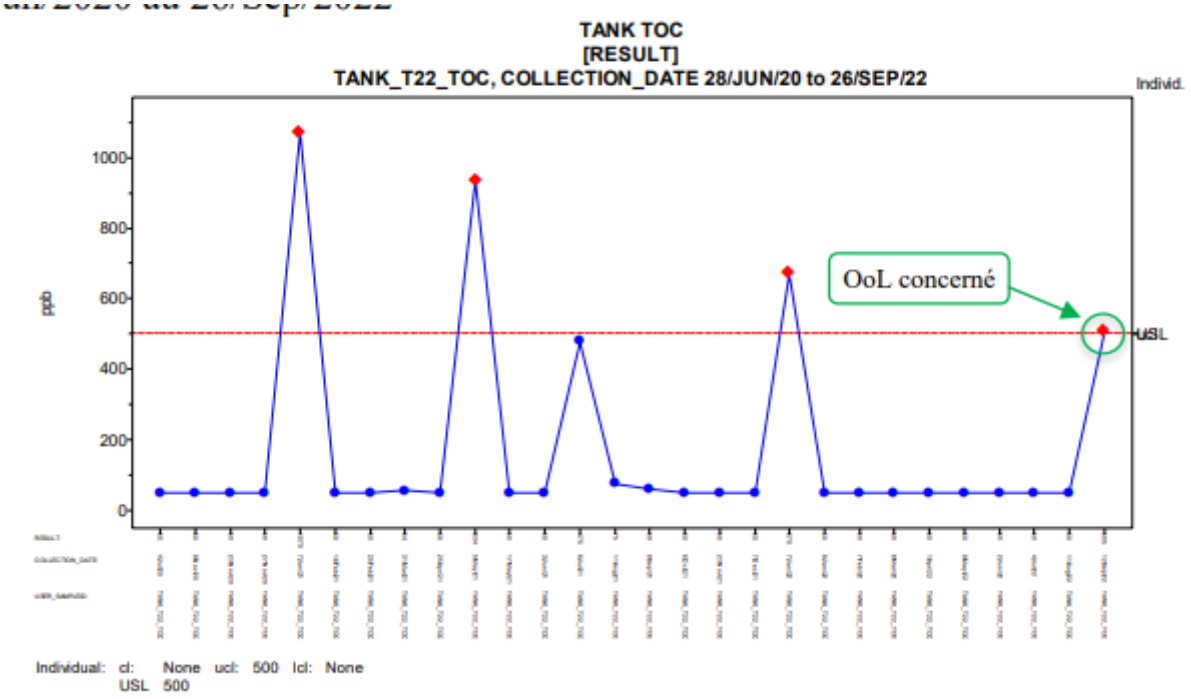

Figure 2 Trend of TOC results on TANK_T22 from 28 June 2020 to 26 September 2022

Rate of occurrence: Beside the OOL TOC concerned in this report, three OoLs of action were reported during the period analysed (PR1791404 on 07 Jan 2021, PR2031480 on 05 May 2021 & PR2996517 on 7 January 2022).

Category: OoLs of action – Tank → Deviation High

Conclusion: the final investigation level is a high deviation according to G-TAK-001563 '*Global Job Aid, Investigating Environmental and Utility Monitoring Excursion* '.

5. ROOT CAUSE INVESTIGATION

An investigation was conducted according to 6M methodology in order to identify the root cause. Each step concerning equipment cleaning, sampling and testing will be further investigated.

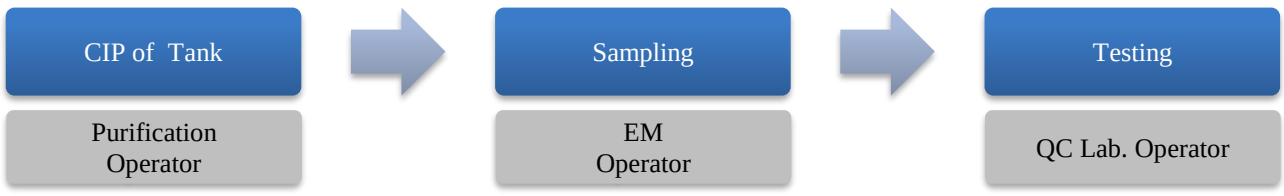

Figure 3 High-level process map

An OoL TOC on a tank could be caused by :

- Presence of residue of carbon residue from the lot previously produced, due to a failed CIP
- Contamination of the tank through the water used for CIP (WFI C102)
- Contamination of the tank through the water used for pH-meter flush and sanitization (WFI C104)
- Contamination of the tank following a maintenance activity
- Contamination of the sample during sampling, the sampling point or the sampling equipment
- Testing error

5.1. ENVIRONMENT

5.1.1. Analysis of CIP cycle

T22 is a non-protein, buffer tank in Purification L2 Post-Nano area and is used during the manufacturing of Cuvitru to prepare the dialysis buffer and the NaCl buffer used to clean the UF605.

T22 CIP cycle was performed and achieved on 12 September 2022 at 17h00 prior to EM sampling performed on 12 September 2022 around 17h21. The CIP was launched after an idle time following the production of Cuvitru lot BE13C095Z (end of production on the 09 September 2022), and before the production of Cuvitru lot BE13C097Z.

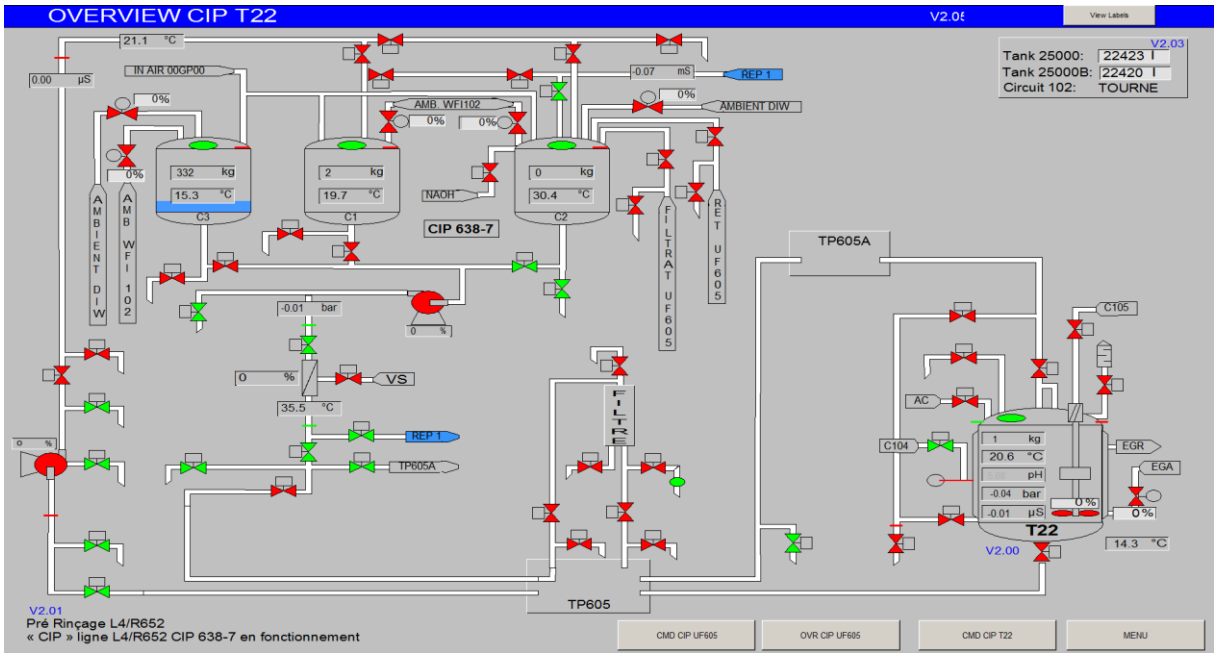

Figure 4 Overview of CIP TANK_T22

The CIP In-line conductivity (ref.: OSIPI database) results before (12 September 2022) and after EM sampling (14 September 2022) were satisfactory (1.40 and 1.31 µS/cm, respectively - ≤ 5.0 µS/cm (Ref.: SOP-013469)).

The CIP cycle of T22 followed the CIP 638-7 sequence as detailed in IT specification (Ref.: B2382_P_D_03_7.0_Design Specification - CIP Buffer & CIP UF & SOP-054471), as shown in Table 3.

Step	CIP638-7 sequence ITS for T22	CIP 12 September 2022
Pre-Rinsing		
0 ➔ 30	Filling of tank Circulation C2 ≥ 1000 kg	1014 kg
30 ➔ 40	Temperature of tank Circulation C2 ≥ 37°C	≥ 37°C
40 ➔ 60	Flush 1/3	Satisfactory
60 ➔ 70	Intermediate draining ≤ 10 kg T22 + no detection LT49602 3 s ➔ draining during 300 s	Satisfactory
80	Flush 2/3	Satisfactory
90 ➔ 200	Final draining ≤ 10 kg T22 + no detection LT49602 3 s ➔ draining during 300 s	Satisfactory
Cleaning Base		
0 ➔ 30	Filling of tank Rinsing C3 ≥ 419 kg and transfer to C2	424 kg
30 ➔ 40	Temperature of tank Circulation C2 ≥ 52°C	≥ 52°C
40 ➔ 50	NaOH Injection (Conductivity CE49561> 89,4 mS/cm during 40 s)	> 89,4 mS/cm during 40 s
50 ➔ 60	Circulation of cleaning base solution during 15 minutes in T22 as soon as TT49548 ≥ 50°C	Satisfactory
70 ➔ 200	Circuit draining (C2 < 15 kg + T22 ≤ 10 kg + no detection LT49602 3 s ➔ draining during 300 s	Satisfactory
Final Rinsing		
0 ➔ 10	Filling of tank Rinsing C3 ≥ 1000 kg	1002 kg
20 ➔ 40	Flush 1/3	Satisfactory
40 ➔ 60	Intermediate draining ≤ 10 kg T22 + no detection LT49602 3 s ➔ draining during 300 s	Satisfactory
70 ➔ 80	Flush 2/3	Satisfactory
80 ➔ 90	Draining ≤ 10 kg T22 + no detection LT49602 3 s ➔ draining during 300 s	Satisfactory
90 ➔ 110	Rinsing recirculation line CIP station + draining	Satisfactory
110 ➔ 200	Complete draining (C2 < 15 kg ➔ draining during 300 s)	Satisfactory

Table 3 CIP 638-7 sequence for Tank T22

The CIP cycle performed on T22 tank on 12 September 2022 was compared with the CIP638-7 sequence (see **Table 3**, **Figure 5**, **Figure 6** and

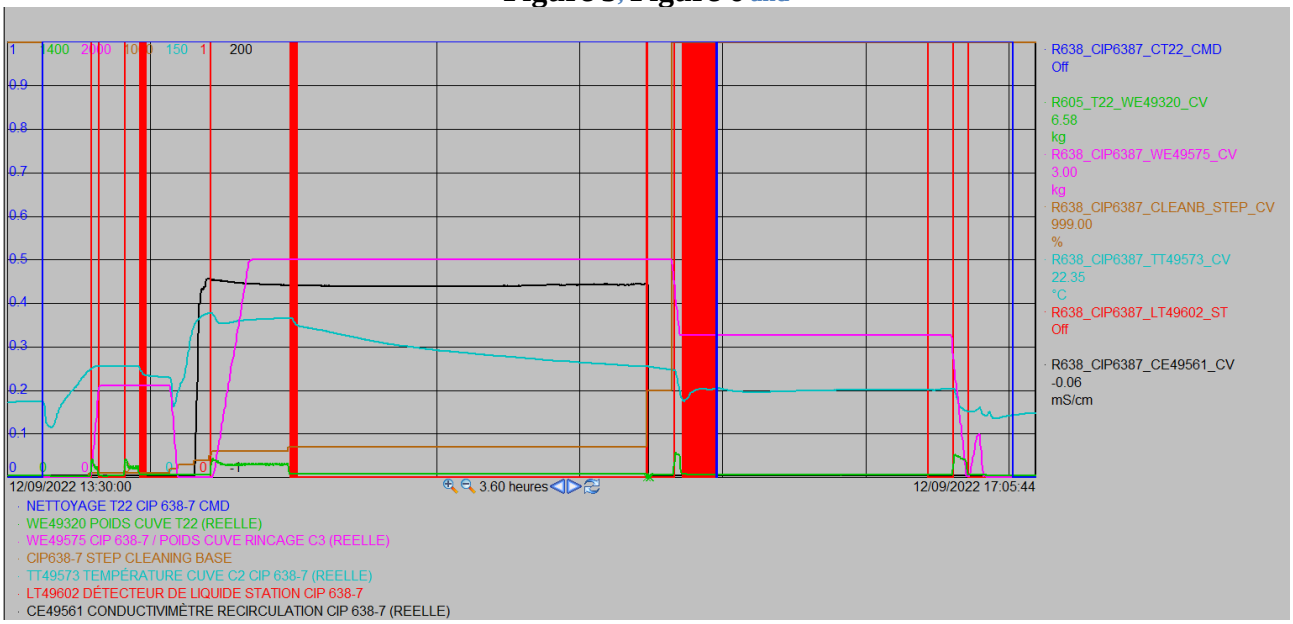

Figure 7). This comparison showed that the Pre-Rinsing, Cleaning Base and Final Rinsing steps were held correctly, what means the rinsing volumes as well as the contact time as defined in CIP638-7 IT specification were respected.

Figure 5 Analysis of the CIP cycle performed on T22 tank on 12 September 2022 - Pre-Rinsing Step

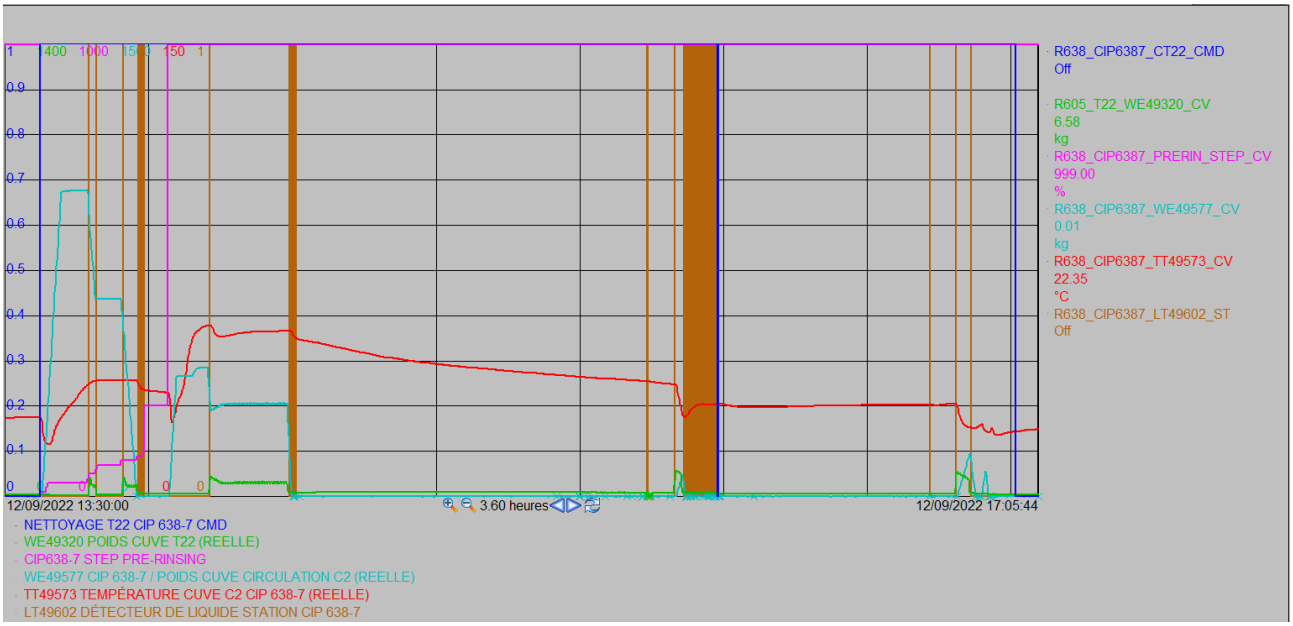

Figure 6 Analysis of the CIP cycle performed on T22 tank on 12 September 2022 - Pre-Rinsing Step.
In blue, the status of the command CIP T22 ; in green, the weight of the tank T22 ; in pink, the status of the pre-rinsing step ; in cyan, the weight of the tank C2 ; in red, the temperature of the tank C2 ; in brown, the liquid detector of station CIP638-7

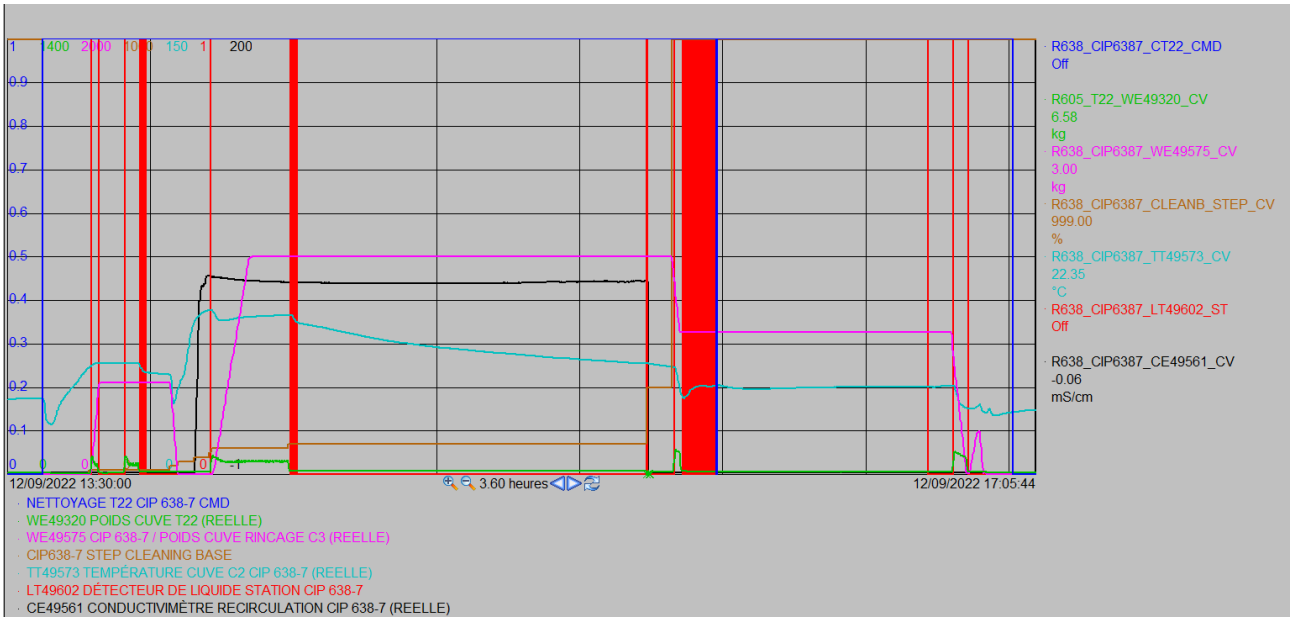

Figure 7 Analysis of the CIP cycle performed on T22 tank on 12 September 2022 - Cleaning Base Step. *In blue, the status of the command CIP T22 ; in green, the weight of the tank T22 ; in pink, the weight of the tank C3; in cyan, the temperature of the tank C2 ; in red, the liquid detector of station CIP638-7 ; in brown, the status of the cleaning base step ; in black, the final conductivity of CIP638-7*

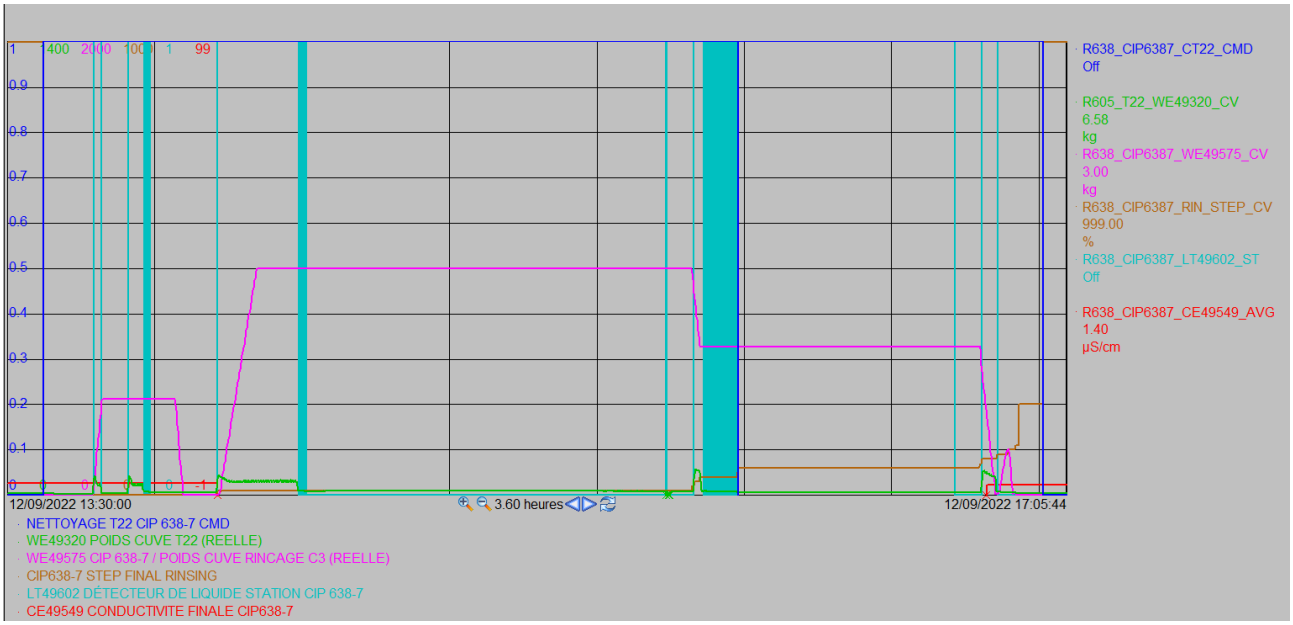

Figure 8 Analysis of the CIP cycle performed on T22 tank on 12 September 2022 - Final Rinsing Step. *In blue, the status of the command CIP T22 ; in green, the weight of the tank T22 ; in brown, the status of the final rinsing step ; in red, the final conductivity of CIP638-7 ; in red, the status of the rinsing step ; in cyan, the liquid detector of station CIP638-7*

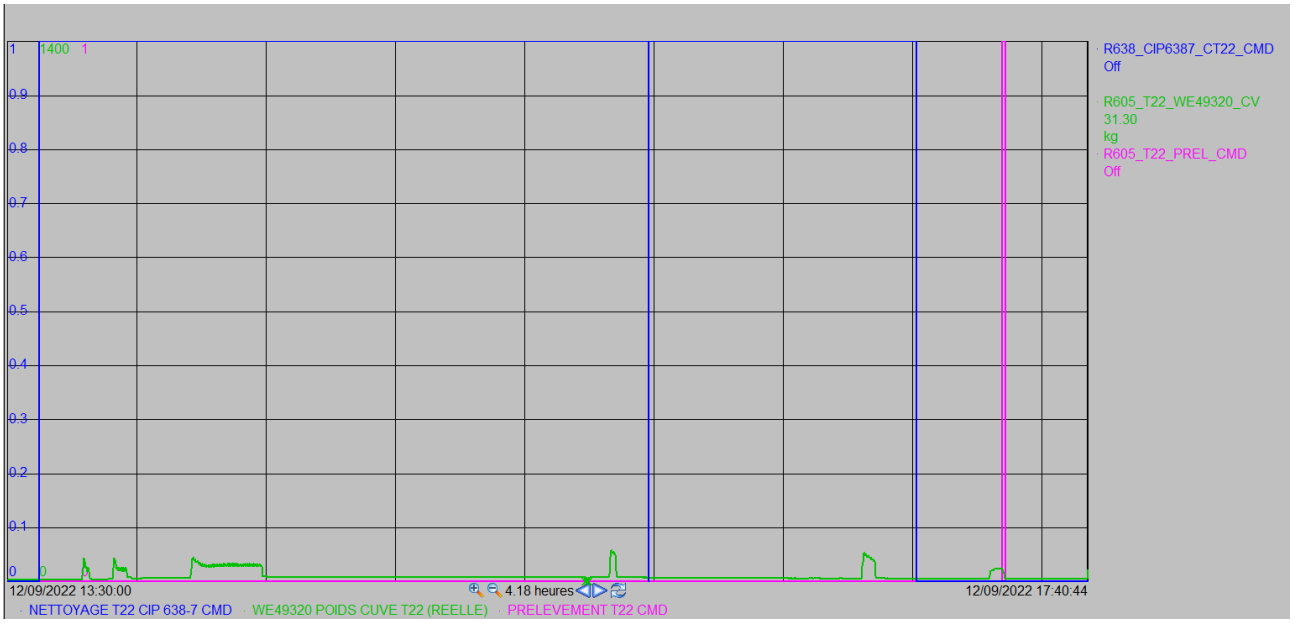

Figure 9 Tank T22 use. *In blue, the status of the command CIP T22 ; in green, the weight of the tank T22 ; in pink, the status of the EM sampling command.*

The CIP lasted about three hours and 30 minutes. This is longer than what is usually observed when compared with other CIP cycles of T22 Tank in OSIPI database (up to 1h30 minutes). After the cleaning base step, the tank T22 is drained. When T22 weight is below 10kg, the final rinsing step is started. On 12 September 2022, after the cleaning base step, T22 weight could not get below 11kg. Therefore, the final rinsing step could not be started which caused the longer CIP time. However, the cleaning base and final rinsing steps duration were usual and were compliant. There is no reason to think that this longer CIP time would be the cause of an OoL TOC or a failed cleaning.

No alarms were reported during this CIP.

The condition of "NaOH Injection (Conductivity CE49561> 89,4 mS/cm during 40 s)" and circulation of cleaning base solution during 15 minutes in T22 tank as well as final rinsing step were held correctly as required by ITS sequence (see Figures 3 & 4).

The final CIP In-line conductivity measured for the CIP cycle of T22 tank performed on 12 September 2022 was 1.40 µS/cm which is below the limit validated to release a CIP cycle for routine manufacturing, i.e. ≤ 5.0 µS/cm (Ref.: SOP-013469). Additionally, the trend of T22 tank final CIP In-line conductivity (11 August 2022 – 21 September 2022), measured after the CIP of T22 did not show any negative tendency, (see Figure 5).

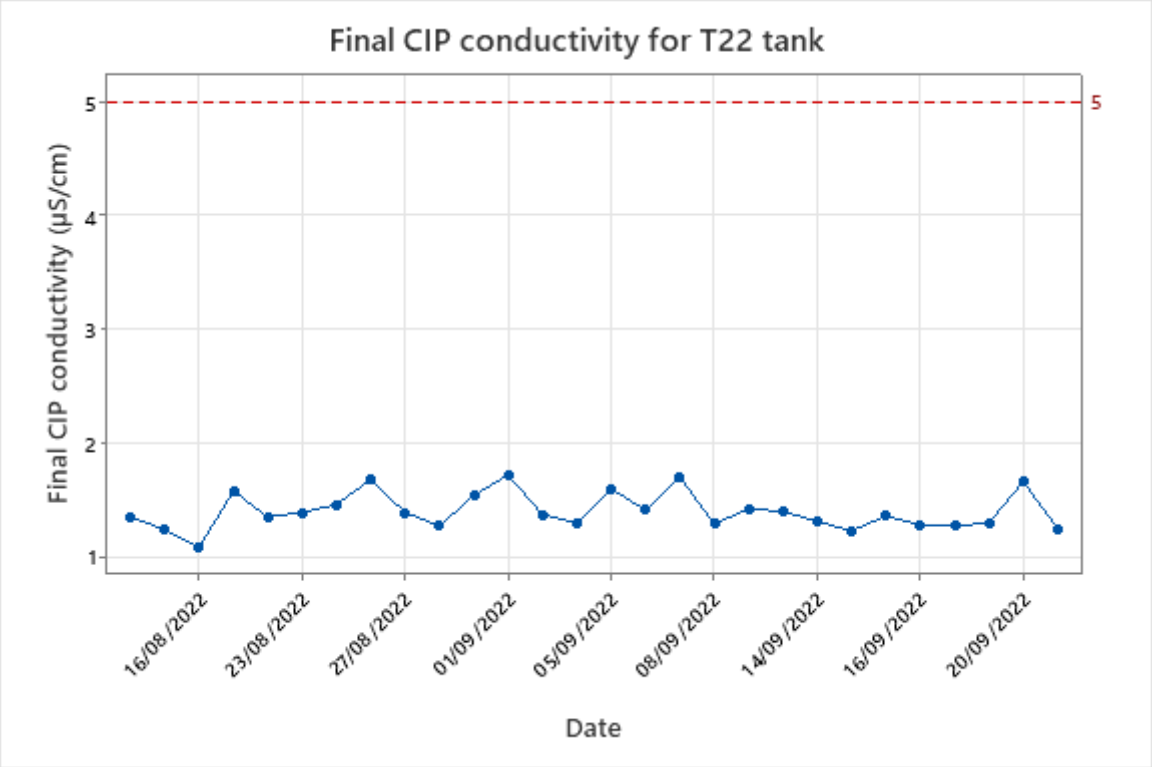

Figure 10 Trend of final CIP In-line conductivity for T22 tank (11 August 2022 – 21 September 2022)

The injection of NaOH for station CIP638-7 is controlled via conductivity probe LECE49561 and final CIP In-line conductivity via conductivity probe LECE49549. These conductivity probes were verified by the metrology on, respectively, 10 September 2022 & 08 September 2022, and it was satisfactory (see Figures 8 & 9). The next due dates for these conductivity probes are, respectively, 10 March 2023 & 08 March 2023. No non-conformance events concerning these conductivity probes were reported.

The temperature of tank circulation C2 is controlled via temperature probe LETT49573. This conductivity probe was verified by metrology on 08 September 2022, and it was satisfactory (see Figure 10). The next due date for this probe is 08 March 2023. No non-conformance event concerning this probe was reported.

Calibration Certificate

(VALIDATED)

Site: Lessines

Asset ID: LECE49561		**Element(s): LECE49561**		**CWO Status: Closed**	**Work ID: CWO-0120276-LE**
Description:	CIP638-7 Cond inject NaOH L1	**Event Name:**	Cal périodique	**Test Conditions(Temp):**	N/A
Manufacturer:	Yokogawa	**Interval:**	6 - Monthly	**Test Conditions(RH):**	N/A
Model:	N/A	**Department:**	Bulk commun	**Related Action:**	N/A
Serial No:	N/A	**Parent System:**	LECIP638.7	**Related Action#:**	N/A
Criticality:	Critical Instrument	**Process Range:**	N/A	**OOT:**	NO
Cal SOP:	LE24QC03036 Rev: 17 Dec 2019	**Location:**	LEBULKL1	**Corrections:**	No Adjustment
Misc. SOP:	LE24QC03056 Rev: 10 Sep 2021	**Room No:**	LE-R638	**Final Results:**	PASS
Date Calibration Completed:	10-Sep-2022	**CWO Due Date:**	10-Sep-2022	**Next Due Date:**	10-Mar-2023

Figure 11 Calibration of the conductivity probe LECE49561

Calibration Certificate

(VALIDATED)

Site: Lessines

Asset ID: LECE49549		**Element(s): LECE49549**		**CWO Status: Closed**			**Work ID: CWO-0120275-LE**
Description:	CIP638-7 Cond retour R638 L1		**Event Name:**	Cal périodique		**Test Conditions(Temp):**	N/A
Manufacturer:	Yokogawa		**Interval:**	6 - Monthly		**Test Conditions(RH):**	N/A
Model:	N/A		**Department:**	Bulk commun		**Related Action:**	N/A
Serial No:	N/A		**Parent System:**	LECIP638.7		**Related Action#:**	N/A
Criticality:	Critical Instrument		**Process Range:**	N/A		**OOT:**	NO
Cal SOP:	LE24QC03036	**Rev:** 17 Dec 2019	**Location:**	LEBULKL1		**Corrections:**	No Adjustment
Misc. SOP:	LE24QC03056	**Rev:** 10 Sep 2021	**Room No:**	LE-R638		**Final Results:**	PASS
Date Calibration Completed:	08-Sep-2022		**CWO Due Date:**	10-Sep-2022		**Next Due Date:**	08-Mar-2023

Figure 12 Calibration of the conductivity probe LECE49549

Calibration Certificate

(VALIDATED)

Site: Lessines

Asset ID: LETT49573		**Element(s): LETT49573**		**CWO Status: Closed**			**Work ID: CWO-0120293-LE**
Description:	CIP638-7 T° C2 R638 L1		**Event Name:**	Calib périodique		**Test Conditions(Temp):**	N/A
Manufacturer:	Rodax		**Interval:**	6 - Monthly		**Test Conditions(RH):**	N/A
Model:	N/A		**Department:**	Bulk commun		**Related Action:**	N/A
Serial No:	190201019		**Parent System:**	LECIP638.7		**Related Action#:**	N/A
Criticality:	Critical Instrument		**Process Range:**	N/A		**OOT:**	NO
Cal SOP:	LE24QC03036	**Rev:** 17 Dec 2019	**Location:**	LEBULKL1		**Corrections:**	No Adjustment
Misc. SOP:	N/A	**Rev:** N/A	**Room No:**	LE-R638		**Final Results:**	PASS
Date Calibration Completed:	08-Sep-2022		**CWO Due Date:**	10-Sep-2022		**Next Due Date:**	08-Mar-2023

Figure 13 Calibration of the temperature probe LETT49573

Tanks P13, P12 and Pipe TP653-TP605A in area R605 are cleaned in place as well by CIP638-7 station. These tanks are compliant for TOC for the year before the OoL TOC on T22 (from 12 September 2021 to 23 September 2022), see Figure.

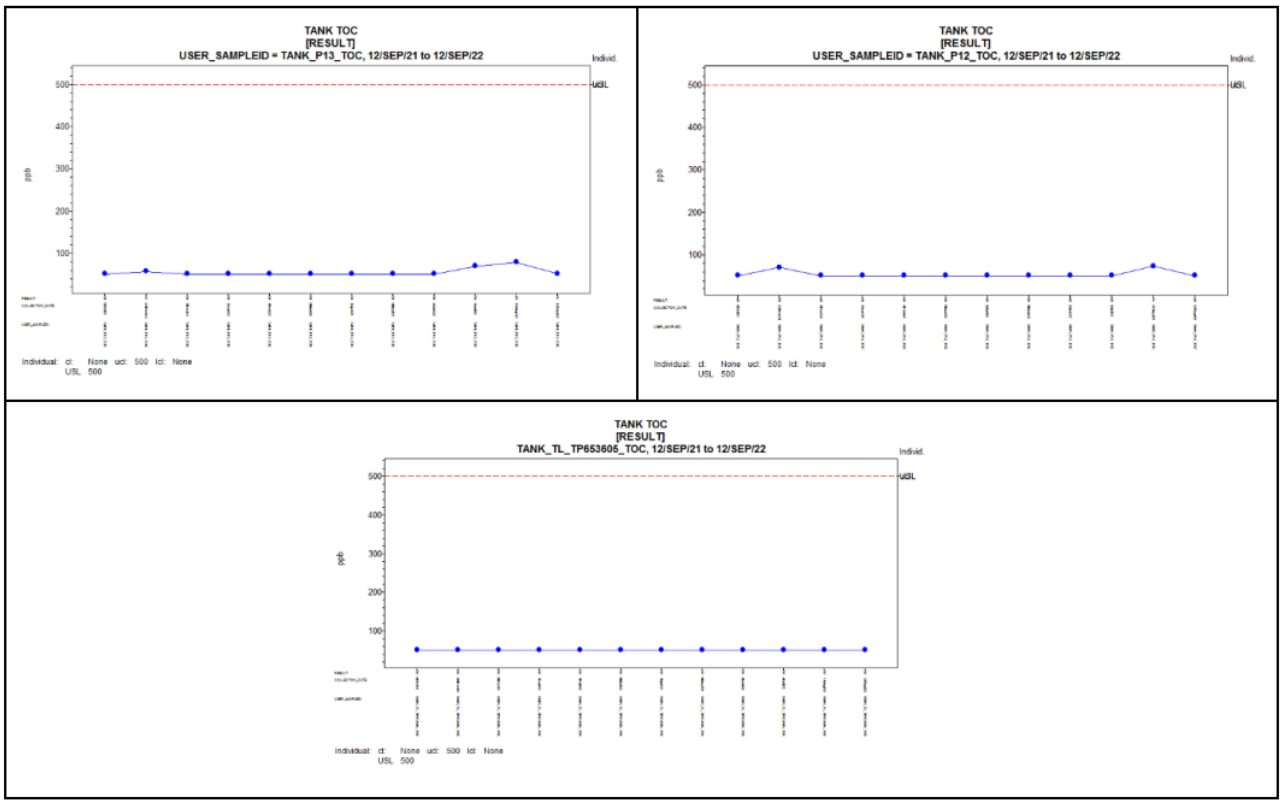

Figure 14 Trend of results TOC for P13, P12 & piping R653-R605 from 12 September 2021 to 23 September 2022

CIP 638-7 station is connected to WFI loop 102. WFI loop C102 is also used for the EM sampling of tank T22. WFI loop C102 TOC was checked for the period of 01 August 2022 till 26 September 2022. NWA data demonstrated that TOC parameters are satisfactory (see Figure 13), *i.e.* not more than (NMT) 500 ppb according to SOP-026359.

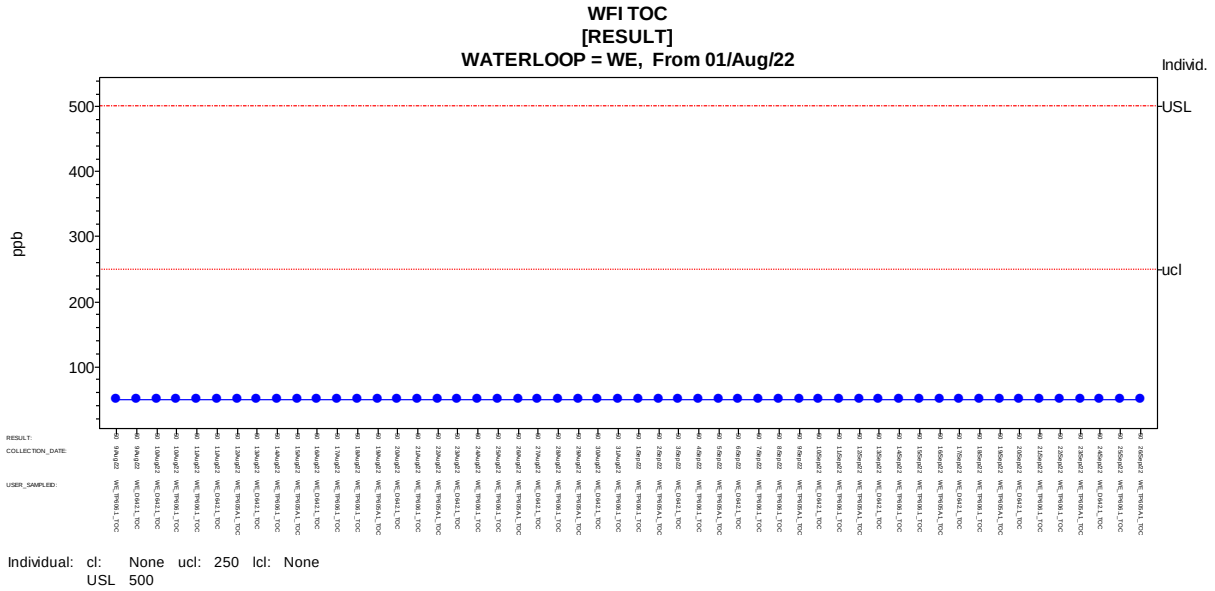

Figure 15 TOC of WFI loop C102 from 01 August 2022 till 26 September 2022

Based on the considerations above, it can be concluded that the CIP cycle of T22 tank performed on 12 September 2022 was valid and the final conductivity of T22 measured in-line was 1.98 µS/cm (ref.: OSIPI database) which is below the limit validated to release a CIP cycle for routine manufacturing, *i.e.* ≤ 5.0 µS/cm (see Figure 5). A potential cross-contamination is therefore excluded.

WFI loop C104 is used for sanitization and flush of pH-meters used on tanks in the R605 area. WFI loop C104 TOC was checked for the period of 01 August 2022 till 26 September 2022. NWA data demonstrated that TOC parameters are satisfactory (see Figure 14),

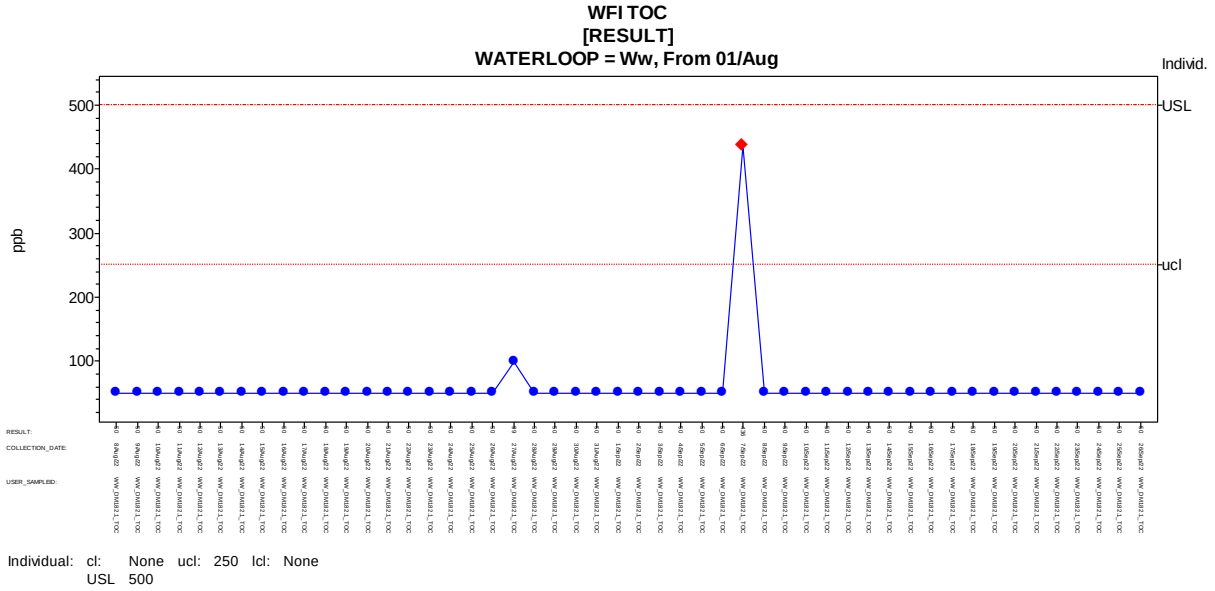

Figure 16 TOC of WFI loop C104 from 01 August 2022 till 26 September 2022

5.1.2. Analysis of the sampling

Based on OSIPI data, EM samples were taken on 12 September 2022 at about 17h21 after the CIP cycle of T22 tank, completed on 12 September 2022 at 17h00. No activities were reported in T22 between end CIP and EM sampling (see Figure 8). It can be noticed that the sampling was performed within 48h (which is the validated clean hold time) after the end of the CIP cycle as per SOP-026466.

The EM sampling was performed according to SOP-026466 as following:

- *At Transfer panel (TP) TP605A, connect elbow « TP605A-4 » from « WFI » to «In T22 »*
- *Fill up T22 with WFI (set-point = 45 Kg)*
- *At Transfer panel TP605, connect elbow « 605-Pré-T22 » at « Out T22 »*
- *Start the sampling function on HMI by selecting command "PRELEV" to open the tank bottom valve and take EM cleaning samples at transfer panel TP605C*

In addition to EM sampling, the flexible TP605A-4 is only used to fill the tanks of the R605 area with WFI. The flexible “605-Pré-T22” is only used for EM sampling of T22 tank.

Cleaning status of small material single elbow “605-Pré-T22” is ensured by manual cleaning. Material was cleaned as per SOP- 048680 “LE09NE03031 - NETTOYAGE MANUEL DU MATERIEL”(*cfr LE99FLNE352 – BE13C097Z*).

It can be concluded that sampling is not the root cause of the out-of-limit TOC value measured on EM monitoring sample of T22 taken on 12 September 2022.

5.1.3. Analysis of the Testing

The laboratory investigation was performed using the 6M methodology. No potential root cause was identified for PR3016700 (ref.: PR2996517).

All others testing performed on EM samples, *i.e*. pH, conductivity, LAL and bioburden were within the specified limits (see Table 2).

5.2. MATERIAL / MACHINE / EQUIPMENT

A review of the maintenance activities on the basis of JDE database was performed on T22, WFI loops C102 & C104, CIP station 638-7 and room 605 (from 11 August 2022 to 21 September 2022).

This review of maintenance activities assessed (ref.: Annexe 1 attached PR3016700 in TW8) that T22, WFI loops C102 & C104, CIP station 638-7 and room 605 were fully operational and that their integrity was ensured for the EM sampling. No potential root cause was identified.

It can be concluded that Material / Machine / Equipment is not the root cause of PR3016700.

5.3. RAW MATERIALS

NaOH 29% is the cleaning agent used for CIP of T22 tank. No carbon in that composition.

The TOC tube used to sample tank T22 on 12 September 2022 corresponds to lot number 21277-4627. This lot number has been quarantined on 14 October 2022 as part of PR3060455 - *Atypical trend of TOC occurrence for EM samples WFI, tanks, UF and columns from 02/Oct/22 to 07/Oct/22*. This PR is still under investigation at the time.

It can be concluded that raw materials is not the root cause of PR3016700.

Nonetheless, deviation PR3060455 has been opened on 14 October 2022 for an atypical trend in the occurrence OoL TOC observed for EM samples. This PR is still under investigation at the time.

5.4. MAN & METHOD

The laboratory investigation was performed using the 6M methodology. No potential root cause was identified for PR3016700 (ref.: PR2996517).

Note that all others testing performed on EM cleaning samples, *i.e.* pH, conductivity, LAL and bioburden were within the specified limits (see Table 2).

According to the laboratory investigation (ref.: PR2996517), the EM operator and QC analyst involved in the OoL treated here were in order of training :

- EM sampling was performed as required in SOP-026466 "*Prelevements des eaux de rincages des tanks*"
- The tests were performed as described in SOP-015413 " *Measurement of Total Organic Carbon with the use of TOC Sievers"*.

An analysis of the above mentioned SOP's revealed that they are explicit, as the methodology to be followed for the collection of rinse samples and their measurement.

It can be concluded that Man is not the root cause of PR3016700.

5.5. CHANGE & NON-CONFORMANCE EVENTS REVIEW

The change & non-conformance events (ref.: Trackwise 8) review was performed on the period from 11 August 2022 (last EM testing satisfactory) to 21 September 2022 (satisfactory retest of EM sampling). The research criteria applied were defined as following: "Zone 605", "Tank T22", "CIP station 638 7", WFI loop C102 & C104".

No other non-conformance events were reported for T22 tank and CIP station 638-7 for the revised here period based on TW8 database.

No change regarding research criteria was implemented for the revised here period based on TW8 database.

The review of the maintenance activities performed on T22 between 11 August 2022 and 12 September 2022 was performed in the Facilities assessment of PR3016700.

5.6. CONCLUSION ON THE ROOT CAUSE INVESTIGATION

The root cause investigation demonstrated that:

- The final conductivity measured in-line for the CIP cycle of T22 performed on 12 September 2022 was satisfactory;
- NaOH 29% is the cleaning agent used for CIP of T22 tank. No carbon in that composition;
- The TOC of WFI loops C102 and C104 was NMT 500 ppb;
- T22 tank as well as the CIP station 638-7 were operational and the integrity of these equipments was ensured during the EM sampling;
- The EM sampling was performed according to the standard operating procedures (within 48 hours after the CIP cycle) and no activities were reported between CIP and EM sampling;
- The QC laboratory testing analysis was satisfactory and no testing error was identified;
- No change impacting T22 and /or CIP station 638-7 were implemented in the period of 11 August 2022 (last satisfactory EM testing) till 21 September 2022 (re-test due to PR3016700);
- The revision of maintenance activities (from 11 August 2022 to 21 September 2022) demonstrated that no maintenance Work Order had impact on this OOL TOC;
- No other non-conformance events concerning T22 were reported;
- LAL, pH, conductivity and Bioburden results obtained for TANK_T22 taken on 12 September 2022 were satisfactory;

No assignable root cause was identified in the investigation of PR3016700.

Nonetheless, deviation PR3060455 has been opened on 14 October 2022 for an atypical trend in the occurrence OoL TOC observed for EM samples. This PR is still under investigation at the time.

6. CORRECTION

Immediate action after the discovery of OOL TOC result on 15 September 2022 was to perform EM re-testing for TOC. The re-test was performed on 21 September 2022 and obtained TOC result (50 ppb) was satisfactory.

7. PRODUCT/PROCESS/EQUIPMENT & RAW MATERIAL IMPACT EVALUATION

7.1. PRODUCT, PROCESS & EQUIPMENT IMPACT EVALUATION

The impact assessment (see *Evaluation PR3016700* attached in TW8) performed for PR3016700 concluded that this event does not have any product, process & equipment impact.

The final conductivity measured in-line for the CIP cycle of T22 performed on 12 September 2022 was 1.40 µS/cm (see Figure 5) which is below the limit validated to release a CIP cycle for routine manufacturing, *i.e.* ≤ 5.0 µS/cm (Ref.: SOP-013469). The CIP638-7 cycle was analyzed in details and was satisfactory.

The trend of T22 final conductivity, measured after the CIP was satisfactory and within required range (see Figure 10).

Additionally, the TOC of the WFI supply loops C102, which is connected to CIP station 638-7 and used for filling T22 are satisfactory (NMT 500 ppb according to SOP-048762) (see Figure 14), The tanks P12 and P13, and the TP653-TP650A pipings are cleaned by CIP 638-7 prior to T22. The TOC results trend for these tanks are satisfactory (see Figure).

All other results, *i.e.* pH, conductivity, LAL and Bioburden obtained for TANK_T22 taken on 12 September 2022 were satisfactory (see Table 2).

Immediate action after the discovery of OOL TOC result on 15 September 2022 was to perform EM re-testing for TOC. The re-test was performed on 21 September 2022 and the obtained TOC result (50 ppb) was satisfactory.

Based on these observations, it can be concluded that PR3016700 does not have any product, process or equipment impact.

7.2. RAW MATERIALS IMPACT EVALUATION

The TOC tube used to sample tank T22 on 12 September 2022 corresponds to lot number 21277-4627. This lot number has been quarantined on 14 October 2022 as part of PR3060455 - *Atypical trend of TOC occurrence for EM samples WFI, tanks, UF and columns from 02/Oct/22 to 07/Oct/22*. This PR is still under investigation at the time.

There is no additional raw material impact following the quarantine of TOC tube lot number 21277-4627.

8. CONCLUSIONS

The investigation performed in the frame of this event showed that:

- All other results, i.e. LAL, pH, conductivity and Bioburden, obtained for TANK_T22 taken on 12 September 2022 were satisfactory;
- The CIP cycle performed on T22 on 12 September 2022 was satisfactory;
- The final conductivity measured in-line for the CIP cycle of T22 performed on 12 September 2022 was satisfactory;
- NaOH 29% is the cleaning agent used for the CIP of T22 tank. No carbon in that composition;
- The TOC of WFI loops C102 and C104 was NMT 500 ppb;
- T22 tank as well as the CIP station 638-7 were operational and the integrity of these equipments was ensured during the EM sampling;
- The EM sampling was performed according to the standard operating procedures (within 48 hours after the CIP cycle) and no activities were reported between CIP and EM sampling;
- The QC laboratory testing analysis was satisfactory and no testing error was identified;

- No change impacting T22 and /or CIP station 638-7 were implemented in the period of 11 August 2022 (last satisfactory EM testing) till 21 September 2022 (re-test due to PR3016700);
- The revision of maintenance activities (11 August 2022 till 21 September 2022) demonstrated that no maintenance Work Order had impact on this OOL TOC;
- No other non-conformance events concerning T22 were reported;

No assignable root cause was identified in the investigation of PR3016700. Nonetheless, deviation PR3060455 has been opened on 14 October 2022 for an atypical trend in the occurrence OoL TOC observed for EM samples. This PR is still under investigation at the time.
Investigation of PR3016700 can be closed without additional action.

There is no quality impact (product nor process/system/equipment) of the OOL TOC value measured on EM sample of TANK_T22 taken on 12 September 2022 as concluded in the impact assessment (see Evaluation PR3016700 attached in TW8).

There is no additional raw material impact following the quarantine of TOC tube lot number 21277-4627 in PR3060455.

Immediate action after the discovery of OOL TOC result on 15 September 2022 was to perform EM re-testing for TOC. The re-test was performed on 21 September 2022 and the obtained TOC result (50 ppb) was satisfactory.

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