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Cleaning Validation of Pegylated Interferon Alpha-2a by Toc Analyzer

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Abstract: *The Total Organic carbon (TOC) test is a quick and successful explanatory strategy to assess the cleaning of biopharmaceutical assembling supplies. This system can help guarantee that the cleaning methods meet foreordained cleanability criteria for single and multiproduct creation territories. This article displays a research endeavor portraying the utilization of the TOC test to accept the cleaning techniques utilized for two sorts of bio-assembling supplies. Stainless steel plates were utilized as a part of the swab recuperation test to recreate producing supplies. One side of each one plate was spiked with an answer of dynamic substance or cleaning specialists. The plates were permitted to dry totally overnight at room temperature. An Alpha Swab Tx761 was saturated with low TOC (< 50 ppb) water and the spiked plate surface was swabbed both vertically and on a level plane. The swab end was decreased off, put into a vial to which we included 40-ml of low TOC water. The vial was topped tight, vortexed, and permitted to remained for one hour before examination. The same volume of each one arrangement that was spiked onto the plates was independently spiked specifically into 40-ml of low TOC water and investigated. The reason for this study is to exhibit how to create and validate a TOC system for cleaning applications. Approval of the cleaning methods for assembling or transforming gear has been exhibited in this paper.*

Keywords: *TOC, Pegylated Interferon α-2a, Swab recovery.*

I. Introduction

Cleaning validation refers to establishing documented evidence providing a high degree of assurance that a specific cleaning process will produce consistent and reproducible cleaning results that meet a predetermined level. The prevention of cross contamination is an essential component of any GMP program and is necessary to ensure the safety of drugs, biologics and medical devices used in human or veterinary applications. A major source of contamination risk to these products is in the form of carryover of compounds and cleaning agent residues from the previous manufactured product or cleaning process.

The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, and/or cleaning agents as well as the control of potential microbial contaminants. In addition one needs to ensure there is no risk associated with cross-contamination of active ingredients. Cleaning procedures must strictly follow carefully established and validated methods. Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to non-contact parts into which product may migrate (e.g., seals, flanges, mixing shaft, fans of ovens, heating elements, etc.).Relevant process equipment cleaning validation methods are required for biological drugs because of their inherent characteristics (proteins are sticky by nature), parenteral product purity requirements, the complexity of equipment, and the broad spectrum of materials which need to be cleaned. 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 single validation study under consideration of the worst case can then be carried out which takes account of the relevant criteria.

For biological drugs, including vaccines, bracketing may be considered acceptable for similar products and/or equipment provided appropriate justification, based on sound and scientific rationale, is given. Some examples are cleaning of fermenters of the same design but with different vessel capacity used for the same type of recombinant proteins expressed in the same rodent cell line and cultivated in closely related growth media; a multi-antigen vaccine used to represent the individual antigen or other combinations of them when validating the same or similar equipment that is used at stages of formulation (adsorption) and/or holding. Validation of cleaning of fermenters should be done upon individual pathogen basis.

II. Materials & Methods

1.1 Instrument detail:
Sievers-900 TOC Analyzer
Make: Sievers
Origin: USA

1.2 Instrument specification:

Description	Specification
Component: Display	
Display	6 inches TFT LCD
Component: Other components	
PFA sampling tube set	01 no (2 x 4 dia,length 100 mm,with nut)
Drain tube	01 no.(2X3 dia,length 150 mm)
LCD Touch system display	01 no.
ICR	01 no.
Power cord	01 no.
Waste Outlet tube	01 no.

1.3 Operating procedure:

The development of this method and validation were performed on a Sievers 900 wide range TOC Analyzer. It measures TOC directly by adding phosphoric acid to the sample to reduce pH to approximately 2 to 3. At this low pH, any inorganic carbon that is present is liberated as CO2 into a nitrogen carrier gas and is directly measured by a non-dispersive infrared (NDIR) detector. Any remaining carbon in the sample is assumed to be TOC, Ammonium persulfate oxidant is then added to the sample, and in the presence of UV radiation, the remaining carbon is oxidized to CO2. The amount of CO2 generated is then measured by NDIR to determine the amount of TOC originally present in the water.

1.4 Instrument software function:
Main screen is divided into three areas.

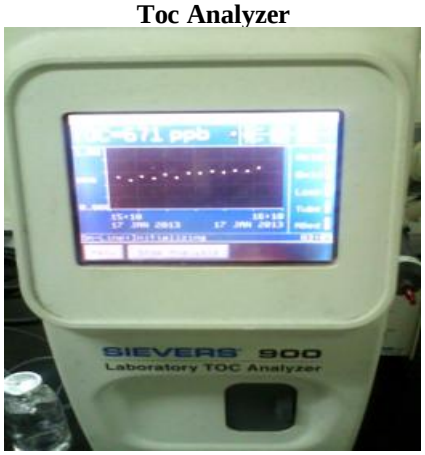
The header contains the name of the screen, the date and time and status icons. The data area shows indicators for the status of the Analyzer's primary consumable (Grab Mode). A table of sample statistics displays on the Main Screen. The status area displays information about the current operation mode. Press the Start Analysis button to initiate TOC measurement; it takes several minutes to complete the analysis after completion result shows in unit ppb on LCD display**.**

1.5 Pre-Requisites: TOC Instrument, 100 ml. glass vial (USP Type I), Dilute HNO3 (B.P.)

1.6 Procedure:
1.6.1 Take 100 ml glass vial and rinse it with diluted HNO3 minimum three times.
1.6.2 Prepare Dilute Nitric acid as per latest B.P.
1.6.3 Thoroughly rinse the vials with water sample.
1.6.4 After rinsing vials with the sample, collect water sample in the vial leaving minimum or no headspace and test it in a timely manner to minimize the impact of organic contamination.

1.6.5 Insert the 'TOC Nebulizer' (Inlet tube) in the vial. End of the tube shall be near the bottom of the vial

Toc Analyzer



III. Results & Discussions

1.7 Sampling Regimen:

Table 01 (Sample Regimen)

S.NO.	Sampling point	Sample Type
1	Dispensing tools	Rinse
2	Manufacturing vessel	swab
3	Holding / Filling vessel	swab
4	Filling Nozzle & connecting tube	Rinse
5	Polypropylene bottles	Rinse
6	Centrifuge tube	Rinse

1.8 Sample Preparation:

Rinse sample:

Take 100ml WFI and pass through the product contact areas of equipment and collect the Rinse in a clean dry glass vial and analyze the sample on TOC Analyzer.

Swab sample:

After cleaning the equipment take sample through sterile cotton swab covering Approx. 10 x 10 cm and then dip the swab in 100ml WFI and analyze the sample on TOC Analyzer.

1.9 Swab Recovery:

Stainless steel plates were utilized as a part of the swab recuperation test to reproduce fabricating gear. One side of each one plate was spiked with an answer of dynamic substance or cleaning operators. The plates were permitted to dry totally overnight at room temperature. An Alpha Swab TX761 was dampened with low TOC (< 50 ppb) water and the spiked plate surface was swabbed both vertically and evenly. The swab end was reduced off, set into a vial to which we included 40-mL of low TOC water. The vial was topped tight, vortexed, and permitted to remain for one hour before investigation. The same volume of every arrangement that was spiked onto the plates was independently spiked straightforwardly into 40-mL of low TOC water and examined. The percent recuperations of the diverse substances are recorded in Table 3. Reported qualities are the normal of three individual swab tests for every substance. The swab recuperations shifted between 80% to 96%.

1.10Results of Swab recovery:

Table 02 (Swab Recovery)

S.No.	Testing Date	Total Organic Carbon (ppb)		% recovery
		Reference 50ppb	sample	
Sample 1	17-10-14	50	40	80**(Min)**
Sample 2	17-10-14	50	42	84
Sample 3	17-10-14	50	45	90
Sample 4	17-10-14	50	46	92
Sample 5	17-10-14	50	48	96**(Max)**
Sample 6	18-10-14	50	43	86
Sample 7	18-10-14	50	40	80
Sample 8	18-10-14	50	41	82
Sample 9	18-10-14	50	47	94
Sample 10	18-10-14	50	48	96

1.11Results of rinse samples:

Dispensing tools:

Table 03 (Dispensing tool rinse sample)

S. No	Batch No	Testing Date	Total Organic Carbon (ppb)		Conductivity (µS/cm)		pH	
			Reference	sample	Reference	sample	Reference	sample
1	40001	20-10-14	143	157	0.7	0.8	5.83	5.90
2	40002	20-10-14	109	121	0.7	0.8	5.71	5.82
3	40003	21-10-14	167	187	0.9	0.9	5.92	6.01
4	40004	21-10-14	128	141	0.7	0.8	5.56	5.68
5	40005	22-10-14	172	190	0.8	0.8	5.67	5.62
6	40006	22-10-14	142	159	0.7	0.8	5.57	5.65
7	40007	23-10-14	135	147	0.8	0.9	5.90	6.00
8	40008	23-10-14	110	122	0.8	0.9	5.50	5.61
9	40009	24-10-14	160	181	0.7	0.8	5.61	5.70
10	40010	24-10-14	150	167	0.8	0.9	5.60	5.69

Remarks: Water for injection is used as reference for the cleaning validation study.

Results: All results of rinse samples correlate to the results of reference (water for injection) sample.

Manufacturing vessel:

Table 04 (Manufacturing vessel rinse sample)

S. No	Batch No	Testing Date	Total Organic Carbon (ppb)		Conductivity (µS/cm)		pH	
			Reference	sample	Reference	sample	Reference	sample
1	40001	20-10-14	143	149	0.7	0.6	5.83	6.00
2	40002	20-10-14	109	120	0.7	0.7	5.71	5.83
3	40003	21-10-14	167	175	0.9	0.9	5.92	5.87
4	40004	21-10-14	128	146	0.7	0.8	5.56	5.69
5	40005	22-10-14	172	196	0.8	0.8	5.67	5.82
6	40006	22-10-14	141	159	0.7	0.8	5.57	5.65
7	40007	23-10-14	131	147	0.8	0.9	5.90	6.00
8	40008	23-10-14	110	122	0.8	0.9	5.50	5.65
9	40009	24-10-14	160	181	0.7	0.8	5.61	5.70
10	40010	24-10-14	155	169	0.8	0.9	5.51	5.65

Holding / Filling vessel:

Table 05 (Holding vessel rinse sample)

S. No	Batch No	Testing Date	Total Organic Carbon (ppb)		Conductivity (µS/cm)		pH	
			Reference	sample	Reference	sample	Reference	sample
1	40001	20-10-14	143	168	0.7	0.6	5.83	5.99
2	40002	20-10-14	109	126	0.7	0.7	5.71	5.76
3	40003	21-10-14	167	182	0.9	0.9	5.92	5.95
4	40004	21-10-14	128	137	0.7	0.6	5.56	5.63
5	40005	22-10-14	172	188	0.8	0.7	5.67	5.74
6	40006	22-10-14	150	167	0.8	0.9	5.60	5.69
7	40007	23-10-14	150	167	0.8	0.9	5.60	5.69
8	40008	23-10-14	110	122	0.8	0.9	5.50	5.61
9	40009	24-10-14	145	157	0.7	0.8	5.50	5.61
10	40010	24-10-14	150	167	0.8	0.9	5.60	5.69

Filling Nozzle & connecting tube:

Table 06 (Filling Nozzle rinse sample)

S. No	Batch No	Testing Date	Total Organic Carbon (ppb)		Conductivity (µS/cm)		pH	
			Reference	sample	Reference	sample	Reference	sample
1	40001	20-10-14	143	128	0.7	0.7	5.83	5.91
2	40002	20-10-14	109	122	0.7	0.8	5.71	5.78
3	40003	21-10-14	167	181	0.9	0.8	5.92	5.84
4	40004	21-10-14	128	139	0.7	0.7	5.56	5.69
5	40005	22-10-14	172	193	0.8	0.9	5.67	5.77
6	40006	22-10-14	150	167	0.8	0.9	5.60	5.69
7	40007	23-10-14	135	147	0.8	0.9	5.90	6.00
8	40008	23-10-14	110	122	0.8	0.9	5.50	5.61
9	40009	24-10-14	160	181	0.7	0.8	5.61	5.70
10	40010	24-10-14	151	162	0.7	0.8	5.60	5.62

Polypropylene bottles:

Table 07 (Polypropylene bottles rinse sample)

S. No	Batch No	Testing Date	Total Organic Carbon (ppb)		Conductivity (µS/cm)		pH	
			Reference	sample	Reference	sample	Reference	sample
1	40001	20-10-14	143	134	0.7	0.8	5.83	5.69
2	40002	20-10-14	109	124	0.7	0.7	5.71	5.77
3	40003	21-10-14	167	145	0.9	0.8	5.92	5.89
4	40004	21-10-14	128	137	0.7	0.8	5.56	5.67
5	40005	22-10-14	172	166	0.8	1.0	5.67	5.54
6	40006	22-10-14	140	155	0.7	0.8	5.57	5.63
7	40007	23-10-14	130	141	0.7	0.8	5.81	5.95
8	40008	23-10-14	122	132	0.8	0.9	5.50	5.65
9	40009	24-10-14	160	181	0.7	0.8	5.61	5.70
10	40010	24-10-14	150	167	0.8	0.9	5.71	5.79

Centrifuge tube:

Table 08 (Centrifuge tube rinse sample)

S. No	Batch No	Testing Date	Total Organic Carbon (ppb)		Conductivity (µS/cm)		pH	
			Reference	sample	Reference	sample	Reference	sample
1	40001	20-10-14	143	130	0.7	0.7	5.83	5.97
2	40002	20-10-14	109	115	0.7	0.7	5.71	5.61
3	40003	21-10-14	167	178	0.9	1.0	5.92	6.05
4	40004	21-10-14	128	145	0.7	0.8	5.56	5.52
5	40005	22-10-14	172	193	0.8	1.0	5.67	5.79
6	40006	22-10-14	150	167	0.8	0.9	5.60	5.69
7	40007	23-10-14	135	147	0.8	0.9	5.90	6.00
8	40008	23-10-14	110	122	0.8	0.9	5.50	5.61
9	40009	24-10-14	171	185	0.7	0.8	5.61	5.70
10	40010	24-10-14	152	167	0.8	0.9	5.50	5.68

IV. Conclusion

This study demonstrates that TOC analysis is suitable for measuring organic residues on stainless steel surfaces, and that it is a reliable method for cleaning validation as demonstrated by surface residue recoveries of 80%-97%. This methodology shows that low limits of detection can be obtained. All of these TOC results making TOC analysis a low cost and less time consuming alternative for cleaning validation.

Proper cleaning validation in pharmaceutical facilities is essential to ensuring strict quality control and providing end-user products that meet official requirements. It is highly efficient to validate cleaning from various viewpoints.

Pharmaceutical drug manufacturers looking for gains in quality and efficiency have led to a growing interest to use Sievers* Total Organic Carbon (TOC) Analyzers for cleaning validation. Most pharmaceutical or biotech facilities currently own a TOC analyzer for compendia USP water testing requirements to release purified water or water for injection for use in cleaning or production. Consequently, most facilities already have a means of determining TOC for cleaning validation.

V. Recommendations / Suggestions

- Surface area calculations should be performed, verified and kept on file for all equipment evaluated.
- Worst case sample residue values can be used to determine the worst case level of contamination on the equipment.
- When the worst case result recorded is less than the limit of quantitation but greater than the limit of detection for the test method, the value denoting the limit of quantitation should be used to perform the calculations.
- When the worst case result recorded is less than the limit of detection for the test being performed the value denoting the limit of detection should be used to perform the calculations.

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