WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 9, 923-933. Research Article ISSN 2277–7105

CLEANING VALIDATION OF LARGE VOLUME PARENTERAL'S (LVP'S) MANUFACTURING LINE AND ITS RISK ASSESSMENT

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Article Received on 05 April 2026,
Article Revised on 25 April 2026,
Article Published on 01 May 2026,

https://doi.org/10.5281/zenodo.19878266

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How to cite this Article: Sayma Pathan[1], Mr. Ronak N. Patel[2], Dr. Divyakant Patel[3], Dr. Jaymin G. Patel[4], Ms. Mugdha Dhimar[5], Dr. Bhumi R. Patel[4]*. (2026). Cleaning Validation of Large Volume Parenteral's (Lvp's) Manufacturing Line And Its Risk Assessment. World Journal of Pharmaceutical Research, 15(9), 923–933.

ABSTRACT

Cleaning validation plays a vital role in pharmaceutical quality assurance by confirming that manufacturing equipment is adequately cleaned to eliminate residues and avoid cross-contamination, particularly in facilities using shared systems. The present study focuses on a structured, risk-based approach to cleaning validation for Paracetamol Intravenous Infusion (1% w/v) produced in a Large Volume Parenteral (LVP) unit. The evaluation included identification of worst-case conditions, careful selection of cleaning agents, and validation of automated Cleaning-in-Place (CIP) and Sterilization-in-Place (SIP) processes. Both swab and rinse sampling techniques were utilized to detect residual contaminants on equipment surfaces. Analytical assessments were performed using parameters such as Total Organic Carbon (TOC), conductivity, and pH to ensure effective cleaning. Acceptance limits were defined based on scientifically sound criteria, including the calculation of Maximum Allowable Carryover (MACO). The results from multiple validation cycles confirmed that both chemical and microbiological residues were consistently reduced to within acceptable limits. Overall, the validated cleaning procedure demonstrated compliance with global regulatory expectations, including guidelines from USFDA, EMA, and WHO. This study emphasizes the significance

of a well-designed and scientifically justified cleaning validation program in maintaining product quality, enhancing process reliability, and safeguarding patient health in sterile pharmaceutical manufacturing.

KEYWORDS: Cleaning Validation, Large Volume Parenteral (LVP), Paracetamol Intravenous Infusion, Cleaning-in-Place (CIP), Sterilisation-in-Place (SIP), Maximum Allowable Carryover MACO).

INTRODUCTION

Cleaning validation is a systematic and well-documented approach used to confirm that equipment cleaning procedures consistently eliminate residues from product-contact surfaces. It is an essential component of pharmaceutical quality systems, ensuring product safety, effectiveness, and compliance with regulatory requirements.[1]

The need for validation was established by regulatory agencies to ensure that manufacturing processes remain consistent and controlled. In this context, cleaning validation focuses on verifying the effective removal of product residues, minimizing the risk of contamination, and enabling safe changeover between different products. These aspects are particularly critical in facilities with shared equipment, where contamination and cross-contamination pose significant risks—especially in the production of sterile preparations such as Large Volume Parenterals (LVPs). Consequently, implementing a validated cleaning procedure is crucial to ensure patient safety.[2,3]

Paracetamol Intravenous Infusion (1% w/v)

Paracetamol Intravenous Infusion (1% w/v) is commonly administered as an analgesic and antipyretic in clinical practice. Given its large-scale production and use of common manufacturing equipment, there is a potential risk of residual carryover. This makes it necessary to establish a robust and scientifically justified cleaning validation strategy to ensure the complete removal of residues and maintain product integrity.[4,5]

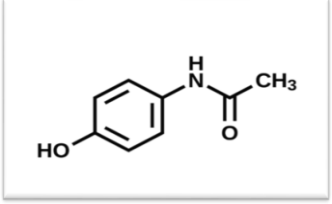

Fig. 1: structure of paracetamol.

Cleaning validation includes the careful selection and optimization of cleaning processes such as Cleaning-in-Place (CIP) and Sterilization-in-Place (SIP), followed by their verification using established sampling methods like swab and rinse techniques. The effectiveness of the cleaning procedure is further confirmed through analytical testing, including parameters such as Total Organic Carbon (TOC), conductivity, and pH.[6-10] The objective of this study is to design and validate a reliable cleaning validation strategy for Paracetamol Intravenous Infusion (1% w/v) based on a risk-oriented approach. The study aims to ensure that the developed procedure meets international regulatory expectations and is suitable for consistent application in routine pharmaceutical manufacturing.

MATERIALS AND METHODS

Chemicals and Reagents

Paracetamol Intravenous Infusion (1% w/v) was chosen as the representative product for this cleaning validation study. All chemicals and reagents employed were of pharmaceutical grade. Purified Water and Water for Injection (WFI) were utilized during the rinsing and final cleaning stages. For microbiological evaluation, culture media such as Soybean Casein Digest Agar (SCDA) and 0.1% peptone water were used. Sample collection was carried out using sterile swabs, sterile templates, and other appropriate sampling tools.

Mobile Phase

Weigh and dissolve 1.6 gm of sodium butane sulphonate in a mixture of 850 ml of water and 150 ml of methanol, and 4 ml of formic acid.

Stationary phase

A stainless steel column 20 cm x 4.6 mm, packed with octylsilane bonded to porous silica (10 µm).

Sampling Procedure for chemical and microbial analysis

Standard and sample preparation for Swab Sample Analysis

Sample preparation: Dip the swab in 10 ml of mobile phase and sonicate.

Reference solution: Weigh accurately 59.8 mg of the paracetamol standard in a 100 ml of volumetric flask and make up the volume with the mobile phase. Transfer 10 ml of this solution 100ml with the mobile phase.

Standard and sample preparation for Rinse Sample Analysis

Sample preparation

Use the rinse sample directly

REFERENCE SOLUTION

Weigh accurately 20 mg of the paracetamol standard in a 100 ml volumetric flask and make up to volume with the mobile phase. Transfer 1 ml of this solution 100ml with the mobile phase.

Sampling locations were selected based on worst-case conditions, such as hard-to-clean surfaces and product contact areas.

MACO Calculation Based on Therapeutic Daily Dose and Safety Criteria

- If therapeutic daily dose is known, we can calculate the MACO value based on TDD (Therapeutic daily dose).

$$\text{MACO} = \frac{\text{TDD (Previous)} \times \text{MBS(Next)}}{\text{SF} \times \text{TDD (Next)}}$$

Where,

MACO = Maximum allowable carryover

TDD previous = Therapeutic Daily Dose of previous product

TDD next = Therapeutic Daily Dose of next product

MBS = Minimum batch size for the next product

SF = Safety factor (normally 1000 is used in calculations based on TDD).

Swab Sample Chromatograph

Table 1: System Suitability Results of Paracetamol Swab Reference Solution.

Injection	Retention Time (min)	Area	Height	Theoretical Plates	Tailing Factor
STD-01	3.742	2397209	207622	16080	0.932
STD-02	3.742	2394588	207303	16075	0.932
STD-03	3.741	2394574	207318	16078	0.932
STD-04	3.741	2394509	207314	16078	0.931
STD-05	3.741	2395100	207373	16076	0.931

The standard solution is injected 5 times because

To check system suitability, verify precision (repeatability), confirm instrument stability & ensure the peak area is consistent & the %RSD value (0.05%) is well within the acceptable limit of NMT 2%, indicating excellent system precision and reproducibility.

After 5 injections

- If %RSD is within limit (generally ≤ 2%)
- Tailing factor is acceptable (Not more than 2)
- Theoretical plates are acceptable
- Retention time is stable, then the system is considered **stable and validated.**

Given Standard Areas (STD-01 to STD-05)

2397209

2394588

2394574

2394509

2395100.

Step 1: Calculate Average (Mean)

$$\text{Mean} = \frac{\text{Sum of all areas}}{5}$$

Sum = 11,975,980

$$\text{Mean} = \frac{11{,}975{,}980}{5}$$

$$\text{Mean} = 2{,}395{,}196$$

Average Area = **2,395,196**

Step 2: Calculate Standard Deviation (SD)

Using the SD formula:

$$SD = \sqrt{\frac{\sum(x - \bar{x})^2}{n - 1}}$$

Where n = 5

$$\frac{5{,}289{,}902}{4} = 1{,}322{,}475$$

$$SD \approx 1150.$$

Step 3: Calculate %RSD

Formula

$$\%RSD = \frac{SD}{Mean} \times 100$$

$$\%RSD = \frac{1150}{2{,}395{,}196} \times 100$$

$$\%RSD = 0.048\%$$

Rounded: $\%RSD \approx 0.05\%$

%RSD = 0.05%

CONCLUSION

- The %RSD value (0.05%) is well within the acceptable limit of NMT 2%, indicating excellent system precision and reproducibility.

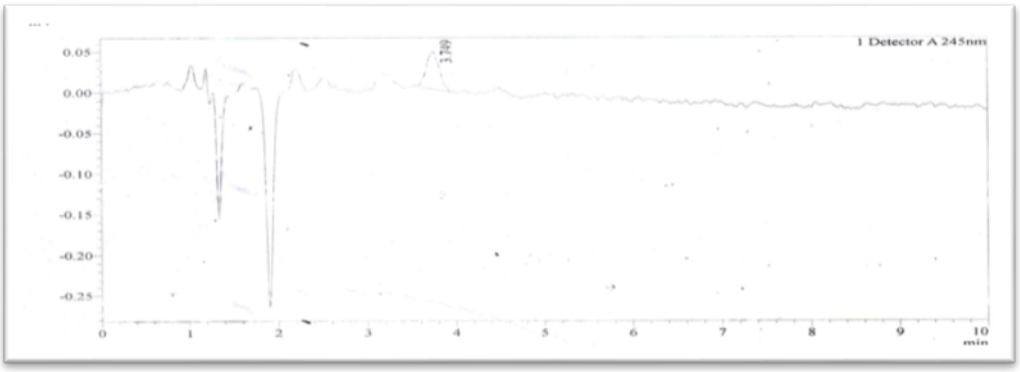

Fig. 2: Paracetamol CV Swab Standard Chromatograph.

- The reference standard chromatogram obtained after five replicate injections was used for comparison and quantification of all swab samples (S1–S8). The system suitability parameters were within acceptable limits, ensuring the reliability of subsequent sample analysis.

System Suitability Results of Paracetamol Rinse Reference Solution

Table 2: System Suitability Results of Paracetamol Rinse Reference Solution.

Sr. No.	Sample Name	Ret. Time	Area	Height	Theoretical Plates	Tailing Factor
1	STD 01	3.745	83228	7234	16077	0.932
2	STD 02	3.745	83291	7237	16098	0.930
3	STD 03	3.744	83268	7244	16122	0.932
4	STD 04	3.743	83198	7239	16129	0.932
5	STD 05	3.743	83259	7241	16117	0.932

The standard solution is injected 5 times because

- To check system suitability, verify precision (repeatability), confirm instrument stability & ensure the peak area is consistent.

After 5 injections:

- If %RSD is within limit (generally ≤ 2%)
- Tailing factor is acceptable
- Theoretical plates are acceptable (not less than 1500)
- Retention time is stable, then the system is considered **stable and validated.**

Given Standard Areas (STD-01 to STD-05)

83228

83291

83268

83198

83259

Step 1: Calculate Mean

$$Mean = \frac{83228 + 83291 + 83268 + 83198 + 83259}{5}$$

$$Mean = \frac{416244}{5} = 83248.8$$

Mean ≈ **83249**

Step 2: Calculate Standard Deviation (SD)

Using SD formula:

$$SD = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$$

After calculation

SD ≈ **35.7** (≈ 36)

Step 3: Calculate %RSD

$$\%RSD = \frac{SD}{Mean} \times 100$$

$$\%RSD = \frac{36}{83249} \times 100$$

$$\%RSD = 0.0432\%$$

%RSD = 0.043%

CONCLUSION

- The %RSD value (0.043%) is well within the acceptable limit of NMT 2%, indicating excellent system precision and reproducibility.

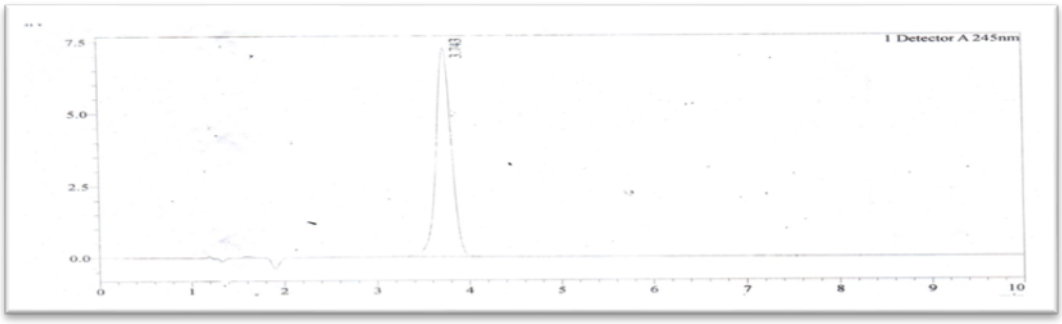

Fig. 3: Paracetamol Rinse Standard Chromatograph.

- The reference standard chromatogram obtained after five replicate injections was used for comparison and quantification of all rinse samples (R1–R8). The system suitability parameters were within acceptable limits, ensuring the reliability of subsequent sample analysis.

RESULT AND DISCUSSION

Swab Sample Report

Table 3: Cleaning samples test report – swab sampling for chemical analysis.

Batch No.: B5457007					
Name of the product manufactured: Paracetamol Intravenous infusion (1% w/v)					
Sr. No	**Sampling Location**	**Sample Type**	**Area of Sampling**	**Product Traces (ppm)**	**Disinfectant Traces (ppm)**
				HPLC	
1	S1	Swab	100 cm^2	0.0114	0.0
2	S2	Swab	100 cm^2	0.0109	0.0
3	S3	Swab	100 cm^2	0.0128	0.0
4	S4	Swab	100 cm^2	0.0111	0.0
5	S5	Swab	100 cm^2	0.0081	0.0
6	S6	Swab	100 cm^2	0.0075	0.0
7	S7	Swab	100 cm^2	0.0074	0.0
8	S8	Swab	100 cm^2	0.0079	0.0

Acceptance criteria

- Product traces should not more than **58.96 ppm.**
- Traces of Disinfectant used Should not more than **10 PPM**

Table 4: Cleaning samples test report – swab sampling for bio-burde.

Batch No.: B5457007					
Name of the product manufactured: Paracetamol Intravenous Infusion (1% w/v)					
Media Details					
Name of Media: Soya bean Casein Digest Agar (SCDA)					
0.1 % Peptone water Lot No:					
Sr. No	**Sampling Location**	**Sample Type**	**Area of Sampling**	**Result (NMT 10 CFU/Plate)**	
				Bacteria	**Fungus**
1.	S1	Swab	100 cm^2	02	Absent
2.	S2	Swab	100 cm^2	05	Absent
3.	S2	Swab	100 cm^2	00	Absent
4.	S3	Swab	100 cm^2	03	Absent
5.	S4	Swab	100 cm^2	04	Absent
6.	S5	Swab	100 cm^2	00	Absent
7.	S6	Swab	100 cm^2	03	Absent
8.	S7	Swab	100 cm^2	02	Absent
9.	S8	Swab	100 cm^2	01	Absent

Acceptance criteria

- Bacterial counts: Not more than **10 CFU/Plate**
- Fungus: Shall be absent.

Rinse Sample Report

Table 5: Cleaning samples test report – Rinse sampling for chemical analysis.

Batch No.: B5457007								
Name of the product manufactured: Paracetamol Intravenous Infusion (1% w/v)								
Sr. No	**Sampling Location**	**Sample Type**	**Area of Sampling**	**Result**		**TOC (NMT 500 ppb)**	**pH (5.0-7.0)**	**Conductivity (NMT 1.3 µs/cm)**
				Product Traces (ppm) HPLC	**Pass/ Fail**			
1	R1	Rinse	NA	0.0098	Pass	99.73	6.40	0.74
2	R2	Rinse	NA	0.0084	Pass	90.37	6.02	0.44
3	R3	Rinse	NA	0.0079	Pass	85.55	6.19	0.74
4	R4	Rinse	NA	0.0090	Pass	84.15	6.48	0.98
5	R5	Rinse	NA	0.0077	Pass	81.14	6.09	0.98
6	R6	Rinse	NA	0.0069	Pass	77.37	6.47	0.81
7	R7	Rinse	NA	0.0076	Pass	74.64	6.33	0.86
8	R8	Rinse	NA	0.0076	Pass	73.37	6.43	0.90

Acceptance criteria

- Product traces should not more than **2.0 ppm**.

Table 6: Cleaning samples test report – Rinse sampling for bio-burden.

Batch No.: B5457007				
Name of the product manufactured: Paracetamol Intravenous Infusion (1% w/v)				
Media Details				
Name of Media: Soya bean Casein Digest Agar				
0.1 % Peptone water				
Sr. No	**Sampling Location**	**Sample Type**	**Result (NMT 10 CFU/100 ml)**	
			Bacteria	**Fungus**
1.	R1	Rinse	02	Absent
2.	R2	Rinse	00	Absent
3.	R3	Rinse	04	Absent
4.	R4	Rinse	02	Absent
5.	R5	Rinse	03	Absent
6.	R6	Rinse	04	Absent
7.	R7	Rinse	00	Absent
8.	R8	Rinse	01	Absent

Acceptance criteria

- Bacterial counts: Not more than **10 CFU/100 ml**.
- Fungus: Shall be absent.

CONCLUSION

The present study successfully developed and validated a robust, risk-based cleaning validation procedure for Paracetamol Intravenous Infusion (1% w/v) in a Large Volume Parenteral (LVP) manufacturing facility. The implementation of optimized Cleaning-in-Place (CIP) and Sterilization-in-Place (SIP) systems, along with the appropriate selection of cleaning agents, ensured effective removal of product residues, cleaning agents, and microbial contaminants from equipment surfaces. And this cleaning validation program for the paracetamol LVP line was found to be effective, reliable, and compliant. A risk-based approach ensures product safety, prevents cross-contamination, and supports consistent quality and regulatory compliance.

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