July 2013, Vol-4, Issue -3

Available online at www.ijppronline.in

International Journal of Pharma Professional Research

ISSN NO:0976-6723

Research Article

TECHNIQUE DEVELOPMENT OF CLEANING VALIDATION FOR CHLORDIAZEPOXIDE IP TABLETS DOSAGE FORM BY MICROBIOLOGICAL METHOD

Anurag Chaudhary[2*], Amit Chaudhary[1]

1.ShriVenkateshwara University, NH-24, VankateshwaraNagar, Rajabpur, Gajraula-244236, U.P., India.

2.Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut Bypass Road, Meerut -250005, U.P., India.

Abstract

The amount or level of cleaning required in order to ensure that the API is free from unacceptable levels of contamination by previous substances varies depending on the step being cleaned and the next substance being manufactured in the same piece of equipment (train).Carefully designed cleaning validation and its evaluation is necessary to ensure that residues of active pharmaceutical ingredient will not carry over and cross-contaminate the subsequent product. Microbiological inspection method was developed and validated for the verification and determination of chlordiazepoxide in the production area and to confirm the efficiency of the cleaning procedure as per CGMP regulations. Microbiological inspection was done on basis of Total Bacterial Count (TBC) criteria. Microbiological acceptance criteria was that TBC should not be more than 30. Range of TBC was 1-24 in dispensing booth, 9 to 26 in granulation room, 8 to 23 in sifter, 5 to 15 in sifter cum multimill, 10 to 25 in rapid mixer granulator, 5 to 18 in fluidized bed dryer, 12 to 27 in conta blender, 2 to 27 in compression cubicle and compression machine, 3 to 26 in coating room and coating machine and 6 to 27 in blister packing room and blister packing machine. Result indicated that TBC value was not exceeded over prescribed limit during three consecutive batches of production after cleaning procedure. Hence, it can be said that this cleaning method validation on solid dosage forms of chlordiazepoxide can be used in routine cleaning to avoid the risk of cross contamination.

Keywords: chlordiazepoxide, validation

INTRODUCTION

In recent years the subject of cleaning validation in active pharmaceutical ingredient manufacturing plants has received a large amount of attention from regulators, companies and customers alike. It is important that the requirements for the finished manufacturing companies are not transferred back in the process to active pharmaceutical ingredient manufacturers without consideration for the different processes that take place at this stage. The manufacturing process of an active pharmaceutical ingredient (API) typically consists of various chemical reaction and purification steps followed by physical changes. In general early steps undergo further processing and purification and so potential carryover of the previous product would be removed. The amount or as we will call it here, level of cleaning required in order to ensure that the API is free from unacceptable levels of contamination by previous substances varies depending on the step being cleaned and the next substance being manufactured in the same piece of equipment (train). API's and related intermediates are often produced in multi-purpose equipment with

frequent product changes which results in a high amount of cleaning. In present work we have done technique development of cleaning validation for chlordiazepoxide IP tablets dosage form by microbiological method[1-9]

MATERIALS AND METHOD

MICROBIOLOGICAL INVESTIGATION METHOD

OBJECTIVE AND SCOPE:

To check the Microbial load (bioburden) on cleaned machinery and equipments used for manufacturing of product at each stage. This procedure is applicable for Cleaning Validation only.

PROCEDURE:

SWABBING PROCEDURE:

Stainless Steel template of dimension 10 X 10cm were used for measurement. Sterile swabs packing at specific location, where swab was to be taken, was removed and soaked in a sterile buffer peptone water with NaCl pH 7.0 solution Equipment was swabbed in area of 10 cm x 10 cm. After collecting the swab, it was put in the test tube containing 5 ml of sterile buffer peptone water with NaCl pH 7.0 solution and test tube was closed by putting cotton plug on it. Test tube was analyzed at microbiology laboratory. Test tubes were labelled for detail such as Name of area, Name & part of equipment. Sampled area was sanitized with lint free cloth dipped in 70% isopropyl alcohol.

RINSE PROCEDURE:

Equipment, under study, was cleaned as per individual equipment cleaning procedure and rinsed with 5 liter of purified water thoroughly. After that 100 ml of rinsed sample was taken in sterile bottle for checking microbial load. Bottle was analyzed at microbiology laboratory.

TESTING PROCEDURE:

a) Estimation of Swab :

swab was agitated in a sterile buffer peptone water with NaCl pH 7.0 solution with the help of vortex mixer. Aseptically, 1 ml solution was transferred to each of the two sterile petri plates.To one Petri plate, 15 to 20 ml of sterile soyabean casein digest agar was added, and to another, sabouraud dextrose agar, that was melted & cooled to 45°C, was added. One plate of each medium was kept as control plate containing only medium. Agar was allowed to solidify. Petri plate was covered; sample was mixed with agar by tilting & rotating the plates. Contents were solidified at room temperature. After solidification petri plates were inverted. Petri plates, containing soyabean casein digest agar, were incubated at 30 to 35°C for 72 hours and sabouraud dextrose agar plates were incubated at 20° to 25°C for 5 days. After incubation, number of colonies, on each plate, were counted and result was reported by multiplying the count by 5 for final count.

b) Estimation for Rinse Sample

For rinse sample, 100 ml of sample was filtered through 0.45 micron filter. Filter paper was put on sterile soyabean casein digest agar. Plate was incubated at 20.0 to 25.0°C for 72 hours and 30.0 to 35.0° C for remaining 48 hours. After incubation the number of colonies, developed on the surface of filter paper, were counted.

c) Evaluation of gram negative bacteria

Plates were observed after completion of incubation period. Cell suspension of all observed colonies of soyabean casein digest agar was prepared. Smear of above suspension was prepared on microscopic glass slide. After that, Gram staining was done. Pink coloured rod shape bacteria, on each & every clone of smear under microscope, were checked. If any Gram negative rod shaped organism was observed, it was isolated on selective agar & identified accordingly.

d) Calculation of result

Total Bacterial Count = cfu/100 sq. cm OR at that specific area or location of equipment or machinery, where quantification is not possible.

In result fungi and gram negative bacteria should be absent.

VISUAL INSPECTION METHOD

The equipment including "Hard to clean areas" should appear clean with no traces of product when observed in wet and dry condition of the surface. The standard of visually clean shall be used for purposes of both validation and monitoring. The dividing line between visually clean and visually dirty is regarded as presence of residual levels of active ingredient.

Test: A representative portion of the sample was transferred to a Nesslers cylinder and view in diffused light.

Calculation of result: Sample should be clear in appearance in Nessler cylinder.

RESULT & DISCUSSION

Validation considerations for new products and existing product lines have both fundamental

differences and similarities. Both may require cycle development and optimization activities prior to validation. They both may also require the development and validation of low level analytical detection methods for the active ingredient, detergent or cleaning solvent, and possibly excipients. For new products, the cycle development and optimization steps are more readily accomplished in the process development phase. At this point the choice of detergent or solvent can be readily made. Critical data such as solubility, conductivity, and pH of the active in the detergent or solvent can be easily developed. Such data can be helpful in the design and development of the process and equipment for the production scale[10-13] All critical monitoring instrumentation such as thermocouples or RTDs, pressure gauges, flow meters, conductivity sensors or pH meters must be identified and calibrated. The function of each monitoring device must be clearly understood. This is particularly true in an automated system, where individual devices may have a controlling influence over particular phases of the process. When specifying equipment to be used for cleaning, it is helpful to select equipment with multiple monitoring devices as they help to establish a reproducible cleaning process. All personnel must be trained and each operator must understand the cleaning steps and process. In order to establish a validated cleaning procedure, whether manual, semi-automated or fully automated, it is generally useful to perform cycle development studies in order to establish the parameters which are to be validated. Proper development of the cleaning cycle provides confirmation of the safety of the process, economic savings, confidence in the validation starting point and experience with the test and sampling methods. At the conclusion of cycle development, it is possible to finalize standard operating procedures (SOPs) for the correct operation and monitoring of the cleaning system. The critical factors which influence the cleaning cycle to be developed include: the equipment, the cleaning agents, cleaning parameters, product or formulation, cleaning procedures, documentation and training. It is important not only that operator training occur, but also that the training be well documented. Without proper documentation, it is impossible to prove that the training was actually accomplished. Operators should be retrained each time a cleaning procedure is changed and the new training must be documented, just as in the case of a change to a manufacturing procedure[1-6].

Organoleptic techniques (i.e., visual, smell, touch) used as a component of the cleaning program and, additionally, as one of the tests useful for the validation of the cleaning procedure. Visual examination of equipment for cleanliness immediately before use is required by the CGMP regulations. Visual examination is a combination of sampling and analysis, where the observer makes an immediate determination of equipment cleanliness. Visual examination of equipment, in particular, is utilized by the majority of pharmaceuticals both as a means of evaluating cleaned surfaces during the cleaning validation stage and after cleaning validation is complete as part of an ongoing monitoring of the cleaning process. In some instances this method has been shown to have a high sensitivity. The visual examination of equipment enhanced by simply passing an ultraviolet “black” light over the surfaces of the equipment. This use of an ultraviolet light would be effective for residueswhich fluoresce when irradiated with ultraviolet light. Another means of visual enhancement is the use of dyes which form colored complexes with certain residues such as proteins producing a colored residue much easier to observe visually than the uncomplexed free residue. For example, methylene blue can detect anionic detergent residues and proteins remaining on equipment but here used the uv lamp for examination of the surfaces of equipments and their parts/components and found visually clean after cleaning procedure which is efficient to clean the equipments and their parts effectively[14-17].

All the equipments, used in the production of chlordiazepoxide, were visually inspected for the cleanliness during production of three successive batches. In dispensing booth floor, walls, door-I and II, platform balance, reverse laminar air flow, scoops and other utensils were inspected and found clean as shown in Table 1.

Table 1 Visual inspection results of dispensing booth (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Walls	Yes	Yes	Yes
3	Door – I	Yes	Yes	Yes
4	Doors – II	Yes	Yes	Yes
5	Platform Balance	Yes	Yes	Yes
6	Reverse Laminar Air Flow	Yes	Yes	Yes
7	Scoops	Yes	Yes	Yes
8	Other Utensils	Yes	Yes	Yes

In sifter sieves, blades of multi mill, feed hopper, dischsrge chute and screw conveyer were inspected and found clean as shown in Table 2.

Table 2 Visual inspection results of sifter (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Sieves	Yes	Yes	Yes
2	Blades of Multil Mill	Yes	Yes	Yes
3	Feed Hopper	Yes	Yes	Yes
4	Discharge Chute	Yes	Yes	Yes
5	Screw Conveyor	Yes	Yes	Yes

In rapid mixer granulator discharge chute, view glass-I and II, impeller, chopper, near discharge chute and RMG lid were inspected and found clean as shown in Table 3.

Table 3 Visual inspection results of rapid mixer granulator (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Discharge Chute	Yes	Yes	Yes
2	View Glass – I	Yes	Yes	Yes
3	View Glass – II	Yes	Yes	Yes
4	Impeller	Yes	Yes	Yes
5	Chopper	Yes	Yes	Yes
6	Near discharge chute	Yes	Yes	Yes
7	RMG lid	Yes	Yes	Yes

In fluidized bed dryer FBD bowl product container, bottom pan, retarding chamber and inner side of view glass were inspected and found clean as shown in Table 4.

Table 4 Visual inspection results of fluidized bed dryer (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	FBD bowl product container	Yes	Yes	Yes
2	Bottom Pan	Yes	Yes	Yes
3	Retarding Chamber	Yes	Yes	Yes
4	Inner side of view glass	Yes	Yes	Yes

In conta blender its lid and inner surface were inspected and found clean as shown in Table 5.

Table 5 Visual inspection result of conta blender (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Lid of conta blender	Yes	Yes	Yes
2	Inner surface of conta blender	Yes	Yes	Yes

In compression cubicle and compression machine section floor, ceiling, walls, doors, electric panels, hopper, feed frame, turret, discharge chute, metal detector and discharge chute of metal detector were inspected and found clean as shown in Table 6.

Table 6 Visual inspection result of compression cubicle and compression machine (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Ceiling	Yes	Yes	Yes
3	Walls	Yes	Yes	Yes
4	Doors	Yes	Yes	Yes
5	Electric panels	Yes	Yes	Yes
6	Hopper	Yes	Yes	Yes
7	Feed Frame	Yes	Yes	Yes
8	Turret	Yes	Yes	Yes
9	Discharge Chute	Yes	Yes	Yes
10	Metal Detector	Yes	Yes	Yes
11	Discharge Chute of Metal Detector (VO-RCM-06)	Yes	Yes	Yes

In coating area and coating machine section floor, ceiling, walls, doors, electric panels and coating pan-I, II, III, IV and V were inspected and found clean as shown in Table 7.

Table 7 Visual inspection results of coating area and coating machine (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Ceiling	Yes	Yes	Yes
3	Walls	Yes	Yes	Yes
4	Doors	Yes	Yes	Yes
5	Electric panels	Yes	Yes	Yes
6	Coating Pan I	Yes	Yes	Yes
7	Coating Pan II	Yes	Yes	Yes
8	Coating Pan III	Yes	Yes	Yes
9	Coating Pan VI	Yes	Yes	Yes
10	Coating Pan V	Yes	Yes	Yes

In blister packing room and blister packing machine floor, walls, doors, hopper, spiral bowl, chute, feed box, machine door, de-blistering machine chute were inspected and found clean as shown in Table 8.

Table 8 Visual inspection results of blister packing room and blister packing machine (after cleaning)

	Areas for visual observation	Visually clean Yes/ No		
		Batch No.		
		Batch – I	Batch – II	Batch - III
1	Floor	Yes	Yes	Yes
2	Walls	Yes	Yes	Yes
3	Doors	Yes	Yes	Yes
4	Hopper	Yes	Yes	Yes
5	Spiral Bowl	Yes	Yes	Yes
6	Chute	Yes	Yes	Yes
7	Feed Box	Yes	Yes	Yes
8	Machine Door	Yes	Yes	Yes
9	De-blistering machine chute	Yes	Yes	Yes

After visual examination all equipment were inspected by microbiological method as discussed below-

The results of the microbiological tests sampled from the dispensing booth and its components, mentioned in Table 9, were within the acceptance criteria and indicated the effective cleaning for the dispensing booth as per defined procedure. Also, no pathogens and no growth of fungus were observed.

Table 9 Microbiological inspection results of dispensing booth (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Serial No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample – I	22	18	24
2	Floor Sample- II	16	10	23
3	Wall Sample – I	12	11	16
4	Wall Sample – II	10	08	07
5	Door Sample – I	05	09	06
6	Door Sample – II	09	11	13
7	Side Wall RLAF – I	03	06	10
8	Side Wall RLAF – II	01	05	02
9	Side Wall RLAF – III	04	03	06
10	Platform Balance – I	12	14	15
11	Platform Balance – II	16	14	13
12	Platform Balance - III	11	10	17
13	Scoop - I	07	06	04
14	Scoop - II	04	07	08

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from the granulator and its components after cleaning for three batches, mentioned in Table 10, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 10 Microbiological inspection results of granulation room (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Serial No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample – I	26	22	18
2	Floor Sample- II	25	26	24
3	Wall Sample – I	13	10	09
4	Wall Sample – II	16	23	15
5	Door Sample – I	18	14	22
6	Door Sample – II	13	16	11

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from sifter and its components after cleaning for three batches, mentioned in Table 11, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 11 Microbiological inspection results of sifter (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Discharge Chute	15	11	16
2	Discharge Chute (Rinse)	12	19	18
3	Feed Bowl – I	18	20	23
4	Feed Bowl – II	13	11	08
5	Sieve – I	15	14	15
6	Sieve – II	16	10	17
7	Sieve – III	12	15	18

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from sifter cum multimill and its components after cleaning for three batches, mentioned in Table 12, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 12 Microbiological inspection results of sifter cum multimill (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Discharge Chute	14	10	13
2	Discharge Chute (Rinse)	10	14	09
3	Feed Hopper – I	06	08	06
4	Feed Hopper – II	08	10	11
5	Multmill Screen	09	05	12
6	Screw Conveyor	12	10	15

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from rapid mixer granulator and its components after cleaning for three batches, mentioned in Table 13, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 13 Microbiological inspection results of rapid mixer granulator (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Discharge Chute	14	16	10
2	Discharge Chute (Rinse)	16	20	15
3	Bottom RMG Bowl – I	20	23	18
4	Bottom RMG Bowl– II	16	15	19
5	Bottom RMG Bowl-III	20	21	25
6	Side wall of RMG Bowl	18	17	14
7	Impeller Center	19	22	21
8	Impeller Rear	18	15	18
9	Chopper Bottom	16	13	12
10	Lid of RMG	12	16	18

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from fluidized bed dryer and its components after cleaning for three batches, mentioned in Table 14, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 14 Microbiological inspection results of fluidized bed dryer (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Retarding chamber - I	05	10	13
2	Retarding chamber – II	08	12	07
3	Side wall of FBD Bowl	09	08	14
4	Bottom wall of FBD bowl - I	06	08	10
5	Bottom wall of FBD bowl - II	10	12	14
6	Bottom wall of FBD bowl - III	12	16	15
7	Center of FBD Bowl	14	18	11

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from conta blender and its components after cleaning for three batches, mentioned in Table 15, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 15 Microbiological inspection results of conta blender (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Serial No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Conta Bin Wall – I	18	16	12
2	Conta Bin Wall – II	24	26	19
3	Conta Bin Wall – III	20	25	26
4	Conta Bin Wall – IV	12	16	19
5	Conta Bin Wall – V	16	13	18
6	Conta Bin Lid	19	22	23
7	Conta Bin (Rinse)	27	24	26

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from compression cubicle and compression machine and its components after cleaning for three batches, mentioned in Table 16, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 16 Microbiological inspection results of compression cubicle and compression machine (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water
Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample - I	24	21	27
2	Floor Sample – II	27	22	25
3	Wall Sample – I	06	11	13
4	Wall Sample – II	09	10	12
5	Door Sample – I	05	08	06
6	Door Sample – II	07	09	05
7	Feed Hopper – I Top	06	08	10
8	Feed hopper – I Bottom	08	11	14
9	Feed hopper – II Top	07	05	03
10	Feed hopper – II Bottom	09	15	12
11	Feed Frame – I	11	08	13
12	Feed Frame – II	13	13	12
13	Feed Frame – III	10	08	06
14	Feed Frame – IV	07	12	16
15	Turret – I	03	05	08
16	Turret – II	02	04	06
17	Discharge Chute – I	08	02	04
18	Discharge Chute – II	12	09	06
19	Discharge Chute – I (Rinse)	21	18	14
20	Discharge Chute – II (Rinse)	16	12	14
21	Discharge Chute Metal Detector – I	14	13	09
22	Discharge Chute Metal Detector – II	11	15	16
23	Y – Chute (Rinse) Arm – I	24	25	27
24	Y– Chute (Rinse) Arm – II	18	19	23
25	De-dusting Unit-I (Rinse)	12	10	11
26	De-dusting Unit-II (Rinse)	19	20	18

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from coating room and coating machine and its components after cleaning for three batches, mentioned in Table 17, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 17 Microbiological inspection results of coating room and coating machine (after cleaning)

Swab Sampled Area :10 × 10 cm^2. **Swab Medium :** Purified Water
Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample - I	22	25	19
2	Floor Sample – II	26	22	23
3	Wall Sample – I	08	08	12
4	Wall Sample – II	12	14	16
5	Door Sample – I	07	06	10
6	Door Sample – II	10	11	08
7	Coating Pan – I Top	10	13	16
8	Coating Pan – I Bottom	06	08	05
9	Coating Pan – I Side	07	10	14
10	Coating Pan – I Lid	08	06	04
11	Coating Pan – I (Rinse)	12	16	21
12	Coating Pan – II Top	08	06	07
13	Coating Pan – II Bottom	12	14	16
14	Coating Pan – II Side	10	11	08
15	Coating Pan – II Lid	06	12	11

16	Coating Pan – II (Rinse)	15	22	16
17	Coating Pan – III Top	07	05	03
18	Coating Pan – III Bottom	10	11	14
19	Coating Pan – III Side	06	08	05
20	Coating Pan – III Lid	08	11	14
21	Coating Pan – III (Rinse)	10	16	19
22	Coating Pan – IV Top	03	05	08
23	Coating Pan – IV Bottom	12	08	06
24	Coating Pan – IV Side	10	11	12
25	Coating Pan – IV Lid	08	09	08
26	Coating Pan – IV (Rinse)	14	16	21
27	Coating Pan – V Top	06	14	13
28	Coating Pan – V Bottom	10	18	19
29	Coating Pan – V Side	12	08	08
30	Coating Pan – V Lid	07	06	04
31	Coating Pan – V (Rinse)	16	22	26

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

The results of microbiological test sampled from blister packing room and blister packing machine and its components after cleaning for three batches, mentioned in Table 18, were within the acceptance criteria. Also, no pathogens and no growth of fungus were observed.

Table 18 Microbiological inspection results of blister packing room and blister packing machine (after cleaning)

Swab Sampled Area : 10 × 10 cm^2 **Swab Medium :** Purified Water

Rinse Volume : 100 ml. **Rinse Medium :** Purified Water

Sr. No.	Sampled Area / Locations	Microbiological Results[a] (TBC)		
		Batch–I	Batch-II	Batch-III
1	Floor Sample - I	25	12	16
2	Floor Sample – II	20	22	`18
3	Wall Sample – I	08	11	13
4	Wall Sample – II	11	14	19
5	Door Sample – I	07	18	08
6	Door Sample – II	13	22	23
7	Feed Hopper	05	08	06
8	Spiral Bowl	08	11	12
9	Chute	10	13	14
10	Hopper (Rinse)	10	15	14
11	Feed Box – I	12	13	08
12	Feed Box – II	10	09	11
13	Machine Door – I	15	18	22
14	Machine Door – II	13	11	21
15	Pass Box	10	08	06
16	De-blistering M/C Chute – I	09	12	16
17	De-blistering M/C Chute – II	13	14	19
18	De-blistering M/C Chute – I (Rinse)	10	08	07
19	De-blistering M/C Chute – II (Rinse)	14	23	27

[a] No pathogen were observed at any sampling location. Total Fungi Count (TFC) were absent at sampling location.

Results for all the equipments, used in the production of chlordiazepoxide, and production section, were found within the pre-determined limits on microbiological inspection during three successive batches study. Microbiological results (TBC) of all product contact surfaces is given in figure 1.

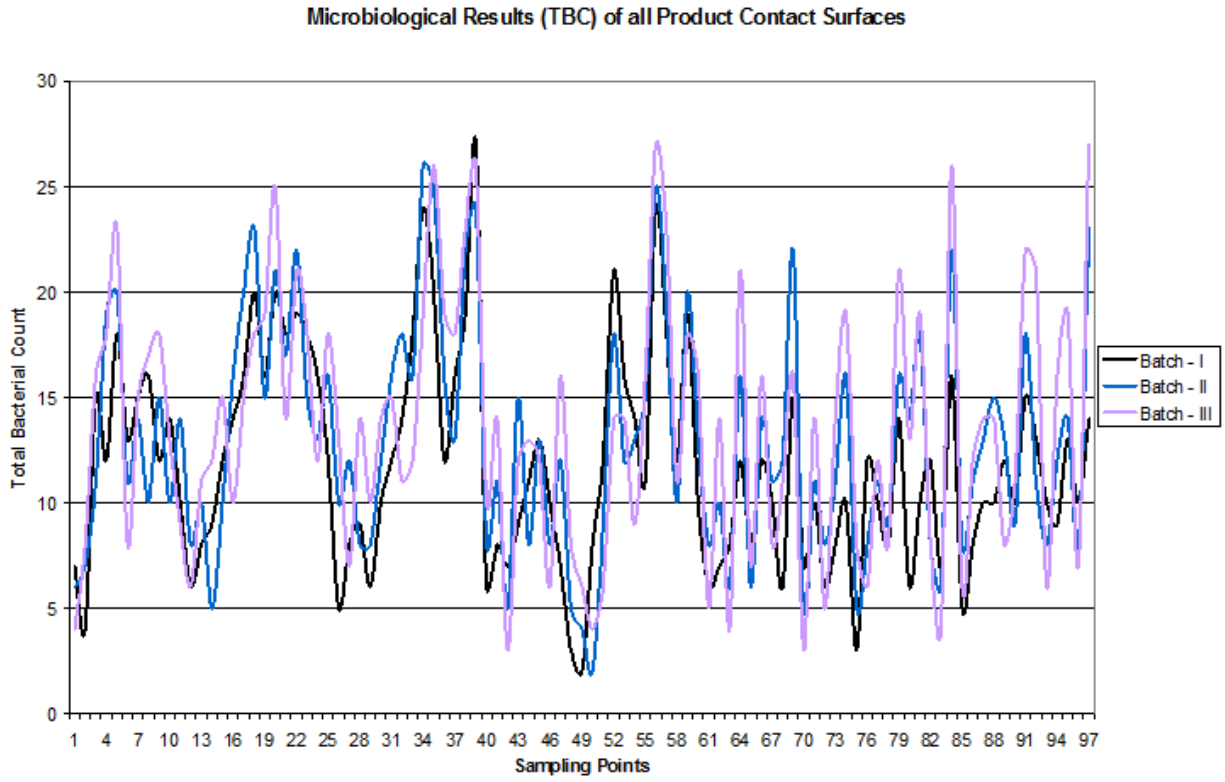

Figure 1 Microbiological results (TBC) of all product contact surfaces.

Results for all the equipments, used in the production of chlordiazepoxide, and production section, were found within the pre determined limits on chemical inspection during three successive batches study.

CONCLUSION

The Final Conclusion has been drawn on the basis of the results obtained during execution of the cleaning validation on solid dosage forms at the manufacturing facility of Cheryl Laboratories Pvt.Ltd. Altogether three consecutive batches of Chlordiazepoxide IP 10 Tablets (Clordiazepoxide 10 mg) were taken under cleaning validation study to prove the effectiveness and consistency of the pre-established standard equipment cleaning procedures. Only product to product change over (B- type cleaning) cleaning method has been validated.

All the qualification studies, calibrations and analytical method validation have been conducted prior to this cleaning validation as a prerequisite. All the results were evaluated against the microbiological acceptance criteria mentioned in cleaning validation master plan, i.e. TBC of NMT (not more than) 30 and 100 for swab samples and rinse samples, respectively. By thorough compilation of the obtained results, we can conclude that microbiological contamination is well under pre-determined acceptance criteria. All collected samples satisfy the microbiological acceptance criteria. The three times repetition of the same results indicates the consistency of the existing cleaning method for achieving expected cleanliness. The worst case approach intensifies the ruggedness of the cleaning method. This risk based study also take care the safety of the products manufactured in this multi product manufacturing facility. This cleaning method validation meets all criteria to satisfy the regulatory requirements on its part. Hence, it can be said that this cleaning method validation on solid dosage form has successfully been completed and can be used in routine cleaning to avoid the risk of cross contamination.

REFERENCES

1. Agalloco JP, Brame W, Ferenc B, Hall WE, Jenkins K, LaMagna JT, Madsen RE, Mullen MV, Wagenknecht D, Wagner CM. Points to consider for cleaning validation: PDA Technical Report No. 29. PDA J Pharm Sci Tech, 1998; 52, November – December Supplement: pp. 7-53.

2.Human Drugs CGMP Notes In: A Memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals, 1997; volume 5, Number 3..

3.Equipment Cleaning and Maintenance, Department of Health and Human Services, CFR 21, Part 211, Subpart 211.67.
4."Guide to Inspection of Validation of Cleaning Procedures", US FDA, 1993.
5."Guide to Inspection of Bulk Pharmaceutical Chemicals", US FDA 1994.
6.Harpaz D, Berry IR. Validation of Bulk Pharmaceutical Chemicals, Interpharm press Inc., Illinois, 1997.
7.LeBlanc DA. Pharm Tech, 1998; 22(5): 66 – 74.
8.LeBlanc DA. Pharm Tech, 1996; 20(1):84-92.
9.Chudzik GM. J Val Tech, 1998; 5(1): 77-81.
10.Forsyth RJ, Haynes DV. Pharm Tech, 1998; 22(9): 104-112.
11.Thomas JA. J. Val Tech, 2000; 6(2): 522-530.
12.Hall WE, J Val Tech, 1997; 4(1).
13.Fourman GL, Mullen MV. Pharm Tech, 1998; 17(4):54-60.
14.LeBlanc DA. Pharm Tech, 1998; 19(5):136-148.
15.Agalloco JP. Points to consider in the validation of equipments cleaning procedure, J Parenter Sci Technol, 1992; 46(5).
16.Baffi R, Dolch G, Garnick R, Huang YF, Mar B, Matsuhiro D, Niepelt B, Parra C, Stephan M. J Parenter Sci Technol, 1991; 45(1), 13-19.

Corresponding Author:
Anurag Chaudhary
Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut Bypass Road, Meerut -250005, U.P., India.
Phn no:- +91-9917062681
E.mail: anurag15182@rediffmail.com