

Process validation of sertraline film coated table

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Abstract

The main Purpose of this study is to generate the sufficient data to establish the documentary evidence to confirm that the above Dosage form can be manufactured on commercial scale meeting all its quality attributes in a consistent manner. The study includes the validation of critical steps of manufacturing such as blending, compression and blister packing all process validation batches had been manufactured and validated in full compliance with cGMP requirement Based on the results of the validation data, it shall be concluded that the manufacturing process as it consistently produces the product of predetermined quality parameters. Hence it can be concluded that the manufacturing process of Sertraline hydrochloride 50 mg tablet was validated and was approved for routine production.

Keywords: sertraline hydrochloride, cGMP, validation, film coated table

1. Introduction

This guidance outlines the general principles and approaches those FDA Considers appropriate elements of process validation for the manufacturing of human and animal drug and biological product, including active pharmaceutical ingredients (API), collectively referred to in this guidance as drugs or product. The guidance incorporate principles and approaches that all manufacturers can use to validate manufacturing process^[1].

The lifecycle concept links product and process development, qualification of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production. The guidance supports process Improvement and innovation through sound science^[1].

This guidance covers the following categories of drugs:

Human drug

- Veterinary drug
- Biological and biotechnology product
- Finished products and active pharmaceutical ingredient (APIs or drug substance)
- The drug constituent of a combination (drug and medical device) product.

The guidance does not cover the following types of products:

- Type A medicated articles and medicated feed
- Medical device
- Dietary supplement
- Human tissues intended for transplantation regulated under section 361 of the Public Health Service act^[1].

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceuticals (drug) manufacturing required that drug products be produced with high degree of assurance of meeting all the attributes they are intended to process^[2].

Validation is act of demonstrating and documenting that any procedure, process, and activity will consistently lead to the

expected results. It includes the qualification of systems and equipment. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of the system whilst in production^[3].



Fig 1: Process Validation Flow

Elements of Validation

Qualification is pre-requisite of validation. The qualification includes the following:

1. **Design Qualification (DQ):** In this qualification, compliance of design with GMP should be demonstrated.
2. **Installation Qualification (IQ):** Installation qualifications should be carried out on new or modified facilities, systems and equipments. Sources of spares and maintenance
3. **Operational Qualification (OQ):** Operational qualification should to Tests developed from the knowledge of the processes systems and equipment
4. **Performance Qualification (PQ):** After IQ and OQ have been completed; the next qualification that should be completed is PQ. PQ should include tests using production materials, substitutes or simulated product^[4].

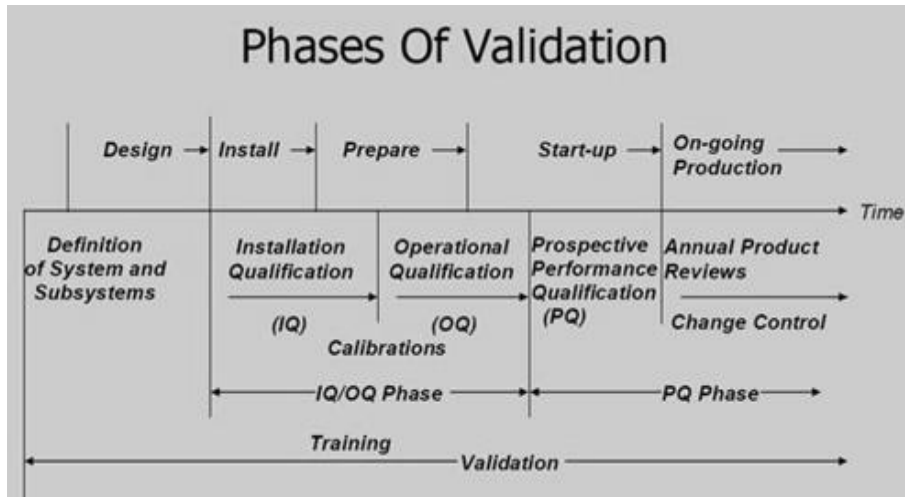


Fig 2: Phase of Validation

Types of validation

There are two type of Validation are as following:

- Analytical validation:** Validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose.
- Process Validation:** documented evidence that provides a high degree of assurance that a specific will consistently produce a product meeting its predetermined specifications and quality characteristics [5].

same as for the initial validation of the process [6].

1.1 Process Validation and Drug Quality

Effective process validation contributes significantly to assuring drug quality. The basic principles of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following condition exists:

Approaches to Process Validations

- Process Design
- Process Qualification
- Continued Process Verification
- Drug Delivery [7]

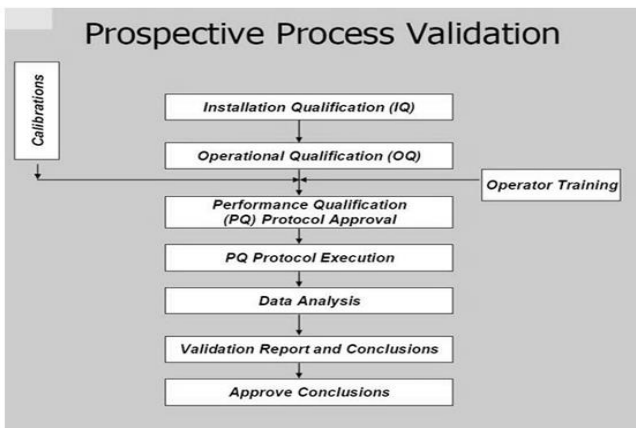


Fig 3: Prospective Process Validation

Concurrent Validation: It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.

Retrospective Validation: It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information.

Revalidation: Documentation requirements will be the

2. Research Envizaged

To conducting the process that summarization of the manufacturing process for product Sertraline Tablets manufactured, at the oral solid dosage form facility.

The main Purpose of this study is to generate the sufficient data to establish the documentary evidence to confirm that the above Dosage form can be manufactured on commercial scale meeting all its quality attributes in a consistent manner.

Manufacturing process is summarized to assure that the quality of product, which is derived from a number of factors including selection of input material, quality parameter, and process designs, control of the critical process and in process and end product testing. Hence, this study may conclude whether Product can be manufactured in large scale or not by the analysis and compilation of the data.

3. Materials and Method

Following Drugs & materials are used in this method-

Table 1: List of Raw materials and their Functions

S. No.	Ingredients	Function
1.	Sertraline Hydrochloride	Active pharmaceutical ingredient
2.	Calcium hydrogen phosphate anhydrous	Diluents
3.	Microcrystalline-cellulose	Diluents
4.	Hydroxypropyl cellulose	Binder
5.	Sodium starch- Glycolate	Disintegrate

7.	Magnesium stearate	Lubricant
8.	Purified Water	Solvent
9.	HPMC	Coating agent, film-former
10.	Titanium dioxide	Opacifier, pigment
11.	Polyethylene glycol (Macrogol 400)	Plasticizer
12.	Tween 80	Nonionic surfactant and emulsifier

Table 2: List of Equipments and their Uses

S. No	Equipment name	Used for
1.	Vibro sifter (20 #, 40 #, 60 #, 80 #, 100 # sieves)	Sifting of raw materials
2.	Rapid mixer Granulator	Dry mixing and granulation
3.	Fluid bed Dryer	Drying
4.	Comminuting Mill	Milling
5.	Octagonal blender	Blending
6.	PIAB Vacuum Conveying system	Conveyer
7.	Pneumatic stirrer	Stirring
8.	Tablet Compression Machine	Compression

Table 3: Process stages, control variables and measuring response / justifications

Stage	Step	Control Variables	Measuring Response / Justifications
Granulation	Dry mixing	Time	Uniform distribution of active ingredients with excipients
	Wet mixing	Mixer speed	Proper mixer speed to ensure that mixing and binding is completed in optimal mixing time.
		Mixing time	Granular composition and characteristic of the granules is affected by over mixing / under mixing
	Drying	Inlet and outlet temperature	Drying of the granules.
		Drying time	Compression problems by over or under drying of the granules. LOD of dried granules.
	Lubrication	Mixing time	Blend uniformity and trouble free compression may be achieved by controlling mixing time and speed of blender.
		Speed of blender	Uniformity of blend at lubrication stage.
Sequence of addition of lubricants		Yield of lubricated granules.	
Compression	compression	Compression force and optimal speed of tablet press	Appearance, uniformity of weight, diameter, thickness, hardness, disintegration test, dissolution rate, assays.
Coating	Coating solution preparation	Homogeneity of coating solution	Surface smoothness and shade uniformity is affected by variation in particle size of insoluble colorant.
		Air pressure	Drop of air pressure causes dripping of coating solution hence cause sticking of tablets.
	Spraying of coating solution	RPM of peristaltic pump	Uneven coating, spray rate may be caused by variation in peristaltic pump, RPM.
		Continuous spray of the coating solution for the set time	Appearance, average weight, weight gain and uniformity of weight of coated tablets, yield.

4. Experimental Work

4.1 Evaluation of Tablet

4.1.1 Wet mixing

Purified water was added into Rapid Mixer granulator through paste window with slow speed impeller and mixed for 2-3 minutes with slow speed impeller, mixing was stopped and mixing was continued with chopper and impeller on at slow speed till granulation point was achieved.

Time of mixing: 2-4 minutes

Agitator speed: Slow speed

4.1.2 Drying

The drying step involves drying of wet mass, dry the wet mass in fluid bed dryer the level of moisture in the granules is important factor.

Analysis: Loss on drying

Acceptance criteria: NMT 2.0% m/m at 70°C

4.1.3 Milling

Sizing of granule is to be obtained by sifting of granules from specified sieve and retention of granules on sieves is to

be milled by using Comminuting Mill, Speed of the Comminuting Midland Forward direction of knives is to be monitored and sample to be withdrawn at the end of the sizing operation for the monitoring of particle size distribution, bulk density and Loss on drying as a part of validation.

Particle size distribution: Tare each test sieve to the nearest 0.1g. Place an accurately weighed quantity of material on the top (coarsest) sieve and replace the lid.

A) Bulk Density: $P_b = M/V_b$

B) Tapped Density: $P_t = M/V_t$

C) Carr's Index: $C = (p_t - p_b) / p_t \times 100$

D) Loss on drying: the drying temperature is indicated by a single value rather than a range, drying is carried out at the prescribed temperature $\pm 2^\circ\text{C}$.

Acceptance criteria

Loss on drying: NMT 2.0% m/m at 70°C

4.1.4 Blending/Lubrication

This step involves mixing of Microcrystalline Cellulose (NF) with drug granules & other blending material. Sifted lubricants shall transfer to Octagonal blender containing

dried granules of Sertraline and mix for 5 minutes at slow speed. Sifted Microcrystalline Cellulose shall transfer to octagonal blender and Mix for 3 minutes at slow speed.

Parameter:

Blending time: 15 minutes

Blending speed: 6 rpm

Analysis: Blend uniformity, particle size distribution, Bulk density, Loss on drying.

Acceptance criteria: A. **Loss on Drying:** NMT 2.0 % at 70

B. Blend uniformity

Weight the sample bottle; transfer the contents of the bottle into Volumetric flask. Add diluents (Mixture of water and acetonitrile) to the sample bottle, shake the bottle for 10 minutes by using mechanical shaker, Diluted the volume with diluents, Mix well and centrifuge. Filtrated the Solution through 0.45 μm PVDF membrane. Placed the empty sample bottle in an oven at 105°C to dry. Cool to room temperature. Reweigh the bottle to obtain tare weight and determine the weight of sample taken (in mg).

Acceptance criteria: 90.0-110% (mean of test results)

4.1.5 Compression

This step involves consistent flow of an adequately Lubricated uniform blend into dies where the granules are being compressed into tablets.

a) **Appearance:**

b) **Thickness, Length and Width:**

c) **Hardness:**

d) **Average Weight:**

$$\text{Average weight (mg)} = \frac{\text{Weight of 20 tablets (g)}}{20} \times 1000$$

e) **Weight variation**

Acceptance criteria

L1 is 15.0 and L2 is 25.0.

X1, x2... xn= individual estimated contents of the dosage units tested; Where

$$x_i = \frac{w_i X}{W}$$

f) **Capability Index**

The capability indices to be calculated for weight sample using following formula:

$$C_p = (USL - LSL)/6s$$

$$C_{pU} = (USL - X)/3s$$

$$C_{pL} = (X - LSL)/3s$$

$$C_{pK} = \min(C_{pU}, C_{pL})$$

(Smallest of the values for CpU and CpL i.e. Capability Index)

g) **Friability:** % F = {1-(Wt/W)} \times 100

h) **In vitro disintegration time**

i) **In Vitro Dissolution Studies**

j) **Uniformity of weight (mass)**

Acceptance criteria

Assay: 95.0 -105.0 %

4.1.6 Coating

Load the Tablets into coating pan. jog the pan intermittently for 3-4 times to remove any adhering power and pre-warm the tablets at an inlet temperature of 55°C -70°C till the outlet temperature reaches 47°C-50°C, set the process parameter (as shown in table) start spraying of coating suspension into tablet bed. Continue the process until the weight gain of 3% m/m (Range: 3 \pm 1 % m/m) with respect to average weight of pre-warmed core tablets is achieved. Dry the tablets with intermittent jogging for 10 minutes at an outlet temperature of 40°C -50°C, once the build-up is achieved.

Parameter	Desired
Inlet temperature	50°C-70°C
Outlet temperature	40°C-50°C
Pan speed	2 – 6 rpm
Spray Rate	20 – 60g/min/gun
Gud to tablet bed distance	20 – 28 cm
Atomization pressure	3 – 5kg/cm ²

4.1.7 Blister packing

Blister packing is to be done as per batch packing record and involves packing of tablets in Clear thermo formable rigid PVC film and Printed Aluminium foil.

Validated parameters

Sealing Roller : 200 \pm 10°C

Forming Temperature : 160 \pm 10°C

Machine Speed : 60 \pm 20 cuts/minute

5. Result & discussion

The quality system regulation defines process validation by establishing objective evidence that a process consistently produces a result or product meeting its predetermined specifications. The goal of quality system is to consistently produce products that are suitable for their intended use.

In tablet dosage form, the critical parameters are:

- Dry Mixing
- Drying
- Milling
- Blending/Lubrication
- Compression
- Blister Packing

The dry-mixing step involves mixing of Sertraline with other additives using Rapid mixer granulator. The mixing of the active ingredient depends on the mixing time. The drying step involves drying of wet mass. Moisture in granules is important factor. The inlet temperature of the FBD is controlled during the drying process and the outlet temperature is monitored and correlated with the corresponding LOD of the granules under drying. Dried granules were than sifted and milled on Camilla the end of milling Results obtained were found well within the limit and recorded. The RSD values meet the acceptance criteria. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous. Hence the blending time of 3 minutes after addition of magnesium stearate as validated. The final stage of compression for all the three batches has been validated

parameters of the tablets, were well within the acceptable limits. This process involves packing of tablets in clear thermoform able rigid PVC film and printed aluminium foil. Temperature of blister sealing rollers, forming rollers and speed of machine are critical variables.

A. Pre-formulation study

1. Melting point: Reported melting point of Sertraline hydrochloride is 244 - 245° C.

2. Calibration Curve:

The absorbance of the solutions were measured at 273 nm against 50% v/v aqueous methanol used as blank and the results observed are as follows:

Table 4: Results of Calibration Curve

Concentration	Absorbance
2	0.02
4	0.045
6	0.072
8	0.11
10	0.15
12	0.18
14	0.21
16	0.25
18	0.3
20	0.35

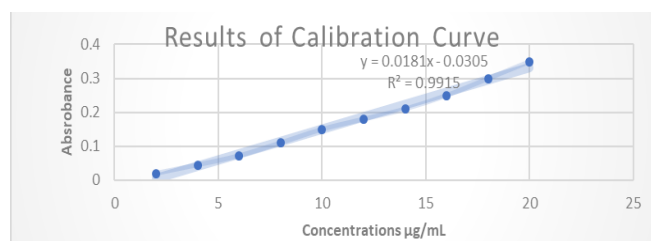


Fig 1: Graphical Representation of Calibration Curve

B. Evaluation of tablet

5.1. Bulk Density

Table 5: Results of Bulk Density

Batch	Untapped bulk density (g/mL)
I	0.58
II	0.59
III	0.59
Acceptance Criteria	(0.50-0.70g/ml)

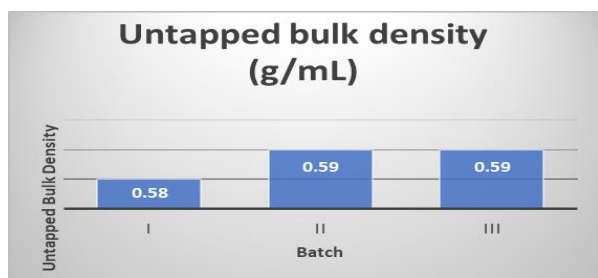


Fig 2: Graphical Representation of Untapped bulk density

5.2. Tapped Density

Tapped density was determined and result observed as:

Table 6: Results of Tapped Density

Batch	Tapped bulk density (g/mL)
I	0.83
II	0.83
III	0.84
Acceptance Criteria	(0.80-0.90g/ml)

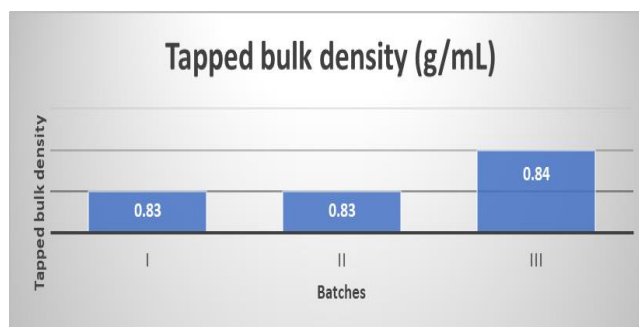


Fig 3: Graphical Representation of tapped bulk density

5.3. Loss on drying

Table 7: Results of Loss on drying

Batch	LOD (% w/w)
I	1.79 %
II	1.58%
III	1.75%
Acceptance Criteria	(NMT 3.0%)



Fig 4: Graphical Representation of Loss on drying

5.4. Particle size distribution

Table 8: Results of Particle size distribution

Sieve Size	Acceptance Criteria	% w/w Retention		
		Batch I	Batch II	Batch III
20%	For information only	1.2% w/w	1.6% w/w	1.6% w/w
40%		13.0% w/w	27.2% w/w	27.0% w/w
60%		38.5% w/w	52.8% w/w	52.8% w/w
80%		50.0% w/w	64.3% w/w	63.6% w/w
100%		54.3% w/w	68.7% w/w	67.8% w/w
120%		60.0% w/w	74.4% w/w	73.8% w/w
% in pan		40.0% w/w	25.6% w/w	26.2% w/w

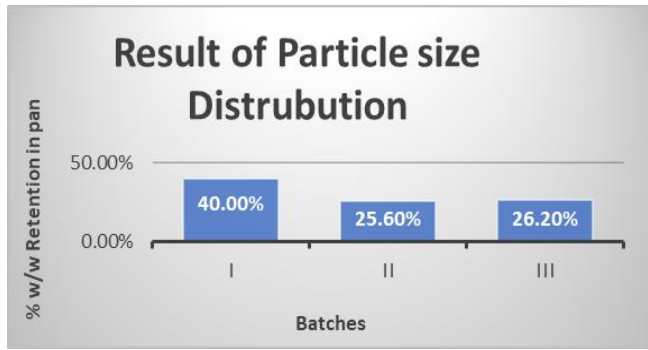


Fig 5: Graphical Representation of Particle Size Distribution

5.5. Blend Uniformity

Blend Uniformity was determined and result observed as

Table 9: Results of Blend Uniformity

Batch	Avg. of Blend Uniformity
I	99.5 %
II	98.3 %
III	99.4 %
Acceptance Criteria	90.0 - 110.0%

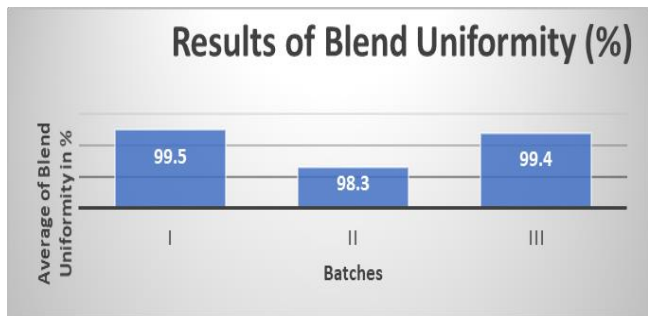


Fig 6: Graphical Representation of Blend Uniformity

5.6. Hardness

Hardness of in process tablet is as follows:

Table 10: Results of Hardness

Batch	Minimum	Maximum
Batch I	8.2 Kp	10.3 Kp
Batch II	8.0 Kp	11.1 Kp
Batch III	9.2 Kp	11.0 Kp
Acceptance Criteria	70 N – 160 N (7 Kp – 16 Kp)	



Fig 7: Graphical Representation of Hardness

5.7. Friability

Friability of in process tablet is as follows

Table 11: Results of Friability

S. No	Friability (%w/w)
Batch I	0.06% w/w
Batch II	0.05% w/w
Batch III	0.06% w/w
Acceptance Criteria	Not more than 1.0% w/w



Fig 8: Graphical Representation of Friability

5.8. Assay: Observed results of assay are as follow:

Table 12: Results of Assay

Batch	Assay (% w/w)
I	99.0 %
II	99.0%
III	98.5%
Acceptance Criteria	95.0 – 105.0 % of stated amount

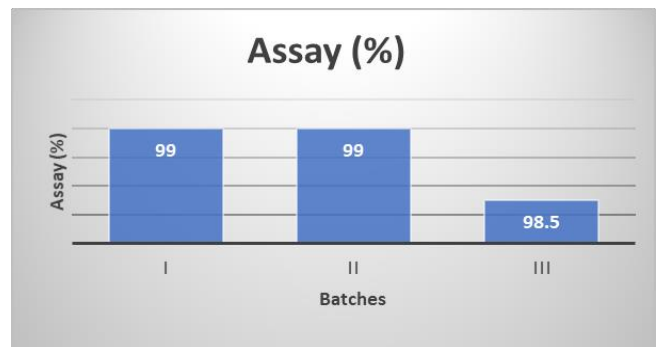


Fig 9: Graphical Representation of Assay

5.9. Weight variation

Table 13: Results of Weight variation

No of tablets	Observation			Acceptance criteria
	Batch I	Batch II	Batch III	
Tablet -1	99.6	100.0	99.2	The AV value should be not more than 15.0 (90.0-110.0%)
Tablet -2	99.0	98.8	99.3	
Tablet -3	99.1	99.4	100.2	
Tablet -4	100.2	98.8	98.7	
Tablet -5	100.2	100.1	100.2	
Tablet -6	98.7	99.0	99.7	
Tablet -7	100.2	99.2	98.7	
Tablet -8	99.5	98.8	99.2	
Tablet -9	98.9	100.1	98.9	
Tablet -10	100.1	99.6	100.1	
Min	98.7	98.8	98.7	
Max	100.2	100.1	100.2	
AVG	99.5	98.3	99.4	



Fig 10: Graphical Representation of Weight Variation

5.10. *In vitro*-disintegration

Table 14: Results of *In vitro*-disintegration

Batches	Disintegration Time
I	6 min 10 sec
II	5 min 43 sec
III	07 min 10 sec
Acceptance Criteria	Not more than 15 minutes

5.11. *In vitro*-dissolution

Dissolution of different batches observed for different time interval. And after 45 minutes following results observed:

Table 15: Results of Dissolution

Dissolution at 45 min		
Batches	Min	Max
I	91	99
II	88	99
III	92	100
Acceptance Criteria	Not Less than 85% (Q=80%)	



Fig 12: Graphical Representation of Dissolution

6. Summary and Conclusion

From the various data generated from the three consecutive batches it can be concluded that the manufacturing process of Sertraline hydrochloride 50 mg tablet was capable of producing the products meeting its predetermined specifications and quality attributes. The study includes the validation of critical steps of manufacturing such as blending, compression and blister packing all process validation batches had been manufactured and validated in full compliance with cGMP requirement Based on the results of the validation data, it shall be concluded that the manufacturing process as it consistently produces the product of predetermined quality parameters. Hence it can be concluded that the manufacturing process of Sertraline hydrochloride 50 mg tablet was validated and was approved

for routine production.

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