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PROCESS VALIDATION OF THE RABEPRAZOLE SODIUM 20 MG INJECTION

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ABSTRACT

The purpose of this study was to evaluate the relationship among numerous variables to enhance the understanding of the effects of materials and process parameters on drug product quality and to develop a validated method for manufacturing of RABEPRAZOLE SODIUM 20 MG INJ.). Rabeprazole is used to treat the symptoms of gastroesophageal reflux disease (GERD), a condition in which backward flow of acid from the stomach causes heartburn and possible injury of the esophagus (the tube that connects the throat and stomach) in adults and children 12 year of age and older.

Key Words: Process Validation, Rabeprozole, GI Reflux, Adult.

1. Introduction:

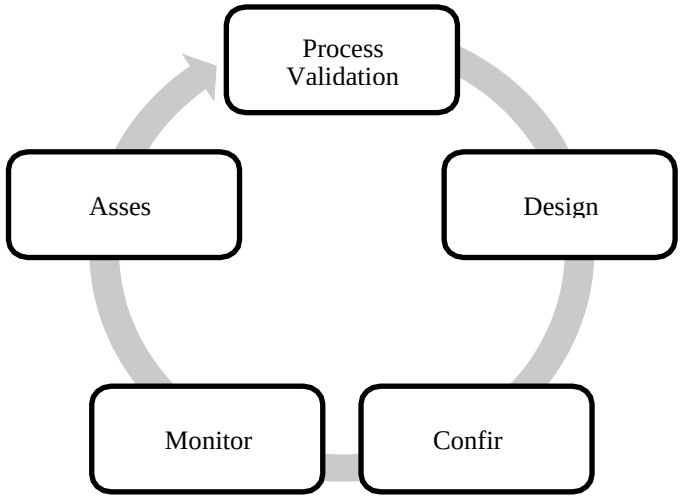
Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics.

1.1 Steps in validating a Process:

- Development Sequence
- Development stage Pilotscale-upphase
- Product design
- Product characterization

- Product selection
- Process design
- Product optimization
- Process characterization
- Process optimization
- Process demonstration
- Process validation program
- Product/process certification

1.2 Life Cycle of Validation:



1.3 Importance of Process validation-

Process validation provides high degree of assurance of quality of product by reducing the quality differences in batches by providing significant processparameters and controls. It helps to find out faults in manufacturing process and toavoid these faults in future. It minimal the chances of batch failures and reduces the wastage of material and increase the productivity.

1.4 Stages of process validation –

- **Process Design**–The commercial manufacturing process is **defined**.
- **Process Qualification**–The design is **evaluated** to determine whether the processes meet demands of reproducibility.
- **Continued Process Verification** – Ongoing assurances that all processes remain in a state of control.

1.5 GMP requirements for Process Design

- Design of Facility
- Design of Equipment
- Design of Production and Control Procedures
- Design of Laboratory Controls
- Propose process steps (unit operations) and process variables (operating parameters) that need to be studied.
- Identify sources of variability each unit operation is likely to encounter.

- Consider possible range of variability for each input into the operation.
- Evaluate process steps and variables for potential criticality.
- Select process steps and variables for test in representative models.
- Development studies to identify critical operation parameters and operating ranges
- Designed experiments
- Lab scale, pilot scale and/or full-scale experimental batches to gain process understanding
- Establish mechanisms to limit or control variability based on experimental data
- Aim for a "robust process", i.e., one that can tolerate input variability and still produce consistent acceptable output

1.6 Types of Validation

- Prospective validation
- Concurrent Validation
- Retrospective Validation
- Revalidation

Prospective validation: The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or the or etical considerations to determine the critical parameters that may affect the quality of thefinished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol [Sumeet et al, 2013].s

Concurrent validation: It is a process where current production batches are used to monitor processing parameters. It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch. Concurrent Validation means establishing documented evidence a process does what it is supposed to base on data generated during actual implementation of the process. Concurrent validation may be the practical approach under certain circumstances. It is important in these cases when the systems and equipment to be used have been fully validated previously [Sumeet et al,2013].

Retrospective validation: Conducted fir a product already being marked, and is basedon extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which is now to be validated to confirm to the requirements of division 2, Part C of the Regulation to be Food and Drugs Act. Retrospective Validation is only acceptable for well-established detailed processes and will be Inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility [Sumeetet al,2013].

Revalidation: Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the

process. Re-validation becomes necessary in certain situations [Sumeetet al, 2013].

2. Material and Method:

Material used: Rabeprazole sodium

2.1 Product Details:

Product Name: Rabeprazole Sodium 20 mg Inj (Lyophilized)

S. No.	Equipment Details
1.	Weighing Balances
2.	SS Manufacturing vessel with stirrer for solution preparation.
3.	Sterile filling tank/ Holding tank
4.	Membrane filtration assembly
5.	Autoclave
6.	Vials washing machine
7.	Sterilizing and Depyrogenation tunnel
8.	Vial filling machine
9.	Vial sealing machine
10.	pH meter
11.	Lyophilizer
12.	SS Pressure vessel
13.	Silicon tubing

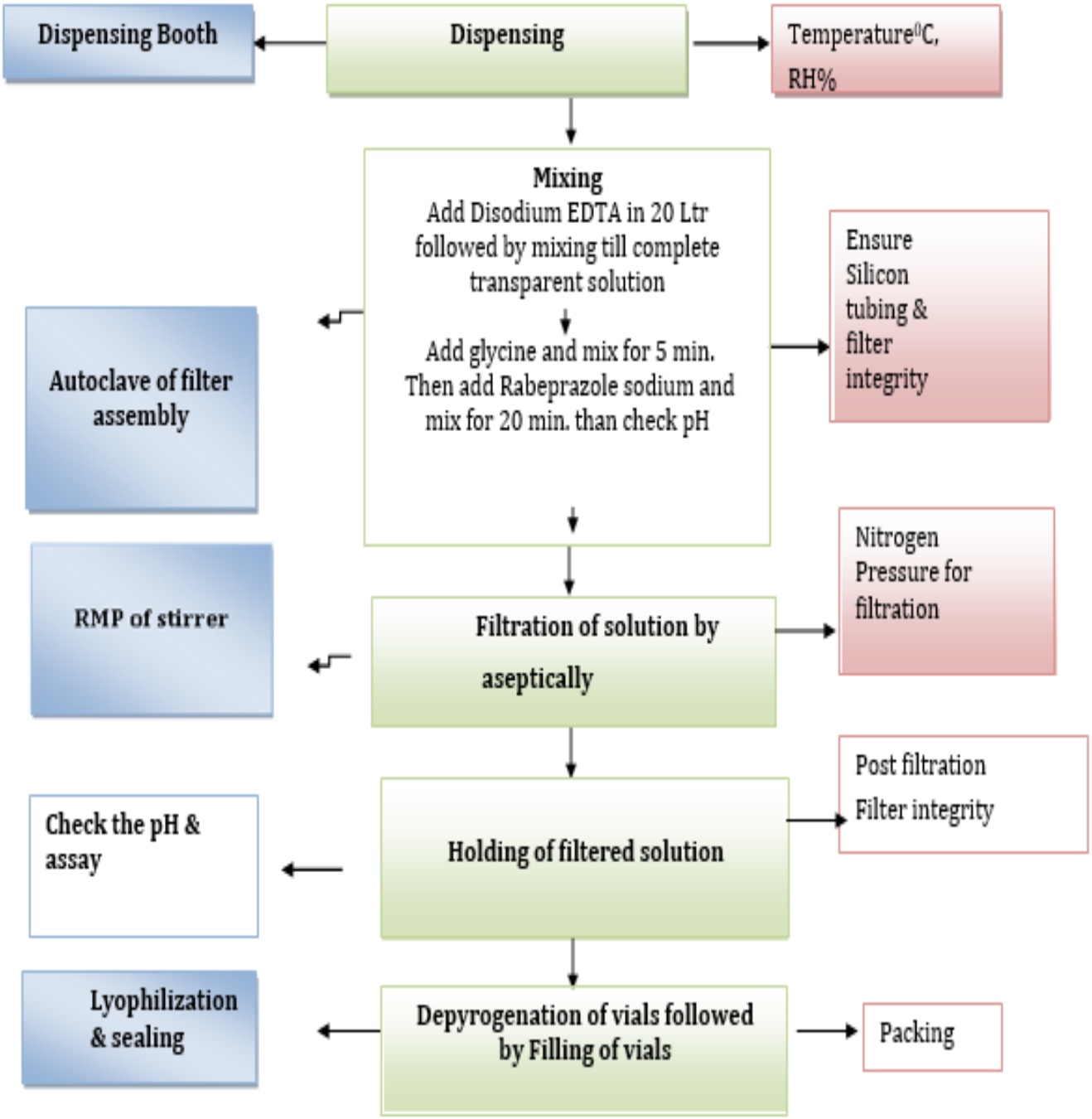
2.2 Method:

Three consecutive batches for process validation of the product Rabeprazole Sodium 20 mg Inj (Lyophilized) shall be manufactured as per approved master batch manufacturing record and shall be tested as preapproved standard testing procedure to demonstrate compliance with the approved specifications.

Three validation batches were manufactured and packed and details as:

Sr. No.	Generic Name	Batch No.	Batch Size
1.	Rabeprazole Sodium 20 mg Inj (Lyophilized)	A23	25000 Vials
2.	Rabeprazole Sodium 20 mg Inj (Lyophilized)	B23	25000 Vials
3.	Rabeprazole Sodium 20 mg Inj (Lyophilized)	C23	25000 Vials

2.3 Manufacturing Details:



2.4 Process Risk on the product Critical Quality Attributes:

Drug Product CQA	Dispensing	Mixing	Filtration	Feeling	Lyophilization	Sealing
Assay	Low	Low	Low	Low	Low	Low
Blend / Content Uniformity	Low	Low	Low	Low	Medium	Low
Related Substances	Low	Low	Low	Low	Low	Low

2.5 Manufacturing process evaluation

Stage	Critical process parameter	Acceptance Criteria	B. No.: A23	B. No.: B23	B. No.: C23	RECOMMENDATION
Vial washing	Ultrasonic vibrations	0.01 -0.9(KW)	Min.: 0.47 (KW) Max.: 0.47 (KW)	Min.: 0.47 (KW) Max.: 0.47 (KW)	Min.: 0.43 (KW) Max.: 0.43 (KW)	0.01 -0.9(KW)
	Compressed Air Filtered with 0.2µm	0.2 - 0.4 (mPa)	Min.: 0.32(KW) Max.: 0.37 (KW)	Min.: 0.30(KW) Max.: 0.33 (KW)	Min.: 0.31(KW) Max.: 0.33 (KW)	0.2 - 0.40 (MPa)
	Recirculation Water for injection Filtered with 3µm	0.05 -0.40 (mPa)	Min.: 0.33 (KW) Max.: 0.36 (KW)	Min.: 0.14 (KW) Max.: 0.23 (KW)	Min.: 0.28 (KW) Max.: 0.30 (KW)	0.05 - 0.40 (MPa)
	Recycled Water for Injection Pre. Filtered with 0.45µm	0.05 -0.40 (mPa)	Min.: 0.33 (KW) Max.: 0.35 (KW)	Min.: 0.31 (KW) Max.: 0.34 (KW)	Min.: 0.32 (KW) Max.: 0.34 (KW)	0.05 - 0.40 (MPa)
	Water For injection Pressure filtered with 0.22 µm	0.02-0.4 (MPa)	Min.: 0.14 (KW) Max.: 0.21 (KW)	Min.: 0.14 (KW) Max.: 0.15 (KW)	Min.: 0.12 (KW) Max.: 0.16 (KW)	0.02 - 0.40 (MPa)
	Washing Quality Check	No particulate matter shall be observed in front of white/ black portion of visual board.	No particulate matter observed in front of white/ black portion of visual board.	No particulate matter observed in front of white/ black portion of visual board.	No particulate matter observed in front of white/ black portion of visual board.	No particulate matter shall be observed in front of white/ black portion of visual board.

2.6 EQUIPMENTS USED:

Sr. No.	Equipment Name	Equipment ID		
		B. No.: A23	**B. No.: B23**	**B. No.: C23**
1.	Thermometer	T01	T01	T01
2.	Weighing Balances	T02	T02	T02
3.	SS Manufacturing vessel with stirrer for solution preparation.	V01	V01	V01
4.	Sterile filling tank / Holding tank	V02	V02	V02
5.	Membrane filter	M01	M01	M01
6.	Membrane filtration assembly	M02	M02	M02
7.	Vials washing machine	V02	V02	V02
8.	Rubber stopper washing machine	P01	P01	P01
9.	Autoclave /DHS/De-Pyrogenating Tunnel	A02	A02	A02
10.	Vial filling Machine	F01	F01	F01
11.	Vial cap sealing	S01	S01	S01
12.	SS Pressure vessel	P02	P02	P02
13.	pH meter	I001	I001	I001
14.	Lyophilizer	L01	L01	L01
15.	Silicon tubing	--	--	--
16.	Hygrometer	---	---	---

2.7 BATCH SIZE: 40 L / 25000 vials

2.8 TESTS/PROCESS PERFORMED:

Stage	**Test/ Process Performed**
Bulk solution preparation	►Preparation of bulk solution as per BMR
	►A sample to be drawn after bulk sample preparation is over. ►Withdraw composite sample from the tank and collect in glass container. ►Send the sample to QC for analysis along with test data slip.
Bulk solution filtration	Filtrations of bulk solution through sterile 2+0.2 µ membrane filter as per the procedure mentioned in BMR
	►A sample to be drawn after filtration is over. ►Withdraw composite sample from the tank and collect in glass container. ►Send the sample to QC for analysis along with test data slip.
Filling & half stoppering of vials	Filling of sterile solution in vials and then half stoppering as per procedure mentioned in BMR ►Record filling & stoppering parameter observation in BMR.
	Withdraw the samples during (initial, middle & end) filling & half stoppering of vials. ►Send the samples to QC for analysis along with test data slip**.**
Lyophilization & Sealing	►Lyophilization & sealing of filled vials as per BMR
	►Withdraw the samples after lyophilization and sealing Send the samples to QC for analysis as per FP Specification along with test data slip**.**

2.9 OBSERVATION & RECOMMENDATION WITH ACCEPTANCE CRITERIA:

STAGE: WASHING AND STERILIZATION VIALS										
	Pressure (kg/ sq.cm)				Clarity of vials	Pressure diff. in tunnel (mm of water)			Sterilization zone Temp. ≥ 300°C	Conv. Speed NMT 110 mm/min
	Recirculated water (1-2 kg/ cm^2)	P.W. (1-2 kg/cm^2)	WFI (1-2 kg/ cm^2)	Comp. Air (1.5-2.5 kg/cm^2)		Drying zone (10-20)	Sterilization zone (35-45)	Cooling zone (10-20)		
B. No. : A23										
Min	1.2	1.2	1.2	2.2	OK	14	41	14	315°C	160 mm
Max	1.3	1.3	1.3	2.3	OK	15	42	15	328°C	160 mm
Avg	1.25	1.25	1.25	2.25	OK	14.5	41.5	14.5	321.5°C	160 mm
B. No.: B23										
Min	1.4	1.4	1.5	2.3	OK	16	42	16	320	110 mm
Max	1.4	1.4	1.5	2.3	OK	16	42	16	325	110 mm
Avg	1.4	1.4	1.5	2.3	OK	16	42	16	322.5	110 mm
B. No.: C23										
Min	1.5	1.4	1.5	2.3	OK	14	42	16	323	150 mm
Max	1.5	1.4	1.5	2.3	OK	14	42	16	327	150 mm
Avg	1.5	1.4	1.5	2.3	OK	14	42	16	325	150

										mm
Recommendation	---	---	---		---	---	---	---	---	NMT 160 mm/min

2.10 OBSERVATION & RECOMMENDATION WITH ACCEPTANCE CRITERIA:

STAGE	**PARAMETER**	**ACCEPTANCE CFRITERIA**	**B. No.: A23**	**B. No.: B23**	**B. No.: C23**
Rubber Plugs	Clarity of wash water	Should be clear	Complies	Complies	Complies
Rubber Plugs	Temperature	121 °C	121.4 °C	121.4 °C	121.4 °C
	Time	30 Mins.	30 Mins.	30 Mins.	30 Mins.
Filling m/c parts, N_2 filter and tubing.	Temperature Pressure Time	121°C 15 psi for 30 min	121.4°C 15 psi for 30 min	121.4°C 15 psi for 30 min	121.4°C 15 psi for 30 min
Uniforms, hand gloves and face masks					
Membrane filter assembly					
SS filling vessel and lyophilizer trays					
Aluminium seals	Temperature	121 °C	121.4°C	121.4°C	121.4°C
	Pressure	15 psi	15 psi	15 psi	15 psi
	Time	for 30 min	for 30 min	for 30 min	for 30 min
Drying of Rubber plugs	Vacuum drying	-500 mbar	-500 mbar	-500 mbar	-500 mbar
	Time	5 Mins.	5 Mins.	5 Mins.	5 Mins.

2.11 OBSERVATION & RECOMMENDATION WITH ACCEPTANCE CRITERIA:

STAGE	**PARAMETER**	**ACCEPTANCE CFRITERIA**	**B. No.: A23**	**B. No.: B23**	**B. No.: C23**
Take about 30 L of WFI IP (20°C – 30°C, pH 4.0 – 7.0) in the mfg. vessel	Qty of WFI	30 L	30 L	30 L	30 L
	pH	4.0 – 7.0	6.00	6.00	6.0

	Temperature	20°C – 30°C	26°C	20°C	20°C
Add Disodium EDTA	Stirring Time	For Record	10 min.	30 min.	30 min.
	RPM	To be established	50 RPM	50 RPM	50 RPM
Add Glycine Make up volume to 40 L with WFI IP (20°C – 30°C)	Volume	40 L	40 L	40 L	40 L
	Stirring Time	For Record	15 min.	5 min.	5 min.
	RPM	To be established	50 RPM	50 RPM	50 RPM
	pH	For Record	6.00	6.00	6.0
	Description	Clear colourless to light yellow coloured solution free from any foreign particles.	Complies	Complies	Complies
Pass about 3.0 Ltrs Water for Injection IP through the filtration membrane (2µ+0.2µ	Integrity of Filter	Should be OK	OK	OK	OK
If membrane integrity is OK then start **filtration of BULK** solutions at 1.8 bar Nitrogen Pressure. Discard initial few ml of filtered solution and collect the sterile solution in Sterile Filling Vessel.	Filtration Time	For Record	70 Mins.	50 Mins.	75 Mins.
After completion of filtration process check the integrity of the filter as per SOP.	Integrity of Filter	Should be OK	OK	OK	OK
	pH	10 – 12	11.20	11.50	11.45
	Description	Clear colourless to light yellow coloured solution free from any foreign particles.	Complies	Complies	Complies

2.12 OBSERVATION & RECOMMENDATION WITH ACCEPTANCE CRITERIA:

STAGE	PARAMETER	LIMIT		Batch Number		
				A23	B23	C23
FILLING & HALF STOPPERING OF VIALS	Description	Clear colorless to light yellow colored solution free from any foreign particles	Initial	Complies	Complies	Complies
			Middle	Complies	Complies	Complies
			End			
	% Yield	To be established		90.39 %	94.24 %	94.83 %
Vial sealing /Visual Inspection	Sealing Quality	Should be OK	Initial	OK	OK	OK
			Middle	OK	OK	OK
			End	OK	OK	OK
	% Yield	To be established		87.64 %	92.70 %	90.26%
Packing	% Batch Yield	To be established		87.64 %	92.70 %	90.26%

2.13 RESULT OF ANALYTICAL TEST PERFORMED WITH ACCEPTANCE CRITERIA:

STAGE	TEST	LIMIT	Batch Number		
			A23	B23	C23
Bulk before filtration	Description	Clear colourless to light yellow coloured solution free from any foreign particles.	Complies	Complies	Complies
	pH	Between 10.0 to 12	11.23	11.30	11.45
	Assay				
	Rabeprazole	90-110%	100.10	101.0 %	100.0%
	Bio burden	For record	Complies	Complies	Complies
Bulk	Description	Clear colourless to	Complies	Complies	Complies

after filtration		light yellow coloured solution free from any foreign particles.			
	pH	Between 10 to 12	11.45	11.30	11.50
	Bulk Sterility	Must be sterile	Sterile	Sterile	Sterile
	Assay				
	Nicorandil	90-110%	100.50	101.15 %	100.0%

2.14 DETAILS OF ANALYTICAL RESULTS AS PER FINISHED PRODUCT ANALYSIS:

TEST	**ACCEPTANCE LIMIT**	**BATCH NUMBER**		
		A23	**B23**	**C23**
Description	Off-white powder or cake in sealed glass vials.	Complies	Complies	Complies
Reconstituted solution i) Completeness and clarity of solution A) Test A	Solution should not be hazy	Complies	Complies	Complies
Reconstituted solution i) Completeness and clarity of solution B) Test B	Solution should be free from undissolved matter	Complies	Complies	Complies
Reconstituted solution ii) Particulate matter	Solution is clear and free from any Particulate matter	Complies	Complies	Complies
Identification - By HPLC	The retention time of Nicorandil peak in chromatogram of the Assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the Assay.	Complies	Complies	Complies
pH of reconstituted	10.0-12.0	11.50	11.45	11.23

solution				
Abnormal Toxicity	To comply the test	Complies	Complies	Complies
Test for Pyrogen	To comply the test	Complies	Complies	Complies
Sterility	To comply the test	Complies	Complies	Complies
Water	Not more than 2.0 %	1.1%	0.82 %	1.70 %
Uniformity of dosage units(By content uniformity)	It must conform to USP general chapter < 905 > criteria.	Between 98.25%-102.30%	Between 97.05%-99.75%	Between 99.35%-103.33%
Assay : Each lyophilized vial contains: Rabeprazole sodium ... 20 mg	Not less than 90.0 % and not more than 110.0 % of label claim	99.71%	100.05%	99.79%

3.0 DEVIATION/CHANGES (IF ANY):

No deviation or any types of changes were observed during manufacturing of **Rabeprazole Sodium Inj 20 mg B. No. . A23, B23 & C23**

4.0 STABILITY PLAN:

The three validation batches of **Rabeprazole Sodium Inj 20 mg B. No. . A23, B23 & C23** have been charged for stability as per storage conditions specified in the stability protocol

5.0 CONCLUSION:

Based on various studies performed and subsequent observations and results of these three batches, it is concluded that manufacturing process of **Rabeprazole sodium inj 20 mg consistently** produces product of its predetermined quality and recommended to carry out next batches.

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CONFLICT OF INTEREST: NIL

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