RISK ANALYSIS STUDY PROTOCOL FOR DISCONTINUATION OF RINSE & SWAB SAMPLING AFTER TYPE B CLEANING (ONLY FOR WATER SOLUBLE API's)

DATE OF RISK ANALYSIS	
SUPERSEDE PROTOCOL No.	**NIL**

PROTOCOL CONTENTS

FAILURE MODE EFFECT ANALYSIS FOR RISK ANALYSIS STUDY PROTOCOL FOR DISCONTINUATION OF RINSE & SWAB SAMPLING AFTER TYPE B CLEANING (ONLY FOR WATER SOLUBLE API's)

1.0 PROTOCOL APPROVAL:

INITIATED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (PRODUCTION)			
HEAD (QUALITY CONTROL)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

2.0 OBJECTIVE:

- To provide documented evidence that there is no risk in discontinuation of Rinse & Swab samples of water soluble API's (Tablets & Capsules).

3.0 SCOPE:

- This risk analysis study Protocol is applicable for performing risk analysis study for discontinuation of Rinse & Swab samples of water soluble API's (Tablets & Capsules).

4.0 RESPONSIBILITY:

Department	Responsibility
Quality Assurance	• Shall prepare & Review the Risk analysis Protocol. • Execution of the Risk analysis Protocol with Production and Quality

	Control. • Shall compile the data & Prepare Summary Report • Risk analysis Protocol shall be approved by the QA prior the execution. • Shall review the executed Protocol to check the compliance and corrective action for any discrepancies found. Also shall prepare the summary and conclusion of the Risk analysis Study.
Quality Control	• Reviewing of Risk analysis Protocol for Correctness, Completeness and Technical Excellence. • Post approval of Risk analysis Protocol after Execution.
Production	• Reviewing of Risk analysis Protocol for Correctness, Completeness and Technical Excellence. • To provide support for execution of Risk analysis Study as per Protocol. • Post approval of Risk analysis Protocol after execution.

5.0 REASON FOR RISK ANALYSIS:

To evaluate the risk in discontinuation of Rinse & Swab samples of water soluble API's (Tablets & Capsules).

6.0 SITE OF STUDY:

Manufacturing area (Granulation/Compression/Coating and Packing).

7.0 RISK COMMUNICATION & TRAINING:

- The Risk analysis team shall be authorized by Head-QA or his/her designee.
- Quality Risk Management Team shall be cross functional team comprised of expert from different areas such as QA, QC and Production.
- Training shall be imparted to the team members before execution of Protocol for proper understanding of the procedure. Training shall be recorded in Training attendance Record.

8.0 RISK IDENTIFICATION & EVALUATION:

- In G-block & F-Block cleaning validation is done on the basis of Dose Criteria.
- In tablet section Alprazolam is the worst case while in Hardgel Capsule section Domperidone is the worst case.
- Type B cleaning is done after every batch change over.

- Both API's are practically insoluble in water, hence cleaning agent Extran MA02 used for Type B cleaning.
- Extran MA02 is water soluble hence during type B cleaning all equipments are finally washed with Purified water.
- After cleaning rinse/swab were sent for residue scanning (no residue should observed).
- Any residue transferred in upcoming batches will leads to contamination. There is the more chance of contamination in water insoluble API's.
- For API worst case (Alprazolam for Tablets & Domperidone for Capsules) has been already validated upto the MACO level by HPLC and results observed below detection level.
- Cleaning agent (Extran MA02) has also been validated upto MACO level by UV method and results observed below detection level.
- Daily verification is done by rinse & swab method by UV scanning method after every batch change over. Till now no deviation observed since 3 years.
- As no deviation has been observed hence on the basis of previous trend, it has been decided that rinse and swab should be discontinued in phase wise manner, in phase I rinse & swab of only for water soluble API's has to be discontinued & in Phase II Rinse & Swab samples for water insoluble API's will be discontinued. That will be done after successful completion of Phase I.

9.0 RISK MITIGATION:

- **Training to be given on Visual inspection:** After discontinuing rinse & swab, visual inspection of remaining residues becomes more critical, hence during training method of visual inspection to be more elaborated (Angle/Distance/Reflection of inspection).

- **Cleaning procedure to be monitored strictly:** Although cleaning procedure is defined and validated for each equipment, still to be monitored strictly to avoid manual chance of error.
- **Visual inspection SOP to be implemented:** Visual inspection of equipments SOP to be prepared & defined.
- **Light intensity to be defined each critical area:** Light intensity for manufacturing area has to be defined more precisely & documented.
- **Cleaning validation to be redefined (Toxicity):** Right now worst case has been selected on the basis of Dose Criteria, as per current scenario cleaning validation to be done on toxicity basis.

10.0 RISK ANALYSIS, RE-RISK ANALYSIS CRITERIA:

10.1 Failure Mode, Effect Analysis:

In the following section a table is produced for the risk analysis using FMEA tool. The significance or instruction for each column is described in the following paragraph.

Column 1:	**Serial number** of Risk Analysis item
Column 2:	**Item/Function:** Identify the process step or component associated with the risk.
Column 3:	**Potential Failure Mode:** Identify the type of risk associated with the process or component.
Column 4:	**Effect of Potential Failure/Cause:** Verify that whether risk have **GMP impact.**
Column 5/6/7/8/9:	**Severity/Occurrence/Detection/Risk level/Risk Acceptance:** Risk Priority Number to be calculated by taking Severity, Occurrence & Detection of potential failure into consideration.
Column 10:	**Risk Mitigation**: Write the risk mitigation strategy as considered in design.
Column 11/12/13/14/15:	**Severity/Occurrence/Detection/Risk level/Risk Acceptance:** Risk Priority Number to be calculated after mitigation by taking Severity, Occurrence & Detection of potential failure into consideration.
Column16:	**Recommended action:** Recommended actions should be given for controlling failure occurrence.

Table 3: Instruction for each column given above

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FAILURE MODE EFFECT ANALYSIS FOR RISK ANALYSIS STUDY PROTOCOL FOR DISCONTINUATION OF RINSE & SWAB SAMPLING AFTER TYPE B CLEANING (ONLY FOR WATER SOLUBLE API's)

FACILITY: DISCONTINUATION OF RINSE & SWAB SAMPLES (ONLY WATER SOLUBLE API's)	**Reference Change Control:** ……

S.No.	Item/ Function	Potential Failure Mode (Failure Mode)	Potential Cause/ Mechanism of Failure	Potential Effect of Failure (Effect)	Current Control	Reference	S	O	D	Risk Priority Number (S*O*D)	Recommend-ended Actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
1.	**Cleaning Verification**	Practically insoluble swab sampling not done	May leads to contamination	• Product failure • Product recall • Product quality	• API's are water soluble, hence will be cleaned easily. As the cleaning process has been validated for Practically insoluble API (Alprazolam). • Cleaning validation already done for Tablets & Capsules. • Cleaning method is robust (Previous trend of swab & rinse).	• SOP No.: "Procedure for sampling & testing of Swab & Rinse water". • Cleaning validation protocol of Tablets:.	7	10	10	700	• List of Water soluble API's to be distributed to all cluster heads. • Training given to all concerned persons. • Visual inspection SOP to be prepared • Cleaning procedure to be monitored.	7	1	5	35
		Improper sampling due to Negligence	Lack of training	• False analysis report may generate	• Cleaning validation already done for Tablets & Capsules. • Cleaning method is robust (Previous trend of swab & rinse).	• SOP No.: "Procedure for sampling & testing of Swab & Rinse water". • Cleaning validation protocol of Tablets:.	7	5	10	350	• Visual inspection SOP to be prepared • Cleaning procedure to be monitored.	7	1	5	35
		Improper Visual inspection	Residue contamination may occur	• Colour contamination may pass on to next batch leading to failure in description. • Cleaning agent residue may leads to toxicity. • Impurity may pass on to next batch leading to batch failure.	• Cleaning validation already done for Tablets & Capsules. • Cleaning method is robust (Previous trend of swab & rinse). • Cleaning validation of cleaning agent (Extran MA02) already validated. • Cleaning agent is water soluble, hence less chance of remains.	• Cleaning validation protocol of Tablets:. • Cleaning validation protocol of Cleaning agent:	10	5	5	250	• Visual inspection SOP to be prepared • Cleaning procedure to be monitored.	1	1	1	1

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S.No.	Item/ Function	Potential Failure Mode (Failure Mode)	Potential Cause/ Mechanism of Failure	Potential Effect of Failure (Effect)	Current Control	Reference	S	O	D	Risk Priority Number (S*O*D)	Recommend-ended Actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
2.	**Cleaning Validation**	Cleaning validation not done	Worst case not selected	May leads to contamination	• Cleaning validation completed for both tablet & Capsules • Rinse & Swab sampling after every change over	• Cleaning validation protocol of Tablets:. • Cleaning validation protocol of cleaning agent:.	1	5	10	50	Cleaning validation to be evaluated periodically	1	1	10	10
		Cleaning validation not effective	• Worst case changed • Deviation in Cleaning method • Proper evaluation not done	May leads to contamination	• Evaluation of new API done • SOP of cleaning strictly followed and verified by QA	• "Evaluation of New product for cleaning validation" • SOP's of equipment cleaning	1	1	10	10	NA	NA	NA	NA	NA
3.	**Swab/Rinse Sampling**	Sampling method not adequate	• Untrained person • Sampling method not followed.	• May leads to contamination • False results generated	• SOP of sampling already distributed • Sampling done by trained QA personnel	• SOP No "Procedure for sampling & testing of Swab & Rinse water".	5	5	10	250	SOP to be revised and location to be defined	1	1	10	10
		Untrained person	• New person • Negligence	May leads to contamination	• Training given to every new joinee	• Employee training card	5	7	10	350	Training frequency to be increased	3	2	10	60
		Sampling/location procedure wrongly selected	• Untrained person • New person • Negligence	May leads to contamination	• Cleaning validation completed for both tablet & Capsules • SOP of cleaning strictly followed and verified by QA	• Cleaning validation protocol of Tablets:	10	5	10	500	SOP revised and freezed and more defined (QAH/069)	2	2	10	40
		Sample hold for long period	• Hold time not defined • Negligence • UV scanner out of service	False results generated	• Hold time defined in Analytical Method Validation Protocol • Testing done online at shop floor and instrument is dedicated	• AVP	5	1	10	50	NA	NA	NA	NA	NA
		Rinse sample collected in plain clear bottle	• Negligency	False results generated	Amber coloured bottles available in stock	SAP System	5	3	5	75	Stock to be verified after every request	1	3	5	15

PHARMA DEVILS

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S.No.	Item/ Function	Potential Failure Mode (Failure Mode)	Potential Cause/ Mechanism of Failure	Potential Effect of Failure (Effect)	Current Control	Reference	S	O	D	Risk Priority Number (S*O*D)	Recommend-ended Actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
4.	**SOP not validated**	Cleaning method of equipment not validated	• New equipment used	Cross contamination chance	• New equipment evaluated after arrival • Change control initiated and shared to QA by Engineering dept.	"Evaluation of New Equipment for Cleaning Validation"	3	3	3	27	NA	NA	NA	NA	NA
5.	**Visual Inspection**	Visual inspector not fit for inspection	Weak eye sight may lead to failure	Cross contamination chance	No current control	No reference	7	7	10	700	• Visual inspection SOP to be prepared • Medical certificate to be verified.	3	3	5	45
6.	**Light Intensity**	Light intensity not suitable	Area not qualified	Cross contamination chance	Area used after qualification	VMP	1	1	1	1	NA	NA	NA	NA	NA
7.	**Cleaning Agent**	Cleaning agent not validated	Cleaning agent changed	Cross contamination chance	Any change initiated as per change control SOP	Change Control SOP	1	1	1	1	NA	NA	NA	NA	NA
		Wrong dilution used for cleaning	• Untrained person • Negligence	Cross contamination chance	SOP of preparation of cleaning agent	SOP	5	5	10	250	Verification of remaining stock	3	3	3	27
8.	**New Formulation**	New API not evaluated	Process validation missed	Cross contamination chance	New API information shared by Validation team	NA	10	5	5	250	Batch offer sheet to be verified daily with current list	1	1	1	1
9.	**API sticky in nature**	Sticky API not identified	New API not evaluated	Cross contamination chance	New API information shared by Validation team	NA	10	5	5	250	Batch offer sheet to be verified daily with current list along with property	1	1	1	1
10.	**Coloring agent**	Coloring agent not identified	New coloring agent not evaluated	Next product will fail in description	No control	No reference	10	10	5	500	New formulation to be identified initially	1	1	1	1
11.	**Method of analysis**	Analysis method not proper	SOP not followed	False results generation	Method of analysis defined	--	10	5	5	250	SOP to be verified before every analysis	1	1	1	1

Table 4: The above table shows Potential failure mode, effect of potential failure along with Risk Probable Number, Risk Mitigation & Recommended Actions.

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*** The Risk Priority Number (RPN/Overall Risk) changes based upon the risk. The Risk Assessment team shall decide the acceptance criteria. For example the risk priority number is categorized as below:**

Risk Priority Number (RPN)	Risk levels
1-64	**Low**
65-343	**Medium**
344-1000	**High**

RPN = Severity x Occurrence x Detection

11.0 FREQUENCY OF RISK ANALYSIS:

Yearly

12.0 CONCLUSION:

Risk analysis data shall be written on Risk Analysis Study Report for Discontinuation of Rinse and Swab sampling after Type B Cleaning (Only for water soluble API's), clearly stating the achievement or non-compliance of the acceptance criteria, effect of the deviations made during the Risk analysis and in case of failure, investigation carried out and their findings.

13.0 RECOMMENDATION:

Recommendation shall be written on the Risk Analysis Study Report for Discontinuation of Rinse and Swab sampling after Type B Cleaning (Only for water soluble API's)clearly stating that there is no impact/adverse impact on the product quality & personnel can be/Can`t be merged under recommended environmental conditions.

14.0 REFERENCES:

SOP "Quality Risk Management"

15.0 DOCUMENTS TO BE ATTACHED:

- Training Record.
- Reference SOP.

16.0 DEVIATION FROM PRE DEFINED SPECIFICATION, IF ANY:

Deviations from pre defined procedures & specification during discontinuation of Rinse and Swab sampling after Type B Cleaning (Only for water soluble API's) shall be investigated in accordance with CQA SOP **"Handling of Deviations"**, and shall be documented in the Risk analysis report.

17.0 CHANGE CONTROL, IF ANY:

Change control during Discontinuation of Rinse and Swab sampling after Type B Cleaning (Only for water soluble API's) shall be authorized in accordance with CQA SOP **"Change Control"**, and shall be documented in the Risk analysis report.

18.0 ABBREVIATIONS:

FMEA : Failure Mode Effect Analysis
GMP : Good Manufacturing Practices
RPN : Risk Priority Number

19.0 Annexure:

Annexure I

S.No.	ACTIVE	PHARMACOPOEIA	SOLUBILITY IN WATER
1.	Acetazolamide	IP/BP	Very slightly soluble
2.	Acetylcysteine	BP	Freely soluble
3.	Alfuzosin Hcl	IP/BP/USP	Freely soluble
4.	Alpha Glycerylphosphorylcholine	IH	Freely soluble
5.	Amitriptyline Hcl	IP/BP/USP	Freely soluble
6.	Betahistine Hcl	IP/BP/USP	Very soluble
7.	Bisoprolol Fumarate	BP/USP	Very soluble
8.	Calcium Ascorbate	BP/USP	Freely soluble
9.	Calcium Dobesilate monohydrate	IP/BP	Very soluble
10.	Cetirizine Hcl	IP/BP/USP	Freely soluble
11.	Chlorpheniramine Maleate	IP/USP	Freely soluble
12.	Choline Bitartrate	USP	Freely soluble
13.	Ciprofloxacin Hcl	IP/BP	Soluble
14.	Citicoline Sodium	IP	Freely soluble
15.	Citric Acid	IP/BP	Very soluble
16.	Clidinium Bromide	USP	Soluble
17.	Clindamycin Hcl	IP/USP	Freely soluble
18.	Clopidogrel Bisulphate	IP/BP/USP	Freely soluble
19.	Colistin Sulphate	IP/BP	Freely soluble
20.	Copper Sulphate	BP	Freely soluble
21.	Cupric Sulfate	USP	Soluble
22.	Dexrabeprazole	IH	Soluble
23.	Dicyclomine Hcl	IP/USP	Soluble
24.	Dosulepin Hcl	BP	Freely soluble
25.	Doxofylline	IP	Soluble
26.	Doxylamine Succinate	BP	Very soluble
27.	Ephedrine Hcl	BP/USP	Freely soluble
28.	Eperisone Hcl	IH	Soluble
29.	Etamsylate	BP	Very soluble
30.	Fructose	IP/BP/USP	Very soluble
31.	Harpagophytum	IH	Soluble
32.	Ibandronate Sodium	IH	Soluble
33.	Inositol	BP/USP	Very soluble
34.	Isosorbide Mononitrate	BP	Freely soluble
35.	Lactitol Monohydrate	BP/USP	Very soluble
36.	L-arginine	IP	Freely soluble
37.	Levetiracetam	BP/USP	Very soluble
38.	Levocarnitine	BP/USP	Freely soluble
39.	Levocetirizine Hcl	IP	Freely soluble
40.	L-ornithine l-Aspartate	IH	Freely soluble

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S.No.	ACTIVE	PHARMACOPOEIA	SOLUBILITY IN WATER
41.	Losartan Potassium	IP/BP/USP	Freely soluble
42.	Lysine Hydrochloride	BP/USP	Freely soluble
43.	Manganese Sulphate	IP/BP/USP	Freely soluble
44.	Melitracen	IH	Soluble
45.	Metformin Hcl	IP/BP/USP	Freely soluble
46.	Methyl Ergometrine Maleate	IH	Soluble
47.	Metoprolol Tartrate	IP/BP/USP	Very soluble
48.	Montelukast Sodium	IP/BP/USP	Freely soluble
49.	Acetylcysteine	BP/USP	Freely soluble
50.	Naproxen Sodium	BP/USP	Freely soluble
51.	Neomycin Sulphate	IP/BP	Very soluble
52.	Niacinamide	IP/USP	Freely soluble
53.	Nickel Sulfate	IH	Soluble
54.	Pantoprazole Sodium	IP/BP	Freely soluble
55.	Paroxetine Hcl	IP/BP	Slightly soluble
56.	Phenobarbitone Sodium	IP/BP/USP	Freely soluble
57.	Phenylephrne Hcl	IP/BP/USP	Freely soluble
58.	Phenytoin Sodium	IP/BP/USP	Soluble
59.	Piracetam	IP/BP	Freely soluble
60.	Potassium Iodide	IP/USP	Very soluble
61.	Pramipexole Dihydrochloride	BP/USP	Freely soluble
62.	Propranolol Hcl	IP/BP/USP	Soluble
63.	Pseudoephedrine Hcl	BP	Freely soluble
64.	Rabeprazole Sodium	IP	Soluble
65.	Ranitidine Hcl	IP/BP/USP	Freely soluble
66.	Secnidazole	IP	Soluble
67.	Selenious Acid	USP	Soluble
68.	Selenium Dioxide	IH	Soluble
69.	Sodium Borate	USP	Soluble
70.	Sodium Molybdate Dihydrate	BP	Freely soluble
71.	Sodium Selenite Pentahydrate	BP	Freely soluble
72.	Stannous Chloride Dihydrate	BP/USP	Freely soluble
73.	Taurine	USP	Soluble
74.	Terbutaline Sulphate	IP/BP/USP	Freely soluble
75.	Thiocolchicoside	IP	Soluble
76.	Tolperisone Hcl	JP	Freely soluble
77.	Tramadol Hcl	IP/BP/USP	Freely soluble
78.	Tranexamic Acid	IP/BP/USP	Freely soluble
79.	Trimetazidine Hcl	IP/BP	Freely soluble
80.	Vitamin B1	IP/BP/USP	Freely soluble
81.	Vitamin B6	IP/BP	Freely soluble
82.	Vitamin C/Ascorbic Acid	BP/USP/IP	Freely soluble

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S.No.	ACTIVE	PHARMACOPOEIA	SOLUBILITY IN WATER
83.	Zinc Gluconate	BP/USP	Soluble
84.	Zinc Sulphate	IP/USP	Very soluble