RISK ANALYSIS STUDY PROTOCOL

FOR

EVALUATION OF EXTRANEOUS MATERIAL IN TABLETS

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

RISK ANALYSIS STUDY PROTOCOL FOR EVALUATION OF EXTRANEOUS MATERIAL IN TABLETS

PROTOCOL CONTENTS

RISK ANALYSIS STUDY PROTOCOL FOR EVALUATION OF EXTRANEOUS MATERIAL IN TABLETS

1.0 OBJECTIVE:

The objective of this Protocol is to evaluate the sources of contamination and its impact on the product quality.

2.0 SCOPE:

Risk analysis study Protocol is applicable for tablets manufactured in Solid Oral dosage section.

3.0 RESPONSIBILITY:

Department	Responsibility
Production Team	• Review & Pre Approval of Risk Assessment Protocol. • Post Approval of Risk Assessment Protocol.
Quality Assurance Team	• Preparation, Review, and Compilation of Risk Assessment Protocol. • Post Approval of Risk Assessment Protocol.
Quality Control	• Review & Pre Approval of Risk Assessment Protocol. • Post Approval of Risk Assessment Protocol.

4.0 REASON FOR RISK ANALYSIS:

To mitigate & monitor the risk of extraneous material in Tablets.

5.0 SITE OF STUDY:……

6.0 RISK COMMUNICATION & TRAINING:

- The Risk analysis team shall be authorized by the Head-QA or his/her designee.
- Quality Risk Management Team shall be cross functional team comprised of expert from different areas.
- Training shall be imparted to the concerned team.

7.0 RISK IDENTIFICATION, EVALUATION& MITIGATION:

INTRODUCTION: Extraneous materials are any foreign matter in product associated with objectionable conditions or practices in production, storage or distribution. The contaminant or extraneous material may be related to the active ingredient, excipient materials or colorant. Particles may be generated from the product container or packaging material. These types of particles include Metal wires, glass pieces, rubber, aluminum, plastics, polythene and paper. Contamination can also result from the manufacture of the product; examples of these include charred product, detergents and lubricant oils. Metal and metal corrosion, Teflon, graphite and rubber particles are indications of tank, filter or equipment failure. Environmental contaminants such as fibers and skin cells are also found. The most common contaminants in pharmaceuticals are cellulose (cotton and paper) fibers, synthetic fibers, silicone, rubber, metal particles and corrosion products, glass particles, skin flakes and char particles.

Contaminants can gain entry into a production process stream from several sources such as, Personnel, Poor facility design, Incoming ventilation air, Machinery and other equipment for production, Raw material and semi-finished material, Packaging material, Utilities, Different media used in the production process as well as for cleaning and Clean room clothing.

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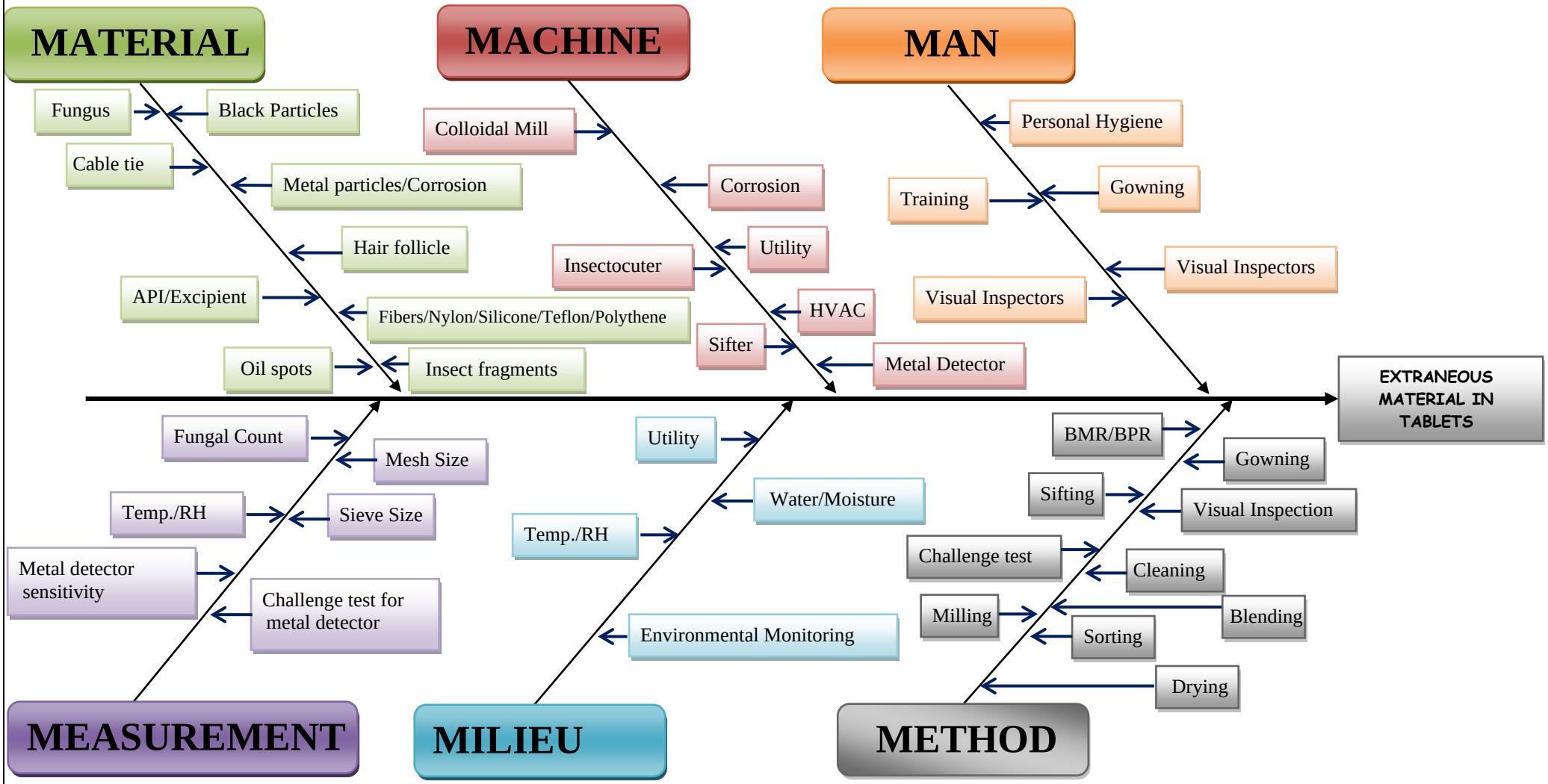
S.No.	RISK IDENTIFICATION	RISK EVALUATION	RISK MITIGATION
1.	Risk associated with extraneous material is from minor to critical. It depends on the type of foreign material observed. Sometimes it is in-built from the system or process (black particles, metal pieces, fibers, silicon pieces, Teflon pieces, Oil spots, detergents, nylon fibers), and sometimes it is from the outside environment (Hair follicle, cable tie, Polythene) pieces, Rubber pieces, Fungus, Water & Pest). Risk associated with the products shall be identified for its criticality.	After risk identification, evaluation shall be done for each component of the factor associated with it. Risk probable number shall be allotted to each factor on the basis of its criticality. Recommendations shall be given against each critical factor.	After Risk evaluation, risk mitigation shall be given to slow down the criticality of the associated risks. More than one control can be allotted for each risk. After the control measures, if risk is still high then recommendations shall be given &the risk is again re-evaluated.

8.0 RISK ANALYSIS TOOLS, RE-RISK ANALYSISCRITERIA:

8.1 Fish bone/6M/Ishikawa diagram:



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8.2 SUMMARY OF THE 6 M/FISH BONE DIAGRAM/ISHIKAWA DIAGRAM: It is used for the evaluation of Impact of extraneous material on finished products; following are the areas of concern considered for investigation. Man, Material, Measurement, Method, Milieu& Machine. It has been evaluated that all of the 6 M may contribute in defects related to extraneous material.

MAN: Personnel who are supervising or performing drug manufacturing or control can be a potential source of microbiological contamination and a vector for other contaminants. The main reasons for contamination from the personnel include:

- Lack of training.
- Direct contact between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product
- Inadequate personnel cleanliness.
- Access of unauthorized personnel into production, storage, and product control areas.
- Inadequate gowning and personnel protective equipment, and
- Malpractices like eating food, drinking beverages, or using tobacco in the storage and processing areas.
- Performing various activities (Non-GMP) which are not the part of manufacturing process.

MATERIAL: The raw materials used for production can be a potential source of contamination. The main reasons for contamination from the raw materials include:

- Storage and handling mistakes causing mix-ups or selection errors.
- Contamination with microorganisms or other chemicals.
- Degradation from exposure to excessive environmental conditions such as heat, cold, sunlight, moisture, etc.
- Improper labeling.
- Improper sampling and testing, and use of materials that fails to meet acceptance specifications.
- Material from unapproved vendor.
- Material with special property of sticking like Sucrose, which further in campaign batches looks like charred particles, if not cleaned properly.
- Some sticky materials like Sucrose is hard to clean and after time being got deposited over equipment surfaces.

MILIEU: The buildings and manufacturing facilities may also contribute to the contamination. The main reasons of contamination due to facility issues include:

- Insufficient size and inadequate organization of the space leading to selection errors like mix-ups or cross contamination between consumables, raw materials, in-process materials, and finished products.
- Inadequate pest controls.
- Rough floors, walls, and ceilings.
- Lack of air filtration systems.
- Improper lighting and ventilation.
- A poor HVAC system can be a potential source of microbes growth and a transportation mode for dispersing contaminants throughout the manufacturing facility.

The main reasons of contamination due to HVAC issues include:

- Accumulations of organic material in or near HVAC air intakes.
- Ineffective filtration of the supply air.
- Insufficient magnitude of pressure differentials causing flow of reversal.
- Erroneous ratio of fresh air to re-circulated air.
- Inability to access ventilation dampers and filters from outside the manufacturing areas.
- Non-directional airflow within production or primary packing areas.

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MACHINE: The equipment and utensils used in processing, holding, transferring and packaging are the common source of pharmaceutical contamination. The main reasons for contamination from the equipment include:

- Inappropriate design, size, material leading to corrosion and accumulation of static material and/or adulteration with lubricants, coolants, dirt, and sanitizing agents.
- Improper cleaning and sanitization.
- Design preventing proper cleaning and maintenance.
- Improper calibration and irregular service, and deliberate use of defective equipment.
- Challenge test not performed before the start.
- Machine not qualified.
- Inappropriate preventive maintenance.
- Metal parts shred during sifting & sieving.
- Polythene used for clamping the equipment parts resulting into shredded polythene pieces contamination.
- Metal detector not used.

METHOD: There are various opportunities for contamination of raw material, intermediates or packaging materials throughout the manufacturing process. The main reasons for contamination during manufacturing process include:

- Inappropriate cleaning in-between batches to minimize the amount of product changeovers.
- Use of an open manufacturing system exposing the product to the immediate room environment.
- Absence of an area line clearance according to approved procedures following each cleaning process and between each batch.
- Lack of cleaning status labeling on all equipment and materials used within the manufacturing facility.
- Sorting not done properly.
- Improper visual inspection.
- Lack of Good manufacturing practices during processing activity.
- Removing deposited material with the help of scrapper, ladle, scoop etc. resulting into metal contamination.

MEASUREMENT: Measurement itself plays important role in evaluation of extraneous material impact on product quality. There are many factors which shall be regularly monitored & recorded such as:

- Temperature & RH of the area not under control & recording time too exhaustive
- Metal detector sensitivity too low to detect any metal piece.
- Sieve size & mesh size are inappropriate to capture any extraneous material.

8.3 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 1: Instruction for each column given above

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Procedure: Risk analysis for evaluation of sources and impact of extraneous material in tablets	**Quality Risk Assessment Date:** **QRA No.:**

S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
MATERIAL															
1.	Metal pieces	• Tablet fail in description	• Improper visual inspection. • Contaminated API/Excipient • Vendor not qualified. • Metal detector not available. • Challenged test not performed before the start. • Too much scrubbing done during sifting & sieving resulting into broken metal parts. • Metal detector sensitivity too low to detect any metal piece. • Gap might be left between assembly & gaskets from where the metal from damage sieve got mixed with the material. • During sifting of the product, the aperture of the sieve get blocked due to the operator use the scoop to wipe off the powder from the blocked apertures	• Market complaint • Product recall • Tablet fail in description.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods • Procedure for vendor qualification is in place. • Procedure for Visual Inspectors qualification is in place. • All tablets are passed through metal detector. • BMR has been revised for adding a note at compression stage that only 05 campaign batches has been taken while manufacturing of product and Punches shall be cleaned on every A type cleaning (batch to batch). • Compressed air is being used to remove the blocked aperture of Dutch mesh. • The Product has been manufactured (granulation and compression) in 05 campaign batches instead of 10 batches, so that B type cleaning has been performed, after 05 campaign batches instead of 10 batches. • Silicone Gasket has been procured for all Sifter Clamp and used in all sifters.	• SOP No.: "Manual Inspection of Tablets" • SOP No.: "Inspection of Tablets" • SOP No.: "Terminal Inspection and Transfer of Finished Goods" • SOP No.: "Qualification Challenge Test of Visual Inspector"	3	3	2	**18**	• Metal detector shall be cleaned on every A Type cleaning (batch to batch) and BMR shall be revised accordingly. • During compression metal detector flap shall be cleaned after every two hour and challenge test also be performed after initial, breakdown, cleaning and at the end of the batch. BMR shall also be revised for the cleaning frequency and challenge test of the metal detector.	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
			due to which there might be possibility that sieve got damage and small particle may drop off which mixed with further granules and proceeded to next stage. • During transferring of material for sizing of material from FBD to sifter via scoop there might be the possibility that Dutch mesh may be damage from where the metal particle got mixed with granules and further compressed in tablet. • There might be possibility that any unwanted material may came into granulation/compression area via un-cleaned containers during manufacturing of product. • During the batch compression metal detector may not detected tablet may be because of • The batch is compressed in the campaign batches due to which the powder get accumulated in the metal detector as formulation is sucrose based which might resulted in the time being		• Sieve integrity shall be checked before and after completion of the batch.(Batch to batch). • Container cleaning shall be effectively monitored as per SOP so as to avoid any possibility of contamination of extraneous matter in product.									

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
			loss in sensitivity. • The formulation is sucrose based due to which powder get accumulated over the flap of metal detector which resulted in loss of sensitivity of metal detection. • The tablet might not have been sensed by the detector as this metal piece was embedded and thus change in shape/inertia of the tablets and resulting in non-detection of the tablet.												
2.	Metal Corrosion	• Tablet fail in description	• Improper visual inspection. • Equipment not dried properly. • Line clearance procedure not followed.	• Market complaint • Tablet fail in description.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods • Procedure for Visual Inspectors qualification is in place. • Line clearance Procedure is in place.		2	1	2	4	Risk is low hence no action plan is required	NA	NA	NA	NA
3.	Fibers	• Tablet fail in description	• Improper visual inspection. • Garments not verified for loose threads. • Lint free cloth not used for type A cleaning.	• Market complaint • Tablet fail in description.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods • Procedure for Visual Inspectors qualification is in place. • Use of lint free cloth procedure is in		1	2	3	6	Risk is low hence no action plan is required	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
					place in respective equipment SOP's.										
4.	Cable tie	• Tablet fail in description	• Improper visual inspection. • Broken tie mixed with granules.	• Market complaint • Tablet fail in description.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods • Procedure for Visual Inspectors qualification is in place.		1	2	3	6	Risk is low hence no action plan is required	NA	NA	NA	NA
5.	Polythene pieces	• Tablet fail in description	• Improper visual inspection. • Shredded polythene mixed with granules. • The polybag used in manufacturing process was found of low thickness, which can be easily torn/peeled off.	• Market complaint • Tablet fail in description.	• Terminal Inspection & Transfer of Finished Goods • Procedure for Visual Inspectors qualification is in place. • O Rings & Gaskets are used for clamping. • The thickness of the polybag (Clear/Black) used in process of 140 gauge, so the quality of polybag was improved from 140 gauge to 160 gauge. • In Sifter, Silicon gasket are used for adjusting of the clamp. • Training provided to all concerned person regarding time to time inspection/replacement of scrapper and setting plate in compression machine. • 100% rubber gaskets are used in IPC Bin.		1	2	3	4	• Risk is low hence no action plan is required	NA	NA	NA	NA
6.	Black particles	• Tablet fail in description	• Improper visual inspection. • Improper sifting. • Improper milling during	• Market complaint • Tablet fail in description.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods		1	2	2	4		NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
			coating. • API & Excipient from unapproved vendor. • Due to friction of punch and turret, black particles got generated and may drop on tablets which may cause black spots over the tablet. • The defective tablets are not segregated by visual inspectors. • The above formulation consist of Sucrose which after time being changes its color to Black, these Black particles got mixed in different stages and the product appeared with black spot.		• Procedure for Visual Inspectors qualification is in place. • Shifting procedure is well defined in respective products BMR. • Procedure for vendor qualification is in place. • AQL procedure is in place. • Dust Extractor shall be made available on compression machine during manufacturing of product. • Punches are cleaned on every A Type cleaning (Batch to Batch). • The Product is manufactured (Compression) in 05 campaign batches. • BMR has been for 05 campaign batches &Punches are cleaned on every A type cleaning (Batch to Batch). • Type B cleaning to be done after 05 campaign batches.									
7.	Oil Spots	• Tablet fail in description	• Improper visual inspection. • Equipment not cleaned properly after preventive maintenance.	• Market complaint • Tablet fail in description.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods • Procedure for Visual Inspectors qualification is in place. • Preventive maintenance procedure is in		1	2	2	4	Risk is low hence no action plan is required	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
					place. • AQL procedure is in place. • Punches are cleaned after every batch.										
					METHOD										
8.	Sifting not performed	• Black Particles. • Insect fragments. • Hair follicle may pass, if sifting not done. • Fibers mix up with granules. • Nylon fibers mix up with granules. • Cable tie may mix up. • Polythene pieces mix ups.	• Improper sieve. • API/Excipient used from unapproved vendor.	• Market complaint • Tablet fail in description. • Product recall. • Health Hazard.	• BMR in place for selection of sieve. • Process validation in place. • Procedure for vendor qualification is in place. • There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods • Procedure for Visual Inspectors qualification is in place.	• BMR in place • Dedicated QA person	3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
9.	Improper Sifting	• Metal Particles generated	• Sifting done forcefully by rubbing the sieve with scrapper resulting into generation of metal particles or small pieces of wires.	• Market complaint • Tablet fail in description. • Product recall. • Health Hazard.	• Sifting procedure in place. • Compressed tablets are passed through metal detector.	• BMR in place • Dedicated QA person • Cleaning SOP's in place	3	1	2	6	Risk is low, as tablets are passed through metal detector	NA	NA	NA	NA
10.	Improper milling	• Metal Particles generated	• Some tool used for scrapping the deposited material resulting into metal contamination.	• Metal contamination • Market complaint	• Milling procedure in place.		3	1	2	6	Risk is low, as milling is done as pre GMP procedure.	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
				• Product recall • Health Hazard.											
11.	Improper drying	• Metal Particles generated	• Scoop & Ladle used for scrapping the deposited material resulting into metal contamination.	• Metal contamination • Market complaint • Product recall • Health Hazard.	• Milling procedure in place.		3	1	2	6	Risk is low, as milling is done as pre GMP procedure.	NA	NA	NA	NA
12.	Metal detector	• Metal part mix up with tablets • Not qualified • Low sensitivity	• Metal detector not available. • Challenged test not performed before the start.	• Market complaint • Product recall • Tablet fail in description.	• Procedure for operation & cleaning of metal detector is in place. All tablets are passed through metal detector.		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
13.	Cleaning of Equipments	• Tablet with stains. • Cross contamination	• Remaining of detergent contaminate the next product.	• Market complaint • Health hazard. • Toxicity.	• Cleaning SOP for each equipment & process in place. • Cleaning agent qualified for its residues.		3	2	1	6	Risk is low hence no action plan is required	NA	NA	NA	NA
14.	Improper Gowning	• Hair follicles in tablets. • Skin flakes in tablets • Unpleasant appearance of tablet.	• Gowning improper. • Some body part exposed. • Unhygienic practices.	• Market complaint • Product recall.	• Procedure for primary and secondary gowning is in place. • Working persons are trained. Procedure for training of personal is in place.	SOP for gowning in place	3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
15.	Sorting & Visual Inspection	• Tablets with black particles. • Tablets with foreign particles.	• Improper visual inspection. • Visual inspection not done. • Visual inspector not qualified.	• Market complaint. • Batch hold. • Re-sorting or re-inspection.	• There is well defining procedure of tablets sorting. We have both procedures for sorting, manual and inspection belt. • Terminal Inspection & Transfer of Finished Goods.		3	2	1	**6**	Risk is low hence no action plan is required	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
					• Procedure for Visual Inspectors qualification is in place.										
MEN															
16.	Untrained Operators	• Non- GMP activities	• Using different tools for scrapping the deposited material resulting into metal pieces generation.	• Metal contamination • Product failure • Market Complaint	• Trained Operators • Online IPQA activities verified by QA & Production personnel.	Training report available	3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
		• Dirty gloves	• Same gloves used during the whole campaign batches may leads to contamination.	• Black Particles generated • Fiber contamination from ruptured gloves • Microbial contamination	• Gloves are changed from time to time.		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
		• Personnel cleanliness	• Dirty gowning may contaminate the product.	• Extraneous material in product • Microbial Contamination • Market Complaint • Cross contamination	• Secondary gowning. • Gowning cleaning schedule available.		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
MACHINE															
17.	Dirty Equipment	• Black particles generated	• Dirty equipment may shred particles. • Steps of cleaning process skipped to save time.	• Market complaint • Product failure • Batch recall.	• Type B cleaning after every product change over. • Type B cleaning after 5 campaign batches. • Cleaning process validated.	• BMR in place • Cleaning SOP's in place • Cleaning Validation	3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
			• Cross contamination.		• Cleaning SOP's in place. • Line clearance is in place	done									
18.	Improper manufacturing process	• Different tools (Scoop, Ladle, SS plate) used for removing deposited material from Sifter, Multimill, FBD etc. • Different manufacturing steps not performed as per BMR.	• Tools (Scoop, Ladle, SS Plate) used too hard for scrapping the deposited material resulting into metal contamination. • Critical step skipped to save time.	• Market complaint • Product failure • Batch recall. • Metal contamination	• BMR in place • Steps verified by QA & Production.		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
19.	Polybags used for clamping	• Shredded polybag pieces contaminate the product	• Shredded polybag may contaminate the product.	• Market complaint • Fail in description.	• Gaskets & O – rings are used for clamping		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
20.	Preventive maintenance not done	• Improper oiling may result into corrosion • Breakdown may take place	• Corrosion may lead to contamination	• Extraneous material contamination	• Preventive maintenance done as per schedule.		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
MILEU															
21.	Poor Air circulation	• Accumulations of organic material in or near HVAC air intakes. • Ineffective filtration of the	• Particle generation	• Black particles • Cross Contamination	• All HVAC systems are qualified.	HVAC qualification available	3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA

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S.No.	Item/Function	Potential failure mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current control	Reference	S	O	D	Risk Priority number	Recommended actions (if any)	Post Risk			
												S	O	D	RPN S*O*D
		supply air. • Insufficient magnitude of pressure differentials causing flow of reversal. • Erroneous ratio of fresh air to re-circulated air. • Inability to access ventilation dampers and filters from outside the manufacturing areas. • Non-directional airflow within production													
MEASUREMENT															
22.	Metal Detector sensitivity	• Metal parts not detected.	• Sensitivity too low to detect any metal.	• Tablets with metal contaminant may skip the metal detector.	• Challenge test starts before the start of compression. • Qualification of metal detector already in place.	• Challenge test done before every batch • BMR in place	3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA
23.	Sifting & Sizing	• Extraneous material skipped and contaminate the product.	• Required mesh size sieve not used.	• Extraneous material may contaminate the product.	• BMR in place • Verified by QA & Production simultaneously.		3	1	1	3	Risk is low hence no action plan is required	NA	NA	NA	NA

Table 2: The above table shows Potential failure mode, effect of potential failure along with Risk Probable Number, Risk Mitigation & Recommended Actions.

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Assessment of Severity, Occurrence and Detection:

Severity Effect	Likelihood Occurrence	Likelihood of Detection	Rating
No Effect	Unlikely	Always Detected	1
Moderate Effect	Possible	Might Detect Failure	2
Serious Effect	Almost Certain (every time)	Lack of Detection Control	3

Evaluation of RPN:

RPN Rating	Category
12 to 27	High
7 to 11	Medium
Upto 6	Low

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9.0 CONCLUSION: On the basis of evaluation of above risk assessment, it is concluded that the risk associated with the extraneous material can be from critical to minor. Complaints related to tablets have shown that the controls are not enough sufficient to avoid incoming of the extraneous materials in the batch. There are several factors related to practices (Scrubbing of Sifter/Multi-mill/FBD etc.) which should be monitored and need to be improved. Also the repeated complaints of metal wire show the ineffectiveness of Metal Detector. To avoid such complaints, manufacturing process need to be re-evaluated and controls shall be strictly followed.

10.0 RECOMMENDATION: Following are the recommendations need to be implemented:

- Metal detector shall be cleaned on every A Type cleaning (batch to batch) and BMR shall be revised accordingly.
- During compression metal detector flap shall be cleaned after every two hour and challenge test also is performed after initial, breakdown, cleaning and at the end of the batch. BMR shall also be revised for the cleaning frequency and challenge test of the metal detector.

11.0 REFERENCES:

- Reference SOP of Risk Assessment.
- https://www.mccrone.com/mm/contaminant-identification-pharmaceutical-products/.
- https://tablettingscience.com/solving-problems/.
- https://www.europeanpharmaceuticalreview.com/article/24118/fungal-contamination-pharmaceutical-products-growing-menace/.
- Related SOP's.

12.0 DOCUMENTS TO BE ATTACHED:

- Related documents.

13.0 DEVIATION FROM PRE DEFINED SPECIFICATION, IF ANY:

Deviations from the pre-defined acceptance criteria observed in accordance with QA SOP **"Handling of Deviations"**, shall be documented in the Risk analysis Protocol cum report.

14.0 CHANGE CONTROL, IF ANY:

Change control observed in accordance with QA SOP **"Change Management"**, shall be documented in the Risk analysis Protocol cum report.

15.0 ABBREVIATIONS:

FMEA	: Failure Mode Effect Analysis
GMP	:Good Manufacturing Practices
RPN	: Risk Priority Number
CAPA	: Corrective action preventive action
WHO	: World health organization

RISK ANALYSIS STUDY PROTOCOL FOR EVALUATION OF EXTRANEOUS MATERIAL IN TABLETS

16.0 PROTOCOL APPROVAL:

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OPERATING MANAGER (QUALITY ASSURANCE)			
HEAD (PRODUCTION)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			