Risk Assessment Study For Manufacturing Facility of Gelatin Preparation & Medicament Preparation

RISK ANALYSIS STUDY FOR MANUFACTURING FACILITY OF GELATIN PREPARATION & MEDICAMENT PREPARATION

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RISK ANALYSIS STUDY FOR MANUFACTURING FACILITY OF GELATIN PREPARATION & MEDICAMENT PREPARATION

1.0 OBJECTIVE:

To provide the documented evidence that there are sufficient controls to avoid any risk in case of two different batches/products manufactured in common facility of Soft gel.

2.0 SCOPE:

This risk analysis study Protocol is applicable for performing risk analysis study for using common areas (Gelatine preparation & Medicament) for manufacturing of 02 different batches/products in the Soft gel area.

3.0 RESPONSIBILITY:

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

RISK ANALYSIS STUDY FOR MANUFACTURING FACILITY OF GELATIN PREPARATION & MEDICAMENT PREPARATION

4.0 REASON FOR RISK ANALYSIS:

Cross Contamination is one of the highest risks for the patients. Small amounts of highly potent compounds carryover into another pharmaceutical product can lead to high risk to the patient. Hence a Risk Analysis shall be done to evaluate the controls in place to avoid any critical condition during manufacturing of 02 batches/products in the same place at the same time.

5.0 SITE OF STUDY:

Gelatine and Medicament preparation area of Soft gel at G Block.

6.0 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 experts from different areas such as QA and Production.
- Training shall be imparted to the team members before execution of Protocol for proper understanding of the procedure.

Quality Risk Management Team:

S.No.	Name	Department
1		**Production**
2		**Production**
3		**QA**
4		**QA**

7.0 REFERENCE DOCUMENTS/DRAWINGS:

S.No.	Document Title	Document Number
1.	**Quality Risk Management**	
2.	**Prevention of Contamination & Cross Contamination**	
3.	**Layout of First Floor (Material movement)**	
4.	**Layout of First Floor (Men movement)**	
4.	**Line Clearance**	
5.	**Status Labelling**	
6.	**Cleaning of Core Processing areas and other areas**	
7.	**Training of Employees**	

RISK ANALYSIS STUDY FOR MANUFACTURING FACILITY OF GELATIN PREPARATION & MEDICAMENT PREPARATION

8.0 EQUIPEMENT / SYSTEM DESCRIPTION:

8.1 Layouts:

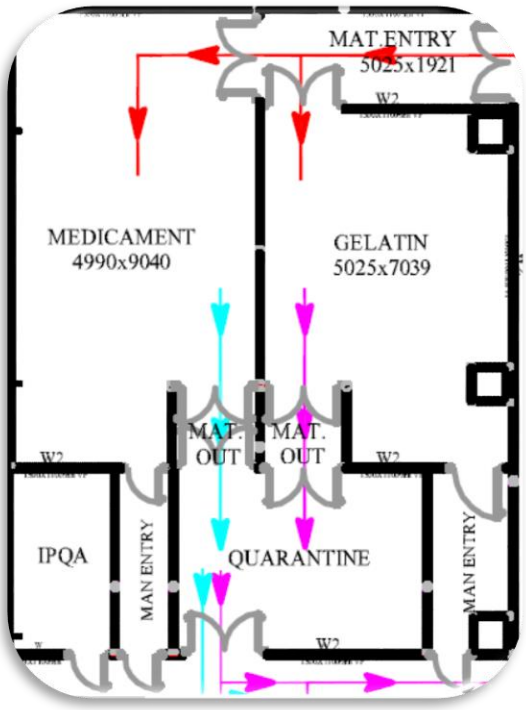

Figure 1: Material Movement

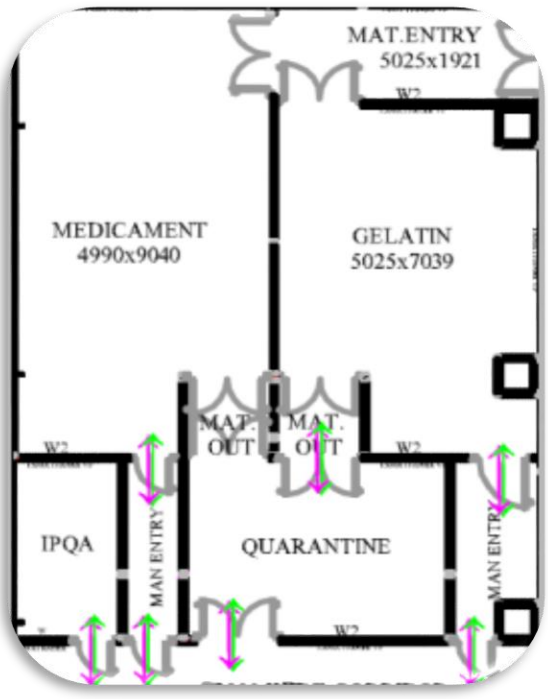

Figure 2: Men Movement

LAYOUT SHOWS SEPARATE ENTRY & EXIT FOR BOTH MEN & MATERIAL

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8.2 Equipment used in Gelatin Preparation Room:

- **Hot Water Jacketed Gelatin Melter:** Hot water Jacketed Gelatin Melter is used to melt the gelatin powder. It contains motor & reducer which drives special shape agitators inside the tank. During preparation, the gelatin melting tank works to keep a constant temperature. The temperature should reach around 95°C, so that inside gelatin solution will reach 70°C.

- **Gelatin Holding Tank:** Gelatin Holding tanks are used for holding the Gelatin mass. There are 12 nos. of Gelatin Holding tanks available in the area. All Gelatin Holding tanks have their separate status labels.

- **Stirrer or Color mixer:** Stirrer is used to mix aqueous colors during Gelatin mass Preparation.

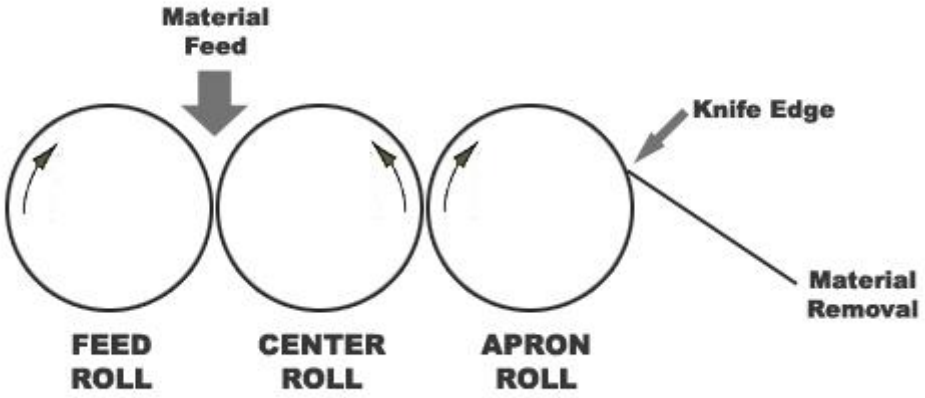
- **Colloidal Mill:** Colloidal mill is used to mix non-aqueous colors.

8.3 Equipments used in Medicament Preparation area:

- **PLANETARY MIXER:** Planetary mixer is used for mixing of Medicament products. The rotation to drives paddle and emulsifier rotating in same direction. Paddle revolves around in the mixing tank with Teflon scraper. So material complete mixing during the process.

- **HOMOGENIZER:** Homogenizer by passing the large globule emulsions through a smaller orifice resulting into smaller globules of uniform size, so that each measured dose has the same composition.

- **TRIPLE ROLLER MILL:**



A **three roll mill** or **triple roll mill** uses shear force created by three horizontally positioned rolls rotating in opposite directions and different speeds relative to each other, in order to mix, refine, disperse, or homogenize viscous materials fed into it.

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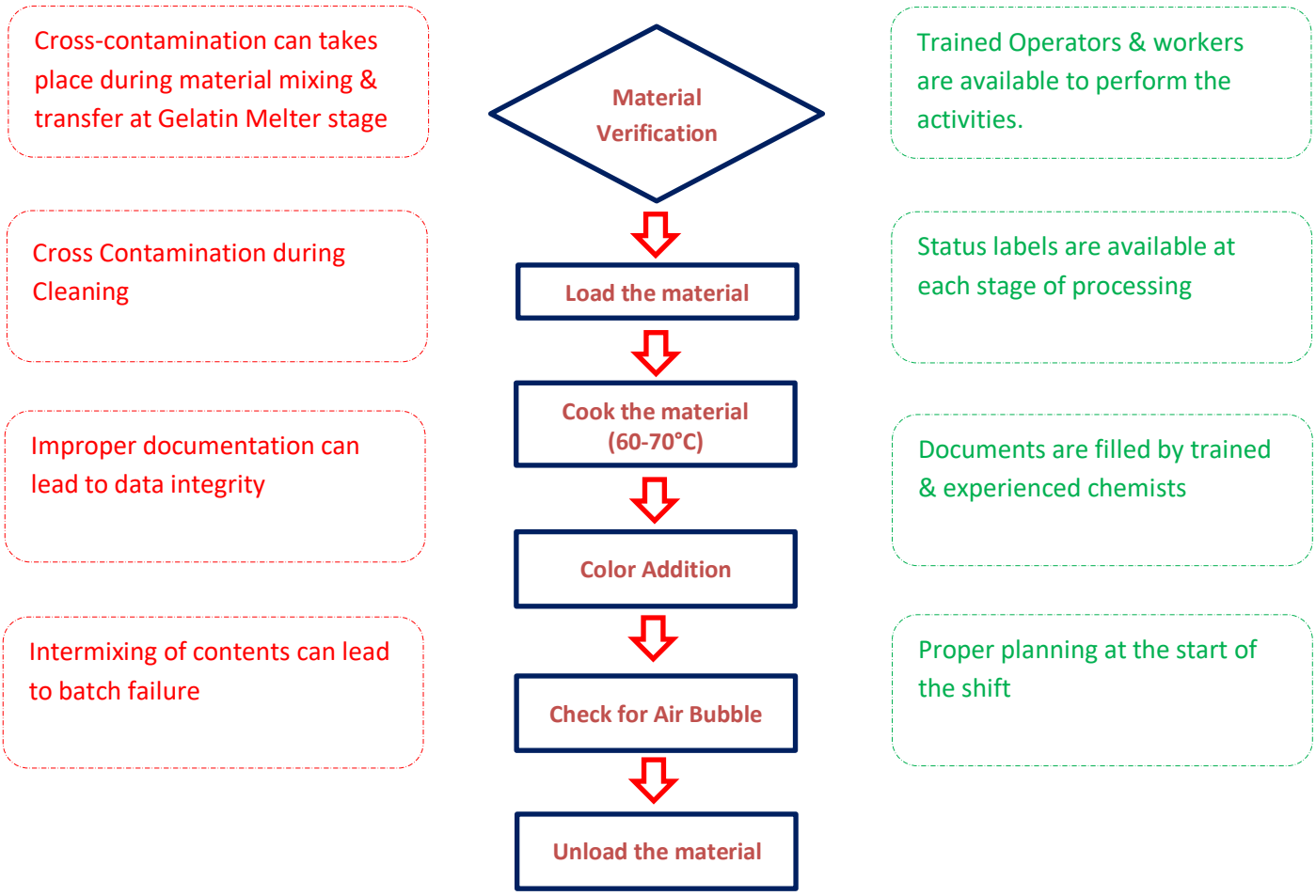
8.4 PROCESS FLOW:

- **GELATIN PREPARATION:**



Gelatine preparation starts with the verification of the dispensed material. Temperature of the Gelatine melting reactor is maintained between 60-70°C, the verified material is mixed in melting reactor. 02 Melting reactor are available with the capacity of 600 ltr. Hence 02 batches can be taken at a time. The whole activity takes place in a closed condition. So the possibility of cross contamination is reduced.

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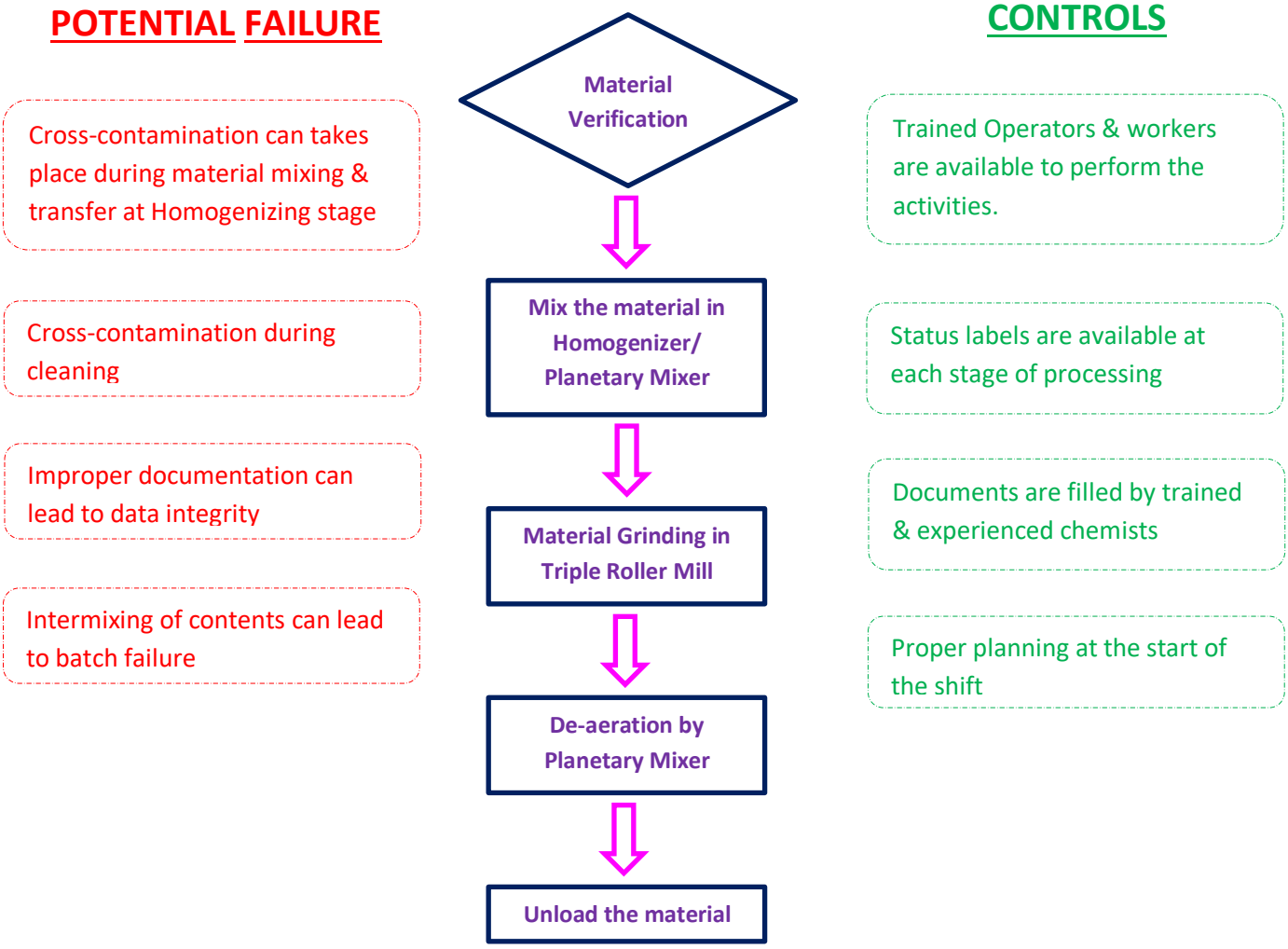
- **MEDICAMENT PREPARATION:**



Medicament preparation starts with the verification of material by Production & QA personals, the weighed material is kept in 02 different staging area, further it is mixed in Homogenizer. For grinding, the homogenized material is then transferred to Triple Roller Mill. After grinding, the medicament is transferred to planetary mixer for de-aeration. During all the processing activities, the status labelling is done stage wise and verified by both Production & QA. Separate dedicated manpower is allotted for separate batches. While during the batch change over, equipment cleaning shall be done, once the type B cleaning started, the parallel activities are closed until the cleaning completed.

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9.0 RISK IDENTIFICATION, EVALUATION & MITIGATION: At the very basic stage of design, the Risk Assessment is carried out to verify that all features are taken into consideration to avoid the risk of failure of critical GMP and EHS parameter in the equipment. During study, all GMP, EHS and operational parameters will be identified and assessed for the risk, appropriate mitigation will be proposed and verification point will be identified and defined. The Risk Assessment report is produced to provide the documented evidence that design concepts or requirement are complete in considering all GMP, EHS and operational risks.

S.No.	Risk Identification	Risk Evaluation	Risk Mitigation
1.	**02 Batches manufactured in Gelatin preparation area**	Interchange of colours by mistake can lead to product failure	Verified by Production & QA
			02 Separate Gelatin melter available
2.	**02 Batches manufactured in Medicament preparation area**	Interchange of material	Verified by Production & QA
		Cross contamination during mixing	02 Staging areas available
		Cross contamination during cleaning	Product B manufacturing on hold during type B cleaning of Product A
3.	**Data Integrity**	Two batch records in same area in same time can lead into misinterpretation resulting into data integrity.	Separately verified by Production & QA
			Trained personals.
4.	**Cleaning**	Cross contamination may take place	Processing of the parallel Product A is stopped during Type B cleaning of Product B. The processing batch is covered and holds till the cleaning completed.
			Rinse & Swab is done
5.	**Single equipment availability for 02 batches**	Using single equipment for 02 running batches	In Medicament preparation area, there are some equipment which are single, when 02 batches are manufactured in parallel, then the single equipment used is cleaned and kept on hold till next confirmation.
6.	**Manpower**	Untrained manpower can lead to cross contamination during processing of 02 activities at a time.	Trained manpower dedicated when more than 01 batch runs.

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10.0 RISK ANALYSIS TOOLS, 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 1: Instruction for each column given above

The purpose of FMEA for manufacturing 02 products/batches in a same area at a same time is to establish documentary evidence to assure that the manufacturing process is capable of producing the pre-determined quality specifications, while guaranteeing the safety of the operator.

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Procedure: 02 Products manufactured in same area of Softgel

Quality Risk Assessment No.: ……

S.No.	Item/Function	Potential Failure Mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current Control	Reference Document No.	S	O	D	Risk Priority Number (S x O x D)	Recommended action (If any)	Post Risk Evaluation			
												S	O	D	RPN
1.	**Design of manufacturing area**	• Material entry & exit done from same area • 02 different batches manufactured at same time	• Mixing of batches	• Batch failure	• Separate entry & exit for material • Verification tags available for each container. • Each equipment is tagged with Status label.	• Layout • SOP No.: "Status Labelling" • SOP No.: "Prevention of Contamination & Cross Contamination "	3	2	1	**3** **Severity:** Serious effect, as intermixing or cross contamination can lead to batch failure. **Occurrence** of batch mixing & cross contamination is possible as sufficient controls are available. **Detection** of failure is always detected.	Not Applicable	NA	NA	NA	NA
2.	**Common Change Room**	• Change Room too crowded	• Man Movement from same area • Used Garment not segregated • Dirty Garments • Multiple garments kept at one place • Crossover bench not cleaned	• Loss the Identity of product • Risk with respect to product Quality, Safety & Efficacy • Non-compliance of SOP/BMR	• Batch taken inside as per planning • Trained Operators & Supervisors • Collect the Used garments separately • Cleaning frequency is on Daily basis	• SOP No. "Cleaning of Core Processing areas and Other areas"	3	2	1	**6** **Severity:** Serious effects in-case of product failure or batch intermixing **Occurrence** of Intermixing of batches is possible **Detection:** Always detect failure	Not Applicable	NA	NA	NA	NA

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Procedure: 02 Products manufactured in same area of Softgel										**Quality Risk Assessment No.: ……**				
S.No.	**Item/Function**	**Potential Failure Mode**	**Potential Cause/Mechanism of Failure**	**Potential Effect of Failure**	**Current Control**	**Reference Document No.**	**S**	**O**	**D**	**Risk Priority Number (S x O x D)**	**Recommended action (If any)**	**Post Risk Evaluation**			
												S	**O**	**D**	**RPN**
			• BMR intermixing		• Microbial monitoring is done as per schedule • Secondary Gowning										
3.	**Common Material Entry & Exit**	Material inward through pass box for different product manufacturing.	• Material movement from same area • Product mixing	• Loss the Identity of product • Non-compliance of SOP/BMR Cross contamination	• Status label on each container • Verified by QA • Line clearance procedure in place • Cleaning procedure is in place	• Layout • SOP "Line Clearance"	**3**	**2**	**1**	**6** **Severity:** Serious effects in-case of product failure or batch intermixing **Occurrence:** Transfer of 02 products at a time may be possible **Detection:** Wrong material movement can be easily detected.	Not Applicable	NA	NA	NA	NA
4.	**Gelatin preparation**	• Cross Contamination • Uncleaned equipment may lead to cross contamination • Color intermixing • Improper line clearance	• Variation in description of gel mass • Failure during in process check • Area Cleaning inappropriate • Color may be interchange during	• Loss the Identity of product • Risk with respect to product Quality, Safety & Efficacy • Non-Compliance of SOP/BMR • Market Complaint	• Separate Gelatin Melter tanks • Activity performed in closed condition. • Variation of color composition as per BMR description. • Area cleaning to	• BMR • SOP "Line Clearance" • SOP "Training of Employees"	**3**	**2**	**1**	**6** **Severity:** Serious effects in-case of product failure or batch intermixing **Occurrence:** Always a possibility of occurrence **Detection:** Tracking of	Not Applicable	NA	NA	NA	NA

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Procedure: 02 Products manufactured in same area of Softgel | **Quality Risk Assessment No.: ……**

S.No.	Item/Function	Potential Failure Mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current Control	Reference Document No.	S	O	D	Risk Priority Number (S x O x D)	Recommended action (If any)	Post Risk Evaluation			
												S	O	D	RPN
			manufacturing of two batches • Status labelling inappropriate • Missing status label • Similar Equipment used for different product • Two different Batches process done by single person. • Different batches BMR handled by same persons. • Two different batches manufactured in same environment. • Traces of the solvent contaminate with other product. • GMP	• Fail in Finished product specification	be done through batch to batch. • Color composition before mixing checked by production officer and verified by QA • Before start every process separate labelling done by SAP method that check and verified by QA. • Trained Operator • Type B cleaning done after every color change • Line Clearance done before the start of the activity. • Dedicated Operator for different activities. • Dedicated accessories are available for both					failure is possible				

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Procedure: 02 Products manufactured in same area of Softgel | **Quality Risk Assessment No.: ……**

S.No.	Item/Function	Potential Failure Mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current Control	Reference Document No.	S	O	D	Risk Priority Number (S x O x D)	Recommended action (If any)	Post Risk Evaluation			
												S	O	D	RPN
			noncompliance. • Failure (OOS) during Finished Product analysis as per specification. • Increase microbial count • Improper line clearance		the gelatine preparation equipment.										
5.	**Documentation & Data Control**	• Data Integrity • Formulation mix-up • Calculation Error	• Wrong batch entry • Wrong yield calculation	• Product failure	• Well Trained Operators & Supervisors • Separate BMR for every batch. • Every step Verified by QA	• SOP "Training of Employees" • SOP "Status Labelling"	**3**	**2**	**1**	**6** **Severity:** Calculation error causes serious effects **Occurrence:** There is always a possibility of failure **Detection:** Always detect failure in case of wrong entry, as already verified by QA	Not Applicable	NA	NA	NA	NA

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Procedure: 02 Products manufactured in same area of Softgel

Quality Risk Assessment No.: ……

S.No.	Item/Function	Potential Failure Mode	Potential Cause/Mechanism of Failure	Potential Effect of Failure	Current Control	Reference Document No.	S	O	D	Risk Priority Number (S x O x D)	Recommended action (If any)	Post Risk Evaluation			
												S	O	D	RPN
6.	**Medicament preparation Area**	• Medicament preparation for two different product in same area • Uncleaned equipment may lead to cross contamination • Intermixing • Cleaning • Line Clearance	• Variation in description of medicament • Failure during in process check • Cross Contamination. • Area Cleaning inappropriate. • Status labelling inappropriate • Similar Equipment used for different product. • Two different Batches process done by single person. • Different batches BMR handled by same persons.	• Loss the Identity of product. • Risk with respect to product Quality, Safety & Efficacy. • Product degradation or impact on product quality. • Non-Compliance of SOP/BMR • Market Complaint • Fail in Finished product specification	• Area cleaning to be done through batch to batch. • Before start every process separate labelling done by SAP method that check and verified by QA. • Trained Operator • Type B cleaning done after every product change • Line Clearance done before the start of the activity. • Dedicated Operator for different activities • Specific products are manufactured single. • Rinse & Swab samples are done.	• SOP "Line Clearance" • Cleaning SOP's • Specific BMR	**3**	**2**	**2**	**12** **Severity:** Product failure is always a serious concern **Occurrence:** Always a possibility **Detection:** Might detect failure in case of any cross contamination	Area to be separated.				

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Procedure: 02 Products manufactured in same area of Softgel										**Quality Risk Assessment No.: ……**					
S.No.	**Item/Function**	**Potential Failure Mode**	**Potential Cause/Mechanism of Failure**	**Potential Effect of Failure**	**Current Control**	**Reference Document No.**	**S**	**O**	**D**	**Risk Priority Number (S x O x D)**	**Recommended action (If any)**	**Post Risk Evaluation**			
												S	**O**	**D**	**RPN**
			• During manufacturing of two product one product is light & heat sensitive and another product is normal Condition • GMP noncompliance. • Non-compliance as per BMR/SOP. • Market complaint. • Failure (OOS) during Finished Product analysis as per specification. • Increase microbial count.		• Environment monitoring is done as per schedule. • Only General products are manufactured in parallel (Multivitamins)										
7.	**Manpower**	• Untrained Manpower	• Misinterpretation	• Batch mixing • Product failure	• Operators are well trained	• SOP "Training of Employees	**3**	**2**	**1**	**6** **Severity:** Batch mixing is always a serious problem **Occurrence:** The is always a	Not Applicable	NA	NA	NA	NA

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Procedure: 02 Products manufactured in same area of Softgel										**Quality Risk Assessment No.: ……**				
S.No.	**Item/Function**	**Potential Failure Mode**	**Potential Cause/Mechanism of Failure**	**Potential Effect of Failure**	**Current Control**	**Reference Document No.**	**S**	**O**	**D**	**Risk Priority Number (S x O x D)**	**Recommended action (If any)**	**Post Risk Evaluation**			
												S	**O**	**D**	**RPN**
										possibility of intermixing when 02 products are manufactured parallel in common place **Detection:** Detection is possible in case of intermixing, as all contents are identified & labelled.					
8.	**Cleaning procedures**	• Improper cleaning • Dirty equipment kept on hold	• Cross Contamination	• Batch failure	• Well trained Operators • Dirty equipment are cleaned immediately after use. • Line clearance before every new process.	• Cleaning SOP's • SOP No.: "Training of Employees • SOP No.: "Line Clearance"	**3**	**1**	**1**	**3** **Severity:** Improper cleaning of equipment & area can lead to a serious cross contamination problem **Occurrence:** No chance of occurrence as verified by QA during line clearance **Detection:** Improper cleaning can be easily detected visually	Not Applicable	NA	NA	NA	NA

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Procedure: 02 Products manufactured in same area of Softgel										**Quality Risk Assessment No.: ……**					
S.No.	**Item/Function**	**Potential Failure Mode**	**Potential Cause/Mechanism of Failure**	**Potential Effect of Failure**	**Current Control**	**Reference Document No.**	**S**	**O**	**D**	**Risk Priority Number (S x O x D)**	**Recommended action (If any)**	**Post Risk Evaluation**			
												S	**O**	**D**	**RPN**
9.	**Specific Environment**	• Light Sensitive & Heat sensitive	• Product got degraded	• Product failure	• Sodium Lamp is available for Light sensitive product • Sensitive product is manufactured under specific environment • Single batch is manufactured in case of sensitive product. • Line Clearance given after every change over.	BMR	**3**	**1**	**1**	**3** **Severity:** Sensitive product will get degraded **Occurrence:** No chance of occurrence as batches are taken after verification by QA **Detection:** Always detected	Not Applicable	NA	NA	NA	NA

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FMEA MATRIX

☆ Risk level is high in case 02 different products with different category are manufactured at a same time

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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:

Severity Ranking:

Severity Effect	Rating
No Effect	1
Moderate Effect	2
Serious Effect	3

Likelihood Occurrence Ranking:

Likelihood Occurrence	Rating
Unlikely	1
Possible	2
Almost Certain (Every time)	3

Detection Ranking:

Severity Effect	Rating
Always Detected	1
Might Detect Failure	2
Lack of detection control	3

Risk Priority Number (RPN)	Risk levels
Up to 6	Low
7-11	Medium
12 to ≤ 27	High

RPN = Severity x Occurrence x Detection

11.0 VERIFICATION OF ACTION PLAN:

All the action points as per QRA shall be monitored through CAPA system.

12.0 CONCLUSION:

On the basis of above assessment, it is concluded that there is high risk in manufacturing of different category products in same area at same time.

13.0 RECOMMENDATION:

On the basis of above conclusion, it is recommended to manufacture same category products (e.g. Multivitamins) at a time in same area. Different category products shall be manufactured once at a time and type-B cleaning shall be performed during changeover of product. Further the medicament area shall be modified & partition shall be made for suitability of manufacturing 02 products at a time.

14.0 DEVIATION FROM PRE DEFINED SPECIFICATION, IF ANY:

Deviations observed from the pre-defined procedures shall be addressed through SOP Titled **"Handling of Deviations".**

15.0 CHANGE CONTROL, IF ANY:

Any changes shall be done through SOP Titled, **"Change Management".**

16.0 ABBREVIATIONS:

FMEA : Failure Mode Effect Analysis

GMP : Good Manufacturing Practices

RPN : Risk Priority Number

RISK ANALYSIS STUDY FOR MANUFACTURING FACILITY OF GELATIN PREPARATION & MEDICAMENT PREPARATION

17.0 QRA APPROVAL:

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

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

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			