RISK ASSESSMENT PROTOCOL CUM REPORT FOR EXCIPIENT MANUFACTURER

Name of material:	**TRI – CALCIUM PHOSPHATE**
Name of manufacturer:	**XXXXX**
Manufacturing site address:	**XXXXXXX**

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1.0 TABLE OF CONTENT

2.0 APPROVAL:

The protocol cum report shall be prepare, review and, approved for execution by quality assurance; if any modification to this becomes necessary an addendum shall be prepared and duly approved by quality assurance.

Prepared By	**Name**	**Signature and Date**
Quality Assurance		
Reviewed By		
Quality Assurance		
Approved By		
Head - Quality Assurance		

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3.0 OBJECTIVE:

The objective of this protocol cum report is;

To evaluate the risk associated in the procurement of the excipient/s: **Tri – Calcium Phosphate** from **XXXX** (Manufacturing Site: **XXXXX**) and in inclusion in the approved vendor list and for continuous.

- Assessment of the associated quality and safety aspects in the procurement of excipient from the said excipient manufacturer.
- To evaluate the criticality of the risk and the classification of the risk (viz; Low, Medium, and High) associated with the procurement of Excipient from the said Manufacturer.
- To establish the need of Physical audit in the case the associated risk is high in the case of procurement of the said excipient from the said manufacturer and closure of audit report prior to inclusion in the approved vendor list.
- Ongoing Risk review during the supply of the said excipient from the said excipient manufacturer.

4.0 SCOPE:

The scope of this protocol cum report is applicable to evaluate the risk associated in the procurement of the excipient from the said Excipient Manufacturer and to establish the needs of physical audit (if required) and closure of audit report prior to inclusion of the excipient manufacturer in the approved vendor list.

5.0 RESPONSIBILITY:

5.1 Authorized designee of Research and Development shall be responsible to provide the documents of technology transfer to the authorized designee of quality assurance prior for effective evaluation of requirements prior to initiate the manufacturing of the products at the site.

5.2 Head Quality Assurance/Designee shall be responsible for the evaluation of excipient manufacturer mentioned in the respective technology transfer document.

5.3 Head Quality Assurance shall establish the need of physical audit of the excipient manufacturer and closure of audit based on the outcome prior to inclusion in the approved vendor list (if required).

6.0 METHODOLOGY:

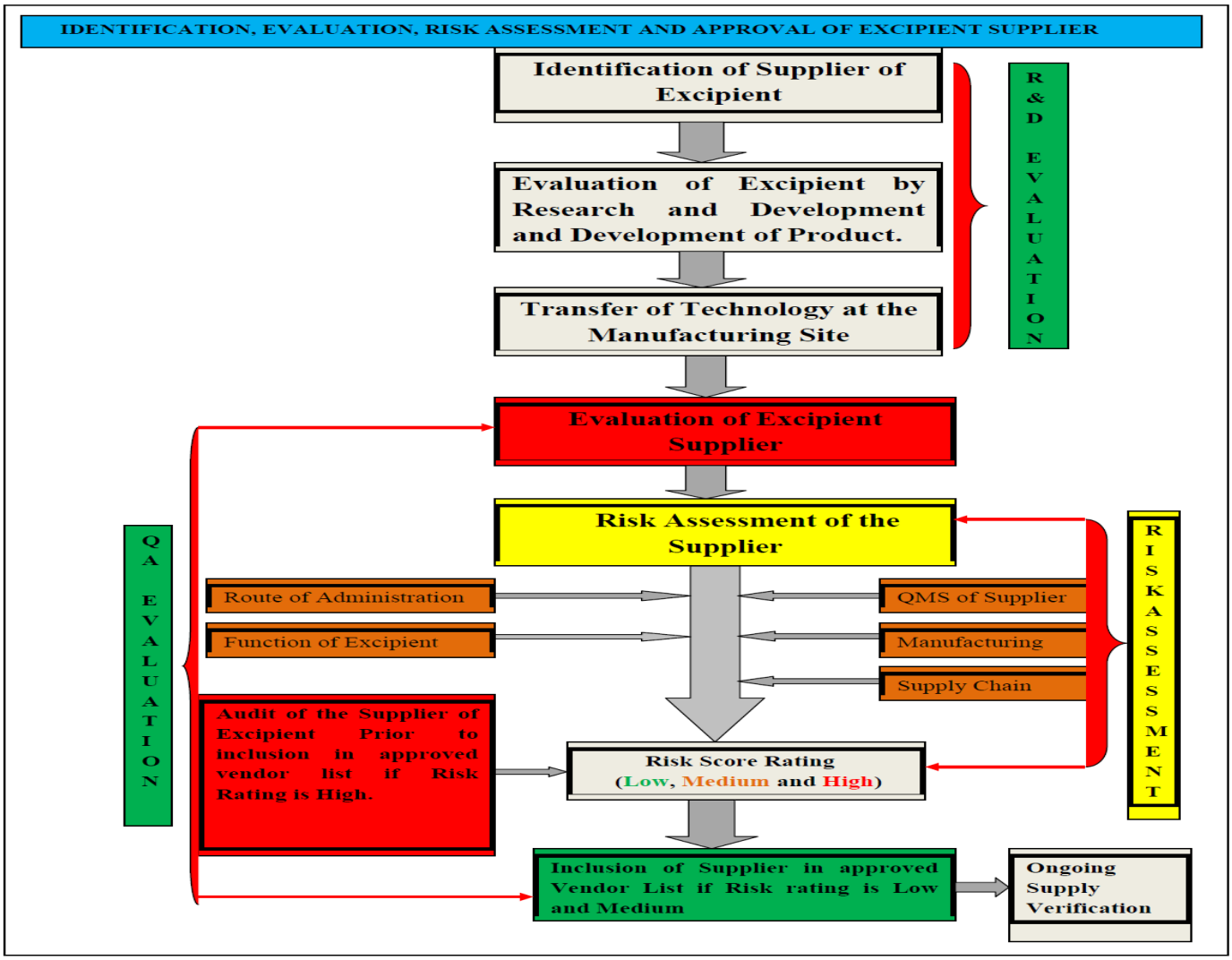
6.1 Authorized designee of Quality Assurance shall send the assessment questionnaires to the respective excipient manufacturer mentioned in the technology transfer of the respective product.

6.2 Authorized designee of Quality Assurance shall evaluate the assessment questionnaires and related documents received from the said excipient manufacturer.

6.3 Authorized designee of the quality assurance shall evaluate the associated risk with the excipient manufacturer based on the received assessment questionnaire and the related documents.

6.4 Authorized designee of the Quality Assurance shall evaluate the risk by considering the below mentioned aspects (but not limited to) after the receipt of assessment questionnaire and the related documents; the mentioned basic flow shall also describe the approach of assessment of excipient manufacturer;

- Route of Administration of Excipient.
- Function of Excipient.
- QMS established at the manufacturing facility of Excipient Manufacturer.
- Manufacturing Process.
- Supply Chain.



6.5 On the basis of the risk assessment authorized designee of quality assurance shall establish the risk associated with the excipient manufacturer and shall establish the need of physical audit (if required), prior to inclusion of the excipient manufacturer in the approved vendor list.

6.6 If the audit the required the said manufacturer shall be physically audited and the audit shall be closed upon the satisfactory review of CAPA provided by the excipient manufacturer and the excipient manufacturer shall be included in the approved vendor list.

6.7 Ongoing risk reviews of excipient manufacturer shall be done at the time of preparation of annual product quality review and on the basis of evaluation in the annual product quality review the evaluation of the excipient manufacturer (not evaluated by audit) shall be carried out (if required). In the ongoing risk review the mentioned parameter shall be evaluated (but not limited to);

- Number of defects on received batch of Excipients.
- Type/Severity of defects on Excipients.

- Monitoring of Excipients quality.
- Loss of relevant quality system and/or GMP certification by Excipients manufacturer.
- Observed organizational, procedural or technical/process changes at the Excipients manufacturer.

6.8 The risk shall be evaluated by Failure Mode Effects Analysis (FMEA) risk assessment tool. FMEA is a systematic method of identifying and preventing process problems before they occur.

6.9 All potential failure modes associated shall be evaluated based on the severity, probability and detectability to decide the RPN (Risk priority number) and classification of risk into low, medium and high.

6.10 The rating on severity, probability and detectability shall be as per the below mentioned pattern;

Severity:

Value	Description
1	Irrelevant
3	Important
5	Disastrous

Probability:

Value	Description
1	An unlikely probability of occurrence
3	An occasional probability of occurrence
5	A high probability of occurrence

Detectability:

Value	Description
1	High degree of delectability
3	Likely to detect
5	Low or no detectability

6.11 On the basis of the risk the risk priority number shall be calculated.

6.12 Calculation Of Risk Priority Number:

The composite risk for each unit operation step of its three individual component ratings: severity, probability and detectability. This composite risk is called as risk priority number (RPN).

RPN = S x P x D

7.0 ACCEPTANCE CRITERIA:

Excipient Manufacturer shall be incorporated in the approved vendor list based on the risk priority number. Excipient manufacturer having risk rating of 75 and 125 shall be incorporated in the approved vendor list only after the physical audit, successful evaluation of compliance and closure of audit report.

***RPN rating**	**Risk category**
75 and 125	High
27 and 45	Medium
1, 3, 5, 9, 15 and 25	Low

*The numbers has been assigned based on the different combination of values of severity, probability and detectability.

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8.0 RISK ASSESSMENT:

S.No.	Perceived Failure Mode	Potential Effect (Process/ End users or consequences)	S	Potential causes	P	Current control measures	D	RPN (SXPXD)	RPN category
Effective Management of Quality Management System by Excipient Manufacturer									
1.	Failure in cGMP Compliance in the Manufacturing of Excipient. No GMP certification of the excipient manufacturer from the FDA/ISO or equivalent authority. Failure in the change Management. Failure in the Management of Incident and Deviation. Failure in Management of OOS and OOT. Failure in the effective management of risk involved at different stages from manufacturing to dispatch.	Product may not meet predefined specification. Cross contamination of the product. Finished product may not comply specifications leading with product failures. Inadequate changes, incident & deviation may lead to contamination / product failure. Inadequate OOS / OOT management may lead to data integrity. Finished product	5	Manufacturers not follow cGMP. Manufacturer not aware about change management system. Manufacturer not aware about incident, Deviation, OOS & OOT management system. Persons not trained about QMS system. Manufacturers not have accessories to avoid risk during different stages of manufacturing to dispatch.	3	Vendor evaluated through vendor questionnaires prior to introduce in approved vendor list & supply of material from manufacturer In the evaluation it was found that all the Quality management to avoid the failures mentioned in the perceived failure is being maintained by the Manufacturer. In the evaluation it is noted that the XXX Pharma maintains the GMP according to IPEC-PQG (2006). XXXX is ISO 9001:2008 certified. The site is authorized by FDA, Gujarat.	1	15	Minor

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S.No.	Perceived Failure Mode	Potential Effect (Process/ End users or consequences)	S	Potential causes	P	Current control measures	D	RPN (SXPXD)	RPN category
		specification out of acceptance criteria / OOS /OOT. Stability failure or OOS /OOT in stability studies.							
Management of Supply Chain:									
2.	**Material Procured from Direct Source;** Failure in Management of storage of the material during the shipment of material. Material Not Supplied in the intact drum with proper seal. Material supplied in the damaged drum and in open transport carriages. Procedure of sending Relevant Document Like COA etc. delivery Challan etc. is not implemented at the manufacturer end. Failure in the procurement	Product may not meet predefined specification. Inadequate storage/ Handling of material. Finished product may not comply specifications leading with product failures.	5	Manufacturers not have facility & procedure for storage of material according to requirement. Manufacturers not have procedure for packing of material. Persons not trained about packing procedure. Manufacturers not have procedure of documentation.	3	Nitika is certified for ISO 9001: 2008 standard for manufacturing and marketing of Bulk Drugs (API/Non – API) and food grade products calcium, potassium, ferrous and phosphates and maintains all requirements to avoid the failures mention in the perceived failure mode and the compliance of the same shall be verified at the time of receipt of material. XXX Pharma is directly supplying the materials and maintains the required storage condition.	1	15	Minor

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S.No.	Perceived Failure Mode	Potential Effect (Process/ End users or consequences)	S	Potential causes	P	Current control measures	D	RPN (SXPXD)	RPN category
	of material directly from the manufacturer of excipient. **Material Procured from indirect source;** Material is procured from the trader of the material. Trader of the material supplies the material into the repackaged drum. Trader of the material performed the repackaging of material in the uncontrolled condition. Trader of the material does not maintain the storage condition at the warehouse.	Inadequate storage/ Handling of material. Cross contamination of material. Manufacturer doesn't have facility for storage of material.		Manufacturer doesn't have facility & procedure for storage of material according to requirement. Untrained persons.					
Manufacturing Process of Excipient:									
03	**Raw Material Origin:** Raw Material used in the manufacturing of excipients derived from the Animal Origin. Failure in Management of TSE/BSE of the material involved in the	Product may not meet predefined specification. Cross contamination of the product.	5	No procedure for handling of TSE/BSE. Untrained persons.	3	TSE/BSE Declaration of the Material is available which indicates that Tri Calcium Phosphate is TSE/BSE free. XXXXX Pharma maintains all the procedures to avoid the failures mentioned in the	1	15	Minor

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S.No.	Perceived Failure Mode	Potential Effect (Process/ End users or consequences)	S	Potential causes	P	Current control measures	D	RPN (SXPXD)	RPN category
	manufacturing of excipient. **Site Organization:** Excipient Manufacturer does not have dedicated site for the manufacturing of Excipient. **Manufacturing Equipment and Process;** Cleaning and sanitization of equipment and area is not in place between the changeovers for the manufacturing of different material. Equipment logs and the preventive maintenance are not in the place. Manufacturing of Excipient is not being carried out in controlled condition. The equipment and utilities are not qualified. Utilities like water/air are not monitored on a periodic	Mix-up & Cross contamination of the product. Unwanted breakdowns. Delay in manufacturing activity / supply of materials. Cross contamination of materials. Failure of product as per product specification.		Dedicated facility / equipment not available. No procedure available. Untrained persons. Inadequate / No information of manufacturing process. No procedure for recording of manufacturing details. No accessories for preventive		perceived failure mode. Cleaning process is validated and both rinse and swab samples are considered for verification. The production Site is involved in manufacturing of bulk drugs for pharmaceuticals and food grade. Tri Calcium Phosphate, Manufactured by XXXXX Pharma is compliant to BP and USP requirement. The relevant batch documentation is maintained by the Manufacturer as per in house policy for retention of documents.			

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S.No.	Perceived Failure Mode	Potential Effect (Process/ End users or consequences)	S	Potential causes	P	Current control measures	D	RPN (SXPXD)	RPN category
	basis. Manufacturer does not maintain the manufacturing record. Deviations are not being maintained at the time of deviation of process parameters and environmental condition.	Cross contamination of material. Shutdown of area / delay in supply of materials. Inadequate manufacturing process due to lacking in standard manufacturing instructions. Inadequate CAPA management & QMS system.		maintenance of equipments. Untrained persons for preventive maintenance of equipments. Inadequate / insufficient man power for preventive maintenance. No procedure for area, equipment & utility qualification. Format of batch manufacturing record not available. No procedure for handling of deviation. Untrained persons for handling of deviation.		Traceability of the products maintained as per batch documentation. Master Validation and Calibration Planner is in place to conduct and track calibration, Qualification / Validation. A CoA is sent to customer for each lot number.			
Route of Administration of Excipient:									
04	The excipients used in the individual dose are more	Inadequate formulation of	5	No procedure for evaluation of R&D	3	The material is used in the Tablet formulation.	1	15	Minor

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S.No.	Perceived Failure Mode	Potential Effect (Process/ End users or consequences)	S	Potential causes	P	Current control measures	D	RPN (SXPXD)	RPN category
	that the recommended daily dose of the excipient in the case of oral dosage of Tablet/Capsule and Pellets.	product.		batches.		Stability data of Product available which indicate that the excipient does not impose any adverse effect in formulation/impurity level.			
Function of Excipient:									
05	Excipient impacts directly on the manufacturing process/bioavailability and the stability of the drug product to be manufactured.	Product may not meet predefined specification. Finished product specification out of acceptance criteria / OOS /OOT. Stability failure or OOS /OOT in stability studies.	5	No procedure for evaluation of R&D batches. No procedure for evaluation of stability data.	3	Stability of Product in which the Tri Calcium Phosphate is used, is available and data indicate that excipient does not impose any adverse impact on the excipient.	1	15	Minor

9.0 DEVIATION:

No Deviation has been observed during the risk evaluation of the quality management system of Tri Calcium Phosphate manufacturer.

10.0 SUMMARY AND CONCLUSION:

On the basis of Risk Assessment it is concluded that XXXXX Pharma maintains the required quality management system for the manufacturing of Tri Calcium Phosphate and used the validated system. Manufacturer has provided all the required information for evaluation. Hence on the basis of risk assessment it is concluded that the manufacture can be included in the approved vendor list. Ongoing quality evaluation shall be carried out during receipt of supply and if any failure in supply and formulation observed, the said manufacturer shall be audited.