PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

FAILURE MODE, EFFECTS AND CRITICALITY ANALYSIS

Unit	**:**		**Department**	**:**	Quality Assurance	**Date**	**:**	
PRODUCT	**:**	Risk Assessment on the Control of Nitrosamine Impurities in product Pantoprazole for injection				**Team leader**	**:**	
FMECA no.	**:**					**Team Members**	**:**	
FMECA subject	**:**	To evaluate the risk of Nitrosamine Impurities in finished product Pantoprazole for injection						

Following scale applied during risk assessment .

S.No.	Severity			Occurrence	Detection Control
1	No effect on output	Predicted to have no impact on quality of the product.	No patient harm, (i.e. functional failure), or perceived quality discourages patient from using.	Unlikely or unexpected to happen	Always detected – Failure can and will be detected in all causes (monitoring, technical solution available)
2	Minor effect on output	Predicted to have minor impact on quality of the product but quality may be within specifications.	Result in temporary injury or impairment not requiring medical intervention.	Very rare – Expected to happen infrequently	Will detect failure – Failure will normally be detected (manual control, routine work)
3	Moderate effect on output	Predicted to cause minor impact on quality. Failure to meet the normal trend range.	Medical intervention required, but permanent injury is unlikely	Possible – Expected to happen in a low frequency	Might detect failure – Failure may be overseen (manual control, spot checks)
4	Serious effect on output	Predicted to cause significant impact on quality. Impact can lead to situations like recall.	Serious deterioration of health, which could possibly be permanent	Likely – Expected to happen in a High frequency	Almost certain not to detect failure – failure very likely to be overlooked, hence not detected (no technical solution, no manual control
5	Hazardous effect on output	Predicted to cause severe impact to quality and safety (Can cause death or a permanent injury/ disability to patient).	Predicted to cause life threatening illness or irreversible injury.	Almost certain (every time) – Expected to happen regularly	Lack of detection control- No chances of detection

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Risk Assessment							**Risk Reduction**							
S.No.	**Potential Failure Mode**	**Potential Effect (Process / end Users) or Consequence**	**Severity (S)**	**Current Control Measures**	**Detection (D)**	**Initial calculus (S X D)**	**Action Plan**	**Responsibility/ Target Completion Date**	**Action Taken**	**Close out date**	**Severity (S)**	**Detectability (D)**	**Revised Initial Calculus (S**	**Remark**
A.) Raw Materials and Primary Packing Materials:														
1.0	Potential source of nitrosamine from raw materials and primary packing materials.	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• Materials are being procured from approved vendor / manufacturer / supplier. • Vendor approval procedure is in place as per SOP. The vendors are being selected, evaluated and approved as per SOP. • During vendor qualification all the certifications like TSE / BSE, Elementary Impurities information etc. are being verified as per Vendor Assessment Questionnaire. The vendors are re-evaluated as per frequency defined in SOP.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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A.) Raw Materials and Primary Packing Materials:														
1.0	Continued…	Continued …	5	• SOP is available for evaluation of Nitrosamine impurities. • All the raw materials (API) used in the manufacturing of said product are checked and verified for presence of Nitrosamine impurities based on functional group (Nitro/Nitrile/Amino) in their chemical formula. (Refer attached annexure). • All the materials are analysed and released after satisfactory analytical results for further batch manufacturing and packing. • Nitrosamine free declarations are available of API, and primary packing materials involved in the manufacturing of the said product.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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B.) Receipt of Materials														
2.0	Potential source of nitrosamine during receipt of raw & packing materials	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• All the materials are being procured from approved supplier. • SOP is available for receipt of material at unit. At the time of receipt, all the raw material & packing material consignments are checked for cleanliness of container externally and any damage to the container by store officer. If any observation noticed during receipt, same is intimated to Quality Assurance for further necessary action.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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B.) Receipt of Materials														
2.0	Continued…	Continued …	5	• During receipt, the material attributes like material name, manufacturer name & address, quantity against PO etc are being verified for originality and authenticity of supplied material by approved vendor. • Persons are trained to carry out the receipt activity. • Balances are daily verified, calibrated as per SOP for material quantity verification. • All the materials are being stored in quarantine area after dedusting of the material containers. All the quarantine areas are qualified for storage condition as per the specific material requirement.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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C.) Sampling and Dispensing of Materials														
3.1	Improper Sampling of Materials	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• SOP entitled "Sampling" is available for Sampling of API, excipient and Packaging Materials. • Sampling area is cleaned and line clearance taken prior to sampling as per SOP. • The sampling accessories are stored in dedicated area. The sampling accessories are ensured that they do not have any crevices, or burrs and their surface is smooth and properly finished. • The sampling accessories are cleaned and dried as per SOP. • Trained personnel are involved in sampling activity.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
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C.) Sampling and Dispensing of Materials														
3.1	Continued…	Continued …	5	• The calibration status of balance is checked prior to sampling. • The sampling accessories cleaning validation is performed as per SOP to ensure effectiveness of cleaning procedure to remove residue of drug substance as well as cleaning agent used. • Material and man movements are controlled through a pass box and air lock respectively in sampling area. • The entry/exit procedure is followed as SOP in sampling area.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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C.) Sampling and Dispensing of Materials														
3.2	Improper dispensing of materials	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• Dispensing of API , excipient and packing material and dispensing area is cleaned and line clearance taken as per SOP. • The dispensing accessories such as scoops, spoons, spatulas etc. are cleaned as per SOP & they are ensured for cleanliness prior to dispensing. • Weighing of the dispensed quantity is done by stores officer and counter checked by production officer.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
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C.) Sampling and Dispensing of Materials														
3.2	Continued…	Continued …	5	• Trained personnel are involved in dispensing activity. • API's are dispensed only after completion of dispensing of excipients. • Material and man movements are controlled through a pass box and air lock respectively in dispensing area. • The cleaning validation of the dispensing accessories performed as per SOP. • The entry/exit procedure is followed as SOP in dispensing area. • The balances used are daily verified and calibrated monthly as per SOP. • SOP available for status labelling.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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C.) Sampling and Dispensing of Materials														
3.3	Inappropriate facility for sampling and dispensing area.	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• Sampling/Dispensing cubicles are available. This individual area is provided with separate man and material entry. • The sampling & dispensing activity is performed under reverse laminar air flow for raw materials and unidirectional air flow for packing materials. • Dedicated air handling unit (AHU) available. • AHU system is qualified and re-qualification is performed as per validation master plan (VMP). • Planned preventive maintenance (PPM) for AHU is carried out as per schedule.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
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C.) Sampling and Dispensing of Materials														
3.3	Continued…	Continued …	5	• Temperature and Relative Humidity monitored as per SOP. • Alarm system is available to highlight AHU malfunctioning. • BMS system is qualified and periodic validation done. • BMS sensors are calibrated periodically by external agency. • SOP is available for handling of power failure.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.1	Inadequate facility	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• Dedicated and adequate facility is available for storage of raw material, packing material and each intermediate stage of bulk and finished product. • Manufacturing facility is equipped with HVAC system and being operated as per the product manufacturing requirements. • All the HVAC are qualified as per SOP for HVAC/RLAF/LAF/Bio Safety Cabinet/Dynamic Pass Box Revalidation, SOP and SOP Periodic planned preventive maintenance program for HVAC systems is in place. • All HVAC systems are operated through BMS. • Alarm annunciation systems are in place for differential pressure.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.1	Continued…	Continued …	5	• Adequate air locks, such as personnel air locks (PAL) and material air locks (MAL), change rooms and passages are provided to protect passage between different cleanliness conditions. • Separate HVAC systems are provided for each of the process area/cubicle • Clean air supplied is filtered through 0.3µ HEPA filters • Supply as well as extract air systems as appropriate are provided. • All process area are having positive pressure gradient with connected corridor. • Biometric access systems are provided in the area wherever applicable to control man movement as per SOP.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.1	Continued…	Continued …	5	• HVAC systems are operated in sequential manner such that high pressure area are started first, then low pressure area and reverse sequence is followed during stoppage which ensures prevention of cross contamination. • Interlocks are provided for sequence of HVAC operation. • SOP is available for entry / Exit procedure through main change room and for entry / Exit procedure through secondary change room.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.1	Continued…	Continued …	5	• Separate area is available for storage of cleaned, dried and duly labelled equipment • Dust extraction systems are provided wherever possibility of dust generation. • DG power backup is available in case of main power source failure. • The manufacturing processes are carried out in closed system. • Temperature and relative humidity requirement for the product manufacturing is as per designed facility. • Only one product is processed at a time in manufacturing area.. • The area and equipment's are cleaned as per respective procedure. Line clearance is checked by production and certified by Quality Assurance before starting the next product.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.2	Inadequate equipment	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• As per the available facility all equipment's used in the processing of the product are designed with cGMP requirements. • Qualified Equipment is available for manufacturing w.r.t its capacity, design,& change parts . SOP is available for qualification of equipment. • Person are trained to operate the equipment. • Process validation SOP is available to demonstrate the equipment capability and reproducibility w.r.t. product process. • All product contact surfaces are inert, non-additive or non-adsorptive. • Periodic preventive maintenance for all equipment is in place. • Validated cleaning procedures are used to clean the equipment.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.3	Inadequate manufacturing of the batches	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• Product specific batch manufacturing records for Pantoprazole for injection available to carry out manufacturing operation. • Standard Operating procedures are available for operation, cleaning and line clearance of respective equipment's available in approved master batch manufacturing record. • Persons are trained to carry out the manufacturing activity. • Multiple checks are available by production & Quality assurance for the assurance of manufacturing activity is in state of controls. • Samples are being sent to QC for analysis as per the approved specification.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.3	Continued..	Continued…	5	• Batches are being released only after compliance to analytical results as per approved specification. • All the raw materials used in the manufacturing of the said product are checked and verified for presence of Nitrosamine impurities based on vendor declaration. • The process flow for the manufacturing of the said product evaluated and there is no possibility for generation of nitrosamines.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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D.) Manufacturing & Packing Process:														
4.4	Inadequate packing of the batches	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• All the primary packaging materials used in the packaging of the said product are checked and verified for presence of Nitrosamine impurities based on vendor declaration. • Product specific batch packing records available to carry out the packing activity. • Standard Operating procedures are available for operation, cleaning and line clearance of respective equipment's available in approved master batch packing record. • Batch packing activity is done at specified environmental conditions. • Persons are trained to carry out the packing activity.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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D.) Manufacturing & Packing Process:														
4.4	Continued..	Continued…	5	• Multiple checks are available by packing & Quality assurance for the assurance of packing activity is in state of controls. • Batches are being released only after compliance to analytical results as per approved specification.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

FAILURE MODE, EFFECTS AND CRITICALITY ANALYSIS

Unit	**:**		**Department**	**:**	Quality Assurance	**Date**	**:**	
PRODUCT	**:**	Risk Assessment on the Control of Nitrosamine Impurities in product Pantoprazole for injection				**Team leader**	**:**	
FMECA no.	**:**					**Team Members**	**:**	
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E.) Cleaning Procedure														
5.0	Inadequate Cleaning of equipment and area during processing of the product.	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • May lead to generate nitrosamine impurity • Product recall	5	• All equipment's and area cleaning procedure are in place. • Cleaning is done as per respective equipment and area cleaning procedure. • SOP available for cleaning validation is available for establishment of worst-case product. Worst case product will be selected in following manner: a.) Worst Case Products on basis of solubility. b.) Worst Case product on basis of least therapeutic dose (Potency). c.) Worst Case product on basis of toxicity (Least PDE value).	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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E.) Cleaning Procedure														
5.0	Continued..	• Continued…	5	• Cleaning procedures for each equipment / area are established based on cleaning validation. • For each new product in the facility, the product is evaluated for its solubility in water, potency and toxicity. • In case any new product is introduced in facility, Risk assessment to be performed for evaluation of worst-case product for cleaning validation. If the product is identified to be a worst case three successful validation studies, • Periodic verification for cleaned and to be cleaned equipment performed.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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E.) Cleaning Procedure														
5.0	Continued..	• Continued…	5	• Cleaning agents are compatible with product contact surfaces are used for cleaning. • Cleaning agent used for cleaning is validated and procured from approved vendor. • Persons are trained to carry out the cleaning activity. • Usage, cleaning and line clearance record is maintained of all area, equipment's and accessories.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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F.) Cleaning Agent, Water, Compressed Air, Nitrogen gas, Inks														
6.0	Potential source of nitrosamine from cleaning agent, water, compressed air, nitrogen gas, inks	• Risk on Patient health and Safety. • Cross Contamination • Impact on product quality • Product recall	5	• Water is a cleaning agent used in cleaning of equipment used in manufacturing of the said product. • Cleaning agent water used, thus no risk for external contamination by using the cleaning agent.	2	10	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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F.) Cleaning Agent, Water, Compressed Air, Nitrogen gas, Inks														
6.0	Continued..	Continued…	5	• Cleaning validation is available and confirms that all cleaning agent residues can be removed below the defined acceptance criteria.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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F.) Cleaning Agent, Water, Compressed Air, Nitrogen gas, Inks														
6.0	Continued..	• Continued…	5	• Purified water is obtained by suitable process. Purified water generation system is designed, constructed, installed, maintained and validated to ensure consistent and reliable production of purified water which meets acceptable chemical and microbial quality. • The water purification plant is qualified as per Current GMP standards. • None of active agents like amines and nitrosating groups are used in generating, cleaning/sanitisation process of purified water. • The water quality is routinely monitored and fulfils current compendial specifications.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk Assessment							**Risk Reduction**							

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FAILURE MODE, EFFECTS AND CRITICALITY ANALYSIS

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F.) Cleaning Agent, Water, Compressed Air, Nitrogen gas, Inks														
6.0	Continued..	Continued…	5	• The purified water is analysed for nitrates and nitrites and there is no possibility for generation of nitrosamines. • No chemicals are used in the production of Nitrogen Gas and Compressed air and no chemical reaction is taking place between amines and Nitro sating group (Nitrite). Further there is no recycled / recovered solvents, catalysts, reagents are used during production of Nitrogen Gas and Compressed air. Hence chances of the formation of Nitrosamine impurities are very low or negligible.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

CONCLUSION (Risk Assessment): The initial calculus (RPN rating) of potential failure mode is less than 20, hence no action plan required for risk reduction.

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QUALITY ASSURANCE DEPARTMENT

FAILURE MODE, EFFECTS AND CRITICALITY ANALYSIS

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Sr. No.	RPN rating	Category
1	20 or 25 (Initial Calculus)	Critical

CONCLUSION (Risk Assessment):

Compiled By / Date: _____
(FMECA Team)

Approved By / Date: _____
(Head Unit Quality Assurance)

Noted By / Date: _____
(Unit Head)

CONCLUSION (Risk Reduction):

Compiled By/ Date: _____
(FMECA Team)

Approved By/ Date: _____
(Head Unit Quality Assurance)

Noted By/ Date: _____
(Unit Head