



## DRAFT WORKING DOCUMENT FOR COMMENTS:

# WHO GMP for excipients used in pharmaceutical products - Appendix 1: Risk Management in the production and control of excipients used in pharmaceutical products.

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## SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.945:

## WHO Good Manufacturing Practices for excipients used in pharmaceutical products

### Appendix 1: Risk Management in the production and control of excipients used in pharmaceutical products.

Description of Activity	Date
Preparation of first draft working document.	December 2023
Review and finalization of the first draft working document with an informal drafting group.	February 2024
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	April 2024
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	May – June 2024
Discussion of the feedback received on the working document in a virtual meeting with an informal consultation group.	June – July 2024
Preparation of a working document for discussion and possible adoption by the ECSPP	August – September 2024
Presentation to the Fifty-seventh meeting of the ECSPP.	October 2024
Any other follow-up action as required.	

## Appendix 1

# Risk Management in the production and control of excipients used in pharmaceutical products

## 1. Introduction

1.1. The WHO Guideline, *Good Manufacturing Practices for excipients used in pharmaceutical products* requires the application of risk management principles in the production and control of these excipients.

1.2. It is essential that manufacturers of these excipients identify and assess the risks associated with the production and control, packaging, storage, re-packaging and distribution of excipients. This will enable manufacturers, packers and distributors to identify and to establish, implement and maintain controls as part of the quality system, to ensure the quality, safety and purity of excipients.

1.3. It may further assist manufacturers to identify for example:

- whether separate, dedicated facilities are required for certain excipients;
- whether premises, equipment, instruments and utilities are suitable for their intended use in production and control of excipients;
- what level and scope of qualification and validation is required;
- whether there are any possible sources of contamination and cross-contamination – including impurities; and
- what scope of documentation is required for the management of production and control of excipients.

1.4. The extent and application of risk assessment may be beyond the above-mentioned examples to ensure continuous improvement in the facility.

## 2. Scope

This document provides guidance to e.g. manufacturers, packers, and distributors of excipients used in pharmaceutical products, to identify risks and harms that may have a negative impact on the production, control, quality and purity of the excipient.

## 3. Risk identification and risk assessment

3.1. There should be a document, such as a risk plan or standard operating procedure, that describes the policy, approach and process of risk identification and risk assessment.

3.2. The risk assessment should be performed in accordance with the principles described in guidelines such as WHO GxP and ICH.

3.3. A suitable, appropriate risk assessment tool should be used by a multidisciplinary team when performing the risk assessment. Failure Mode Effect Analysis is an example of such a frequently used tool.

3.4. Although a quantitative or qualitative analysis can be done, quantitative assessments are recommended.

3.5. The risk assessment should be thorough, comprehensive and appropriately documented. It should cover a variety of aspects including raw materials, packaging materials, processing steps, solvents, equipment, utilities, environment, storage, distribution, intended use of the excipient, and the dosage form of the finished pharmaceutical product in which it may be used.

3.6. A list of the potential risks or harms (such as biological, chemical and physical) which may be introduced or increased in each area should be identified and assessed.

3.7. In performing the risk assessment, the following basic questions (listed as examples), should be addressed:

- What might go wrong?

The materials, equipment, utilities or excipient (finished product) may be contaminated. The contaminants may be hazardous or are sensitising – and may be carried over into another product causing possible contamination. This may in turn be result in an adulterated product, or may be harmful to patients consuming a pharmaceutical product that is contaminated with a material containing traces of such a substance.

- What is the nature of possible risks?

The contaminants or material may be hazardous or poisonous and contaminate other materials (e.g. excipients, APIs) or pharmaceutical products.

- What is the probability of their occurrence?

Considering the chemical structure and manufacturing process, as well as storage and distribution, it may be possible that materials can be contaminated, substituted or mixed, and may result in contaminants and impurities being formed and be present in such material.

- Is it possible to detect them?

Contaminants, impurities and traces or residues in materials, or on surfaces of equipment, or in the environment, or in solvents, water and carrier material may be difficult to remove. In addition, they may be difficult to analyse and quantify as appropriate analytical procedures, which are sensitive, selective and validated are available.

- What are the consequences (the severity)?

Some impurities, contaminants may be carcinogenic, teratogenic.

## **4. Individual excipient risk assessment**

- 4.1. Risk assessment should be done for every excipient produced. A checklist may be prepared and used to identify and assess risks and harms.

4.2. In assessing the risk, consideration should be given to the raw materials used, solvents used (fresh and recovered); premises, equipment, water, environment and any other possible impacting factor.

4.3. Consideration should be given to the possible toxicity of the excipient (e.g. when contaminated), the risk of the excipient being contaminated or adulterated, cleanability of equipment, impurities and degradation where applicable.

4.4. The risk of contaminated solvents used in the synthesis should be considered.

4.5. The risk of formation of impurities should be assessed.

## **5. Collective excipient production assessment**

In addition to individual excipient risk assessment as described above, where several excipients are produced or packed in the same facility, the risk of contamination and cross contamination should be identified and assessed. In particular, where a risk or harm had been identified in one or more excipients handled in the same facility or common equipment chains, the risk of cross-contamination should be assessed.

## **6. Nitrosamine contamination**

6.1. The risk of the formation of nitrosamine formation or contamination should be identified and assessed. For example, nitrite in water used in production and present in the environment, packaging materials and ink should be considered.

## **7. Example**

7.1. Risk statement: Are the premises appropriately designed, located and maintained for the manufacture of excipients used in pharmaceutical products?

Area	Failure Mode		Effect	Risk			
	Primary failure	Secondary and tertiary failure(s)		S	O	D	RPN
Premises	Design	Old design with areas not dedicated to steps of manufacture	Where different steps of production taking place, increased risk of residue, cross-contamination.				
	Layout	Lacks space	Increased risk of error; May restrict movement; May impact on storage; May impact on cleaning.				
		Storage of material	Insufficient segregation; Increased risk of mix-ups; Impact on cleaning.				
		Placement of equipment	Insufficient segregation; Increased risk of error in sequence of steps; Impact on cleaning.				
		Material flow					
		Personnel flow					
	Location	Access					
		Services					
	Adapted	Additional rooms added					
		Extended utilities					
	Construction	Materials of construction	Not smooth; Adsorb, absorb.				
		Cleanability	Residue remaining.				
		Recesses	Accumulation of dirt, dust, residue.				
	Maintenance	No SOP or program					
	Cleaning	No SOP No program	No standard manner of cleaning resulting in risk of carry over, contamination.				
	Water	Use potable water	Potable water may contain nitrate and be a source of contamination (formation of nitrosamine).				
	Environment	Insufficient HVAC	Air may contain nitrate and nitrite resulting in reaction with amines (formation of nitrosamine).				

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172 7.2. Risk statement: Are pieces of equipment appropriately designed, located and maintained for  
 173 the manufacture of excipients used in pharmaceutical products?

Equipment	
Design	Residue accumulate; Access to all surfaces restricted; Inappropriate design but still being used as there is no alternative on site and primarily used for other excipients – risk of contamination.
Location	Equipment located in unsuitable location in facility; Located in unsuitable environment; Located in areas where other materials or products are produced; Inappropriate location with restricted access for use and cleaning.
MOC	Not smooth and impervious; Absorb and adsorb material; Not easily cleanable; May result in risk of cross-contamination.

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175 7.3. Risk statement: Are the materials used in the production of the excipient of appropriate  
 176 quality and purity, or is there a risk of formation of impurities and undesired contaminants  
 177 that may be present in pharmaceutical products?

Materials	
Raw material	Contains nitrite or nitrate; No supplier qualification; Obtain through re-packer, agent; May be contaminated; Sampling plan and sampling procedure inappropriate; Sampling area may result in contamination; Storage of materials inappropriately may result in contamination and interaction; Containers used not appropriate, not sealed; Re-packaging taking place; Certificate of analysis not original, or not available.
Solvent	Fresh or recovered solvent are used, but are not of appropriate quality / purity; May result in contamination of material with unwanted reaction and formation of nitrosamine.

178



- 179 7.4. Risk statement: Are the utilities appropriately designed, located, maintained and controlled to  
 180 prevent contamination of material, and prevent the risk of the formation of impurities and  
 181 contaminants?

Utilities	
Water	Inappropriate water purification; Result in water containing nitrite / nitrates; May interact with amino groups in materials in process resulting in nitrosamine contamination.
Compressed air and environmental air	Inappropriate purification; Result in air containing nitrite / nitrates; May interact with amino groups in materials in process resulting in nitrosamine contamination.
Nitrogen	

- 182  
 183 7.5. Risk statement: Are the personnel experienced, appropriately qualified and trained to ensure  
 184 that their actions and conduct do not present a risk of contamination of materials?

Personnel	
Education	Does every person have the appropriate education to handle excipients, including production, storage, distribution?
Qualification/validation	Is every person qualified, to perform the required procedure, where validated activities are required?
Training	Does every person have appropriate on the job and GxP training?
Gowning	Is there a gowning procedure? Are garments appropriately cleaned? Are garments a possible source of contamination or cross-contamination?

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 186 7.6. Risk statement: Is the production process appropriately developed and controlled, to ensure  
 187 that interaction between materials, or any step in production and purification will not result  
 188 in the contamination of the excipient which will result in a material of unacceptable quality  
 189 and purity?

Production process	Processing steps include reactions between materials, containing nitrate/nitrates; Materials containing amino groups in process; Nitrosating agents are used in the process; Above aspects may result in contamination of the material with impurities (nitrosamine).
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191 7.7. Risk statement: Is the re-packaging process appropriately controlled, to prevent any risk of  
 192 contamination, mix-up or substitution of materials which may result in a material of  
 193 unacceptable quality and purity?

Re-packaging	Insufficient sampling and testing of incoming material for re-sale; No COA obtained from suppliers; Mix-up of materials for re-packaging; Contamination of material with other material such as DEG or EG because of re-packaging into dirty / contaminated containers or the use of dirty contaminated equipment (such as pumps and transfer lines); Substitution of material with a cheaper, lower quality material (not appropriate grade); here is a risk of contamination of material with unwanted material or product such as methanol, DEG or EG.
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195 7.8. Risk statement: Is the storage process appropriately controlled, in accordance with storage  
 196 requirements, to prevent any risk of uncontrolled degradation, increase in level of impurity,  
 197 contamination, mix-up or substitution of materials which may result in a material of  
 198 unacceptable quality and purity?

Storage	The use of inappropriate storage containers that are not suitably sealed or cleaned; Unsuitable storage conditions including temperature, humidity; Degradation of material resulting in increase in degradation product; Risk of interaction of an amine group with nitrate / nitrite may result in formation of nitrosamine, degradation may occur during storage resulting in an increase in degradation product.

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200 7.9. Risk statement: Is the distribution process appropriately controlled, in accordance with good  
 201 practices, to prevent any risk of uncontrolled degradation, increase in level of impurity,  
 202 contamination, mix-up or substitution of materials which may result in a material of  
 203 unacceptable quality and purity?

Distribution	Inappropriate packaging of materials; Spillage during distribution;
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	Inappropriate conditions during distribution including temperature and humidity, as well as moisture; Loss in identification of materials as labels are lost or damaged; Inappropriate seals of containers with exposure to the environment.
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205 7.10. Risk statement: Is there any risk of contamination or mix-up of material during any stage of  
206 procurement of materials, production, control, storage and distribution which may result in a  
207 material of unacceptable quality and purity?

Contamination and mix-ups	Adulterated material; Incorrect material used on production of a pharmaceutical product; Death.
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## 209 8. Risk control

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211 8.1. Once risks and harms have been identified and assessed, controls should be identified to  
212 mitigate the risks and harms.

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214 8.2. Controls should be proven to be effective.

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## 216 9. Risk communication

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218 9.1. Risks and controls should be appropriately communicated to personnel.

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## 220 10. Risk review

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222 10.1. Risk assessment and risk controls should be reviewed when changes are considered, for  
223 example introduction of new excipients or products, changes in manufacturing process, or  
224 change in suppliers of materials and solvents.

225

226 10.2. Risk review should be periodically to assure that the mitigating tools are still effective and the  
227 risk not changed or increased.

228

## Further Reading

- WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report. WHO Technical Report Series, No. 986, Annex 2. Geneva: World Health Organization, 2014 (<https://www.who.int/publications/m/item/trs986-annex2> accessed on 27 March 2024)
- Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. WHO Technical Report Series No. 1010, Annex 8. Geneva: World Health Organization; 2018 (<https://www.who.int/publications/m/item/Annex-8-trs-1010> accessed on 27 March 2024)
- WHO Good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series No. 1033, Annex 3. Geneva: World Health Organization; 2021 (<https://www.who.int/publications/m/item/annex-3-trs-1033> accessed on 27 March 2024)
- WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. WHO Technical Report Series No. 981, Annex 2. Geneva: World Health Organization; 2013 (<https://www.who.int/publications/m/item/trs981-annex2> accessed on 27 March 2024)
- WHO good manufacturing practices considerations for the prevention and control of nitrosamine contamination in pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: X. WHO Technical Report Series No. X, Annex X. Geneva: World Health Organization; 202X (In development)
- ICH Q9 quality risk management. Geneva: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2005 (<https://www.ich.org/page/quality-guidelines>)
- ISO 31000-2018. Risk management – Guidelines. International Organization for Standardization; 2018, reviewed and confirmed 2023
- The IPEC Risk Assessment Guide for Pharmaceutical Excipients. Part 1- Risk Assessment for Excipient Manufacturers. First Version. 2017. International Pharmaceutical Excipients Council.