



1 DRAFT WORKING DOCUMENT FOR COMMENTS:

2
3 WHO good manufacturing practices
4 considerations for the prevention and
5 control of nitrosamine contamination
6 in pharmaceutical products
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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.943:

WHO good manufacturing practices considerations for the prevention and control of nitrosamine contamination 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.	

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43 WHO good manufacturing practices
44 considerations for the prevention and
45 control of nitrosamine contamination
46 in pharmaceutical products.
47

48 Table of contents

49	1. Introduction
50	2. Scope
51	3. Glossary
52	4. Points to consider
53	5. Risk assessment
54	6. Root cause analysis
55	7. Excipients
56	8. Active Pharmaceutical Ingredients
57	9. Finished Pharmaceutical Products
58	10. Acceptable Intake limits
59	11. Analytical procedures
60	12. Recommendations
61	References and further reading
62	

63 1. Introduction

64

65 1.1. Nitrosamines and their precursors are found in food products and other consumer products
66 such as processed meats, alcoholic beverages, and cosmetics. In these cases, they are
67 normally present in small quantities.

68

69 1.2. Foods such as meats, dairy products and vegetables as well as drinking water may contain low
70 levels of nitrosamines. There is no immediate health risk associated with the use of
71 pharmaceutical products containing levels of a nitrosamine impurity below recommended
72 acceptable intake limits. The actual health risk varies from person to person and also depends
73 on the chemical structure of the nitrosamine contaminant. Nitrosamine impurities may
74 increase the risk of cancer in case of exposure above acceptable levels and over long periods
75 of time (i.e., lifetime intakes below acceptable limit is not expected to significantly increase
76 cancer risks). The risk further depends on several factors, such as:

77

- the daily dose of the medication;
- how long the medication is taken;
- the level of the nitrosamine impurity in the finished product.

80

81 1.3. In recent years, some manufacturers of pharmaceutical products have identified that their
82 products were contaminated with N-nitrosodimethylamine (NDMA), hereafter referred to in
83 general, as nitrosamines). This has led to worldwide recalls of certain products that contained
84 levels of nitrosamines above acceptable limits.

85

86 1.4. Nitrosamines is a group or class of compounds which have the chemical structure of a nitroso
87 group bonded to an amine ($R_1N(-R_2)-N=O$). The compounds can form by a nitrosating
88 reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (coming
89 from nitrite salts under acidic conditions) (1).

90

91 1.5. Nitrosating agents include nitrites (e.g. sodium nitrite, $NaNO_2$) and nitrous acid (HNO_2), nitric
92 oxide (NO), nitrosyl halides (e.g. $ClNO$, $BrNO$), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide
93 (N_2O_4) and organic nitrites (e.g. t-BuONO). Some can arise from recycled solvents or reused
94 catalysts from different processes or across manufacturing lines with inadequate control and
95 inappropriate monitoring.

96

- 97 1.6. N-Nitrosamines are a class of substances of concern to international regulators and the
98 pharmaceutical industry. This is because many nitrosamines are highly potent mutagenic
99 agents that have been classified as probable human carcinogens. In order to control the
100 presence of nitrosamines in pharmaceutical products, manufacturers should be familiar with
101 the root causes of nitrosamine impurities in their products. A comprehensive risk
102 management plan should be established and implemented.
103
- 104 1.7. Manufacturers should perform risk assessments to determine whether their products are at
105 risk of containing nitrosamine impurities, and ensure that the levels of impurities do not
106 exceed the acceptable limits. Risk assessment should include the assessment of information
107 relating to excipients, active pharmaceutical ingredients (APIs) and finished pharmaceutical
108 product manufacture. It should cover potential formation and presence of nitrosamine
109 impurities, as well as the potential for contamination of other products from e.g. materials,
110 other products or residue on commonly used equipment.
111
- 112 1.8. New impurities of concern may be identified on an ongoing basis. The following nitrosamine
113 impurities are currently of concern: (Note: This not an exhaustive list)
- 114 • N-nitrosodimethylamine (NDMA)
 - 115 • N-nitrosodiethylamine (NDEA)
 - 116 • N-nitrosodiisopropylamine (NDIPA)
 - 117 • N-nitroso-N-methyl-4-aminobutanoic acid (NMBA)
 - 118 • 1-methyl-4-nitrosopiperazine (MNP)
 - 119 • N-nitrosoethylisopropylamine (NEIPA)
 - 120 • N-nitrosodibutylamine (NDBA)
- 121
- 122 1.9. Materials, equipment and utilities, may contain contaminants that may be carried over into
123 another material, intermediate, excipient or finished product resulting in contamination or in
124 the formation of nitrosamines. This may result in an adulterated product which could be
125 harmful to patients.
126
- 127 1.10. Traces or residue of unwanted substances present in materials, on surfaces of equipment, in
128 the environment, or in carrier material such as water - may be difficult to remove. These may
129 also be difficult to detect through conventional analytical procedures and basic tests.

130 Validated, sensitive, selective analytical procedures may have to be used to detect these
131 contaminants.

132
133

134 **2. Scope**

135

136 This guideline is applicable to all manufacturers of excipients, active pharmaceutical ingredients and
137 finished pharmaceutical products.

138

139 **3. Glossary**

140

141 **Acceptable Intake Limit.** The maximum Intake level that poses negligible cancer risk, or for serious/life-
142 threatening indications where risk and benefit are appropriately balanced. The acceptable intake limits
143 can be bound to a specific time-period e.g. daily or cumulative.

144

145 **Carcinogenic.** Having the potential to cause cancer

146

147 **Maximum daily dose.** Highest dose per day that has been proven to be safe and effective for the
148 intended use, without leading to unacceptable side effects or toxicity.

149

150 **Mutagenic.** Capable of causing changes or mutations in the genetic material of an organism.

151

152 **Mutagenic impurity.** An impurity that has been demonstrated to be mutagenic in an appropriate
153 mutagenicity test model, e.g., bacterial mutagenicity assay.

154

155 **Nitrosamine.** Nitrosamines are organic compounds with the chemical structure $R_2N-N=O$, where R is
156 usually an alkyl group. They feature a nitroso group bonded to a deprotonated amine

157

158 **Nitrosamine impurities.** Undesired substances which are formed by the reaction of secondary amines,
159 amides, carbamates, derivatives of urea with nitrite or other nitrogenous agents

160

161 For other definitions, see the WHO Quality Assurance of Medicines Terminology Database - List of
162 Terms and related guideline ([https://www.who.int/publications/m/item/quality-assurance-of-
163 medicines-terminology-database](https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database)).

164

165 **4. Points to consider**

166

167 4.1. Manufacturers of excipients, active pharmaceutical ingredients (APIs) and finished
168 pharmaceutical products (FPPs) should comply with current Good Manufacturing Practices.
169 (2-4).

170

171 4.2. Manufacturers should ensure that a pharmaceutical quality system consisting of e.g.
172 procedures, instructions and specifications is in place to ensure the production and control of
173 materials and products that meet safety, quality, purity and efficacy standards.

174

175 4.3. Quality risk management should be an important component of the PQS. Manufacturers
176 should identify risks, assess those risks (harm) and implement appropriate controls to
177 eliminate or mitigate those risks.

178

179

180 **5. Risk assessment**

181

182 5.1. Manufacturers should perform risk assessments to determine whether their products are at
183 risk of being contaminated with nitrosamine impurities.

184

185 5.2. The risk assessment should be comprehensive and include but not be limited to the premises,
186 equipment, materials, route of synthesis, production process, interaction between chemicals,
187 excipients, solvents, APIs, packaging components as well as the intended use of the product
188 and route of administration.

189

190 5.3. Biological, chemical and physical risks or harms which may be introduced or increased; or
191 should be controlled in each step or stage of production, should be identified.

192

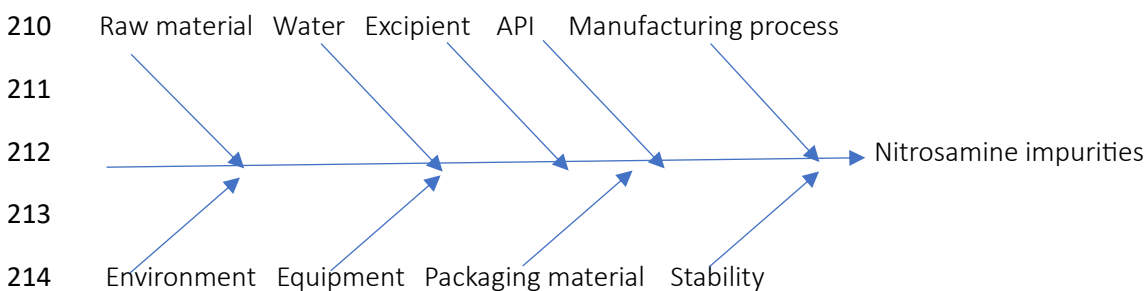
193 5.4. An appropriate tool should be used when conducting risk assessment. (5).

194

195 5.5. As a minimum, the following basic questions should be considered during the risk
196 assessment:

- 197 • Is there a possibility of formation of nitrosamine impurities? If so, what are the controls
198 to reduce/eliminate the formation?

- 199
- How easy is it to detect these nitrosamine impurities?
- 200
- What could be the possible source of the formation of nitrosamine impurities?
- 201
- What is the nature of possible risk(s)?
- 202
- What is the probability of their occurrence?
- 203
- What are the consequences and what is the severity?
- 204
- Is a separate, or dedicated facility or equipment needed?
- 205
- Has an appropriate supplier qualification been done to ensure that there is no risk of
- 206
- contamination of material at the supplier?
- 207
- Are the raw and starting materials, and excipients used, of appropriate purity and
- 208
- quality?
- 209



215 Figure 1. Ishikawa diagram (Example)*

216 *Include primary, secondary and tertiary causes

217

218 6. Root cause analysis

219

220 6.1. With the identification and assessment of risks for nitrosamine contamination, manufacturers

221 should also do root cause analysis to determine the possible, or probable cause of the

222 formation of, or contamination with nitrosamine.

223

224 6.2. As a minimum, the following questions should be considered:

- 225
- Have solvents (fresh and recovered) been considered for possible contamination?
- 226
- What is the quality and purity of the solvent used in any step of the processing?
- 227
- Are solvents recovered (on-site or off-site/contracted out)?
- 228
- did you perform an on-site assessment on contracted facility? Did you assess potential
- 229
- risk of contamination and cross-contamination during the recovery of solvents?

- 230 • Is there an appropriate procedure in place to ensure purity of the solvent obtained from
231 the recovery process?
- 232 • Is any nitrate such as sodium nitrate used, including in reagents and catalysts?
- 233 • Is any nitrosating agent used?
- 234 • Is there any risk that nitrates/nitrosating agents can be generated as an impurity during
235 the manufacturing process?
- 236 • Are there test results for materials showing nitrites, nitrates and nitrosamines?
- 237 • Has water been tested for the presence of potential nitrosamine forming agents, such
238 as chloramines, nitrites and nitrates?
- 239 • Is there any secondary or tertiary amine present in the manufacturing process, e.g. raw
240 materials, intermediate, reagent, solvent?
- 241 • Is there any amide, amine or ammonium salt present in the substance(s) e.g. raw
242 materials, intermediate, reagent, solvent?
- 243 • Have utilities such as water been considered as a possible source of contamination?
- 244 • Have equipment been considered as a possible source of contamination, including
245 efficiency of cleaning procedures?
- 246 • Are nitrites (NO₂-), nitrous acid, nitrates (NO₃-), nitric acid, or azides (N₃-) or their
247 sources present in any excipients (e.g., microcrystalline cellulose), processing aids (e.g.,
248 water, nitrogen)?
- 249 • Are peroxides present in any of the excipients, processing aids?
- 250 • Are nitrites (NO₂-), nitrous acid, nitrates (NO₃-), nitric acid, or azides (N₃-) or their
251 sources present in packaging components (including ink, and materials permeability
252 factors)?
- 253 • Is there a risk that secondary or tertiary amine-contaminants may be present in any
254 primary amines used in your manufacturing process?
- 255 • Are any components containing/potentially containing nitrites and amines present
256 together in solution or in suspension during processing (e.g., during granulation,
257 coating)?
- 258 • Are nitrites (NO₂-), nitrous acid, nitrates (NO₃-), nitric acid, or azides (N₃-) or their
259 sources present in chemically synthesized APIs?
- 260 • Based on the structure of drug substance and excipients, is there any possibility of
261 formation of nitroso compounds by interaction of drug substance and excipients?
- 262 • Are any components containing/potentially containing nitrites and amines maintained
263 together at elevated temperatures (e.g., during drying, coating stages, autoclaving)?

- 264
- Do solvents or any other process materials undergo recycling/recovery?
- 265
- In the manufacturing process of the drug product, are any of the solvents, spent
- 266
- solvents, or process materials treated prior to or during recovery (in-house or by a third
- 267
- party) such that the treatment could lead to formation of amines or nitrosonium ions
- 268
- that could be introduced back into the process through the recovered solvents?
- 269
- Are the recovered materials, if any, dedicated to the process?
- 270
- Is there a potential for nitrosamine impurity formation during the finished product
- 271
- manufacturing, through degradation and by-products (i.e., if certain excipients, APIs, or
- 272
- packaging components containing sources of amines and nitrite are used together)?
- 273
- Are “sartan” products manufactured in the same facility? Is there a risk of cross-
- 274
- contamination?
- 275
- Are manufacturing equipment material of construction of any concern?
- 276
- Are chemicals such as sodium azide or sodium nitrite, which are primary sources of
- 277
- nitrosamine impurity, used in the facility?
- 278
- Are cleaning procedures of equipment involved in manufacturing validated using worst-
- 279
- case product consideration (i.e., solubility, potency, toxicity and cleanability)?
- 280
- Are there amines and nitrosonium ions (degradation and by-products) likely to come
- 281
- into contact with each other either in the same processing step or through carryover
- 282
- into subsequent processing steps?
- 283
- Is there any potential of nitrosamine formation during storage throughout the finished
- 284
- product’s shelf life?
- 285
- Is chloramine used as part of the water treatment process, for water used for cleaning,
- 286
- or as part of the production process?
- 287
- Have the cleaning solvents/cleaning agents used, been assessed for nitrosamine or
- 288
- nitrosamine precursor risk?
- 289
- Does any of the manufacturing processes contribute toward formation of N-
- 290
- Nitrosamines?
- 291
- Is there any risk of nitrosamine formation due to the use of nitrogen?

292

293 6.3. Examples of possible root causes are listed below. Appropriate controls should be identified

294 and implemented to mitigate risks:

295

296 6.3.1. Amines and nitrite reaction

297
298 Formation of nitrosamines is possible in the presence of secondary, tertiary, or
299 quaternary amines and nitrite salts under acidic reaction conditions. Under these
300 conditions, nitrite salts may form nitrous acid, which can react with an amine to form a
301 nitrosamine. Nitrites used as reagents in one step can carry over into subsequent steps,
302 despite purification operations, and react with amines to generate nitrosamine
303 impurities. Therefore, whenever nitrite salts are present, carryover into subsequent steps
304 cannot be ruled out. In general, processes that use nitrites in the presence of secondary,
305 tertiary, or quaternary amines are at risk of generating nitrosamine impurities (1).

306

307 6.3.2. Amine functional groups in processing

308

309 Amines are sometimes added as reagents or catalysts during a manufacturing process.
310 Nitrosamine formation is possible when amines react with nitrous acid or other
311 nitrosating agents. Another source of secondary amines is amide solvents. These are
312 susceptible to degradation under certain reaction conditions. (*Note the degradation of*
313 *N,N-dimethylformamide, N-methylpyrrolidone, N,N-dimethylacetamide, and N,N-*
314 *diethylacetamide).*

315

316 6.3.3. Introduction of Nitrosamine impurities

317

318 Nitrosamine impurities can be introduced into materials and products when
319 contaminated materials such as starting materials and raw materials, are incorporated
320 into products. Starting materials and intermediates may be at risk through cross-
321 contamination if they are manufactured at sites where nitrosamine impurities are formed
322 during other processes. In addition, materials are sometimes contaminated during
323 storage, shipment, distribution.

324

325 6.3.4. Solvents

326

327 Fresh solvents can be contaminated at different stages in the supply chain, as well as
328 during transfer between storage vessels. Recovered materials such as solvents, reagents,
329 and catalysts may also pose a risk of nitrosamine impurities due to the presence of
330 residual amines (such as trimethylamine or diisopropylethylamine). The use of recovered

331 solvents that are comingled from different processes or across manufacturing lines
332 without control and monitoring can introduce nitrosamine impurities. Outsourcing of
333 recovery of raw materials (e.g., solvents, reagents, and catalysts) can pose a risk of
334 contamination.

335

336

337 6.3.5. Inadequate equipment cleaning

338

339 The suitability of use of equipment (and management of utilities), as well as their
340 cleaning, should be assessed to ensure that the risk of introducing nitrosamine impurities
341 through their use, is appropriately controlled.

342

343 Materials, intermediates and products can be contaminated if adequate cleaning of
344 equipment between different materials, products or batches is not carried out, or is not
345 validated as being capable of removing residue or impurities of concern.

346

347 Inadequate and unvalidated cleaning procedures can also lead to cross-contamination if
348 precautions to avoid nitrosamine contamination are not in place before materials are
349 combined for recovery.

350

351 The nature and composition of the cleaning solvents used for the cleaning of reactors
352 used during API synthesis/purification and for the cleaning of finished dosage form
353 equipment should be considered as cleaning solvents (e.g. amines) could react to form
354 nitrosamines under certain conditions if the equipment is not perfectly dry prior to its
355 used for subsequent manufacture and/or if there are residues remaining. The
356 contaminants found in the cleaning solvents, could also react to form nitrosamines (6).

357 6.3.6. Utilities

358

359 Utilities such as HVAC and water systems, may also be a source of contamination. Risk
360 assessment should be done to consider the contaminants in air and water, as well as the
361 treatment of air and water - as these contain nitrites and other contaminants.

362

363 Potable water is sometimes used in the production of materials such as excipients and APIs;
364 or to clean equipment. Water may contain low levels of chloramine and or nitrites/nitrates,
365 which are known to potentially react with secondary amines to form nitrosamine
366 impurities, depending on specific conditions. The source, quality and purification of water
367 may impact on the absence, presence or formation of nitrosamine impurities. For example,
368 chlorination may contribute to the formation of nitrosamine impurities. Chloramine,
369 nitrite/nitrate and nitrosamine levels in water should thus be determined.

370

371 Where required, water should be purified to remove unacceptable impurities before use.

372

373 6.3.7. Nitrosamines from environmental contamination.

374

375 Atmospheric NO₂ is a nitrosating agent for various secondary amines, such as DMA. It has
376 been shown that there is a correlation between the concentration of atmospheric NO₂ and
377 the NDMA content in certain products. The following examples are controls that could be
378 considered:

- 379 • Inlet air to equipment, such as fluidized bed friers, should be appropriately
380 controlled as it may be contaminated;
- 381 • APIs with low DMA content should be used where possible;
- 382 • Risks associated with process parameters such as granulation drying time and
383 temperatures should be controlled.

384

385 6.3.8. Quenching Process as a Source of Nitrosamine Contamination

386

387 The risk of nitrosamine formation when a quenching step is performed directly in the main
388 reaction mixture should be avoided or controlled.

389

390 Inadequate removal of impurities, or operations which are not optimized for removing
391 specific impurities of concern, may increase the risk of nitrosamine impurities carried over
392 to subsequent steps.

393

394 6.3.9. Poorly controlled reaction conditions

395

396 The manufacturing process for APIs should be optimized. Reaction conditions such as
397 temperature, pH, or the sequence of adding reagents including catalysts, intermediates, or
398 solvents should be appropriate and controlled to prevent the formation of impurities.
399

400 **7. Excipients and packaging material**

401
402 7.1. Excipients should be manufactured in compliance with WHO GMP for excipients used in
403 pharmaceutical products (2).
404

405 7.2. Impurities, such as nitrite/nitrate, can be found in a range of commonly used excipients. This
406 may lead to nitrosamine impurities forming in pharmaceutical products during production and
407 storage of the product. The supplier qualification program should cover the verification of
408 controls over the possibility of nitrite impurities.
409

410 7.3. Packaging materials may be a source of contamination. Nitrocellulose in PTP aluminium
411 printing ink is commonly known as a nitrosating agent.
412

413 7.4. Where the excipient is identified as a probable cause for formation of nitrosamine impurities,
414 appropriate controls should be implemented. This may include consideration to change the
415 supplier of the excipient or the change of the excipient to reduce the risk of nitrosamine
416 impurities formation.
417

418 *Note: See reference to water, under the section "utilities"*
419

420 **8. Active Pharmaceutical Ingredients (APIs)**

421
422 8.1. APIs should be manufactured in compliance with WHO GMP for APIs.
423

424 8.2. API manufacturers should carefully design route of synthesis (ROS) to minimize or prevent the
425 formation of nitrosamine impurities. (3, 7-9).
426

427 8.3. Reaction conditions that may produce nitrosamines should be avoided as far as possible,
428 starting from the process development stage. Where this is not possible, the process should

- 429 be adequately controlled and should be capable of consistently reducing nitrosamine
430 impurities.
431
- 432 8.4. Bases other than secondary, tertiary, or quaternary amines (when possible) should be used if
433 ROS conditions may form nitrosamines.
434
- 435 8.5. Caution should be used when the ROS involves the use of amide solvents (e.g., N,N-
436 dimethylformamide, N,N-dimethylacetamide, and N-methylpyrrolidone).
437
- 438 8.6. Where possible, nitrites should be replaced with other quenching agents for azide
439 decomposition processes.
440
- 441 8.7. Sequences of reactions, processes, and reaction conditions (such as pH, temperature, and
442 reaction time) should be optimized and consistently controlled for avoiding the formation of
443 nitrosamine impurities.
444
- 445 8.8. Manufacturing process should be designed to facilitate the purge of nitrosamine impurities in
446 the subsequent processing steps
447
- 448 8.9. Supply chains should be audited and monitored for any at-risk raw materials, starting
449 materials, and intermediates.
450
- 451 8.10. Records including the name of the raw material manufacturer and its supplier, roles of the
452 actual manufacturers of such materials, and any re-packers and distributors who handle the
453 materials before API manufacture, should be maintained.
454
- 455 8.11. When appropriate, controls and additional specifications should be considered for at-risk
456 materials to prevent nitrosamine contamination.
457
- 458 8.12. API manufacturers should verify with their suppliers whether the purchased materials used in
459 their processes are recovered.
460

461 8.13. Recovered materials such as solvents, reagents, and catalysts should be used only in the same
462 step or in an earlier step (if there is sufficient purification) of the same process from which it
463 was collected.

464

465 8.14. The recovered materials should meet appropriate standards before reuse. If the recovery of
466 materials is outsourced to third-party contractors, the API manufacturer should audit the
467 contractors' validation of procedures, including cleaning procedures.

468

469 8.15. Potable water may contain low levels of nitrite and even nitrosamines from environmental
470 contamination. Nitrite and nitrosamine levels in water should be determined. Where
471 required, water should be purified to remove unacceptable impurities before use.

472

473 8.16. API batches containing nitrosamine impurities may be reprocessed or reworked under
474 oversight of the quality unit. Records should be kept.

475

476 8.17. Batches of API containing levels of nitrosamine impurities above the recommended limits
477 should not be released for sale or distribution.

478

479 8.18. Batches of API with unacceptable levels of nitrosamine impurities already in distribution,
480 should be reported to the national medicine regulatory authority. A batch or product recall
481 should be considered.

482

483 **9. Finished Pharmaceutical Product (FPP)** 484 **manufacturers**

485

486 9.1. Products should be manufactured in compliance with WHO GMP for pharmaceutical products
487 (4).

488

489 9.2. Risk assessments should be conducted to determine the potential for nitrosamine impurities
490 in FPPs.

491

492 9.3. A control strategy should be defined to prevent or mitigate the risk of nitrosamine
493 contamination of FPPs.

494

495 9.4. The risk assessment should include evaluation of the supply chain, any excipient, API
496 processing, utilities, as well as storage, re-packaging, distribution pathway and degradation
497 that may introduce nitrosamines during production or storage. Consideration should be given
498 to establish whether nitrosamines could form in an FPP, over the product's shelf life.

499

500 9.5. If a risk of nitrosamine presence is identified, confirmatory testing of batches should be
501 conducted using sensitive, appropriately validated, analytical methods.

502

503 9.6. If a nitrosamine impurity is detected, the root cause should be determined. Where
504 appropriate, changes in the manufacturing process to mitigate or reduce the nitrosamine
505 impurities should be made.

506

507 9.7. The risk of nitrosamine impurity formation during the manufacture and packaging of the
508 finished pharmaceutical product (such as when certain containers, API or packaging
509 components come into contact with amines or nitrites, e.g. reaction of secondary amines in
510 printing inks with certain nitrocellulose lacquers or coating materials when heated) should be
511 considered in the risk assessment.

512

513 9.8. Processing steps such as granulation or drying may increase the risk of nitrosamine impurity
514 formation. Where appropriate, changes in the manufacturing process to mitigate or reduce the
515 nitrosamine impurities should be made.

516

517

518 *Note: Purification steps during the production of an API may assist in mitigating risks of the*
519 *presence of nitrosamine impurity in the API. This may not be the case with the production steps*
520 *of a finished pharmaceutical product.*

521

522

523 **10. Acceptable Intake (AI) limits**

524

525 10.1. The low levels at which the nitrosamine impurities occur create challenges for testing.

526

527 10.2. Appropriate procedures should be developed and validated. (See also methods
528 recommended by SRAs). Note: Higher temperature conditions of some test methods may
529 cause the sample to generate NDMA.

530

531 10.3. Generally, sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb)
532 should be used. The LOQ and limit of detection (LOD) should be as low as reasonably practical
533 for products for which the maximum daily dose is high (e.g., greater than 1 g).

534

535 10.4. Where more than one nitrosamine listed in appendix 1 is detected, the analytical procedure
536 should be validated for LOQs below 0.03 ppm to accurately quantify a total nitrosamine level
537 of not more than 26.5 ng/day. *(For example, if the MDD is 1200 mg, the LOQ should be below*
538 *0.02 ppm. FDA's public webpage includes validated analytical test methods recommended for*
539 *detecting nitrosamine impurities in several different APIs and products) (1).*

540

541 10.5. Only limited impurity-specific toxicity data is available for NDMA and NDEA. Based on this
542 information interim acceptable intakes for these specific impurities have been adopted by
543 most major regulators.

544 *Acceptable Intake (AI) limits for nitrosamines in FPPs (10)*

545 10.6. AI limits should be established. (Note: Different approaches are described in the literature
546 and guidelines as those published by ICH, Health Canada, and the US FDA). For example:

547

548 10.6.1. If N-nitrosamines are identified with sufficient substance specific animal carcinogenicity
549 data, the TD50 should be calculated and used to derive a substance specific limit for
550 lifetime exposure as recommended in ICH M7 guideline (9);

551

552 10.6.2. If N-nitrosamines are identified without sufficient substance specific data to derive a
553 substance specific limit for lifetime exposure as described above, the Carcinogenic
554 Potency Categorization Approach (CPCA) for N-nitrosamines should be used to establish
555 the AI, unless other robust data are available that would override this AI;

556

557 10.6.3. A negative result in an GLP-compliant Enhanced Ames Test (EAT) allows control of the N-
558 nitrosamine at 1.5 µg/day. For substances testing positive, the AI should be established
559 using options 1 or 3;

560

- 561 10.6.4. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the
562 TD50 from the surrogate substance can serve as a point of departure for derivation of AI
563 by SAR and read across.
564
- 565 10.7. A negative result in a relevant well-conducted in vivo mutagenicity study can allow control of
566 the N-nitrosamine as a non-mutagenic impurity, i.e., according to Q3A/B limits, irrespective of
567 the limit calculated through option 1, 2 or 3. For substances testing positive, the AI should be
568 established using options 1 or 3.
569
- 570 10.8. In setting AI limits for nitrosamines, consideration should be given to:
571
 - the Enhanced Ames Test (EAT) conditions and the Carcinogenic Potency Categorization
572 Approach (CPCA);
 - the threshold below which a nitrosamine impurity is not expected to be included in routine
573 testing specifications;
 - testing approaches where more than one strength of a dosage form is concerned, and
574
 - expectations when a nitrosamine impurity cannot be synthesized or isolated and purified.
575
576
- 577
- 578 10.9. Recommended AI limits are presented in literature. (The AI limit is a daily exposure to a
579 compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a
580 1:100,000 cancer risk after 70 years of exposure. See ICH M7 (9) and USA FDA regulatory
581 information note¹)
582
- 583 10.10. Examples of Interim allowable daily intake limits for a selection of N-nitrosamine impurities
584 are presented in Annex 1. For a nitrosamine impurity that is not included in the appendix, the
585 principles as outlined in ICH's M7 guideline are recommended to be used to determine an
586 acceptable Intake (9).
587
- 588 10.11. The conversion of AI limit into ppm varies by product and is calculated based on a product's
589 maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)). These
590 limits are applicable only if a drug product contains a single nitrosamine (1).
591
592

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related>

593 11. Analytical procedures

594

595 11.1. Validated analytical procedures should be used when testing for the presence of
596 nitrosamines. The procedure should be sensitive for the determination of the specific
597 nitrosamine(s) in the product.

598

599 11.2. Where the presence of a nitrosamine is confirmed, it should not exceed the acceptable limits.
600 Where it exceeds the acceptable limit, appropriate corrective action should be taken. If the
601 manufacturing procedure needs to be changed, the change management procedure should
602 be followed for the relevant variation. In this case, where relevant, the NMRA should be
603 informed.

604

605 11.3. Where appropriate, analytical methodology to separate thermally labile nitrosamine
606 impurities using gas chromatography (GC) coupled with detection by thermal energy analysis
607 (TEA) or mass spectrometry (MS), should be used.

608

609 11.4. Liquid chromatography (LC) coupled with detection by TEA, MS, or ultraviolet light (UV) may
610 be an alternative analytical methodology applicable to both volatile and non-volatile
611 nitrosamines.

612

613 11.5. High performance liquid chromatography (HPLC) with UV detection has low sensitivity and
614 may only be adequate for analysis of low dose drugs with lower limits.

615

616 11.6. Examples of analytical procedures are presented in table 1.

617

618 Table 1. Examples of analytical procedures*

Methodology	Detector	Limit of Detection
Gas chromatography	TEA	< 0.1 to 5 ppb
	MS	1 to 5 ppb
Liquid chromatography	TEA	1 to 50 ppb
	MS	1 to 5 ppb
	UV	1 to 200 ppb

619

* used for detection of nitrosamine in e.g. water and food products

620

621 **12. Recommendations**

622

623 12.1. Excipient, API and FPP manufacturers should take steps to mitigate the risk of nitrosamine
624 impurities in their products.

625

626 12.2. Risk assessment of nitrosamine impurities should be conducted in a timely manner, as early
627 as during product development as well as thereafter during the manufacturing of excipients,
628 APIs and FPPs.

629

630 12.3. It should be noted that:

631 • average nitrosamines and potential nitrosamine precursors content and batch to batch
632 variance differ among excipients;

633 • for solid dosage forms, the nitrosamine and potential nitrosamine precursors contribution
634 is dominated by the highest formula % excipients, e.g., the fillers (diluents), which are
635 typically used in larger proportion, and are characterized by low nitrite levels and low
636 variability, leading to an average value of 1 µg/g nitrite in a typical formulation;

637 • substantial differences may occur in average nitrosamine and potential nitrosamine
638 precursor content in batches from different excipient vendors potentially reflecting
639 differences in source materials or processing methods for excipient manufacturing;

640 • selection of raw materials or processing by excipient manufacturers may help reduce nitrite
641 levels in finished drug product formulations, and thus the overall risk of nitrosamine
642 formation in cases where the product contains vulnerable amines (11).

643

644 12.4. The benefit and the risks of products with levels of nitrosamines exceeding acceptable limits
645 or more than one nitrosamine should be reviewed by the NMRA. When considering the
646 withdrawal, the NMRA should balance the impact on the patient if the product will no longer
647 be available. This should involve determining the availability of alternative products or
648 treatments on their own market and the clinical impact of stopping or switching to a different
649 treatment.

650

651 12.5. Where manufacturers identify contamination of nitrosamines above acceptable limits,
652 appropriate action should be taken. Risk and impact assessment should be done with root
653 cause determination. Thorough investigations should be done to identify whether shared

654 facilities, shared equipment or other batches may be impacted, whether common excipients,
655 starting materials or solvents were used which may be the potential source of contamination.
656 The investigation should be extended to other batches which may have been impacted.

657

658

659

660 **References**

- 661 1. Control of Nitrosamine Impurities in Human Drugs: Guidance For Industry. U.S. Department of
662 Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and
663 Research (CDER). February 2021 (Revision 1).
664
- 665 2. WHO good manufacturing practices for excipients used in pharmaceutical products. In: WHO
666 Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. WHO
667 Technical Report Series No. 1052, Annex 2. Geneva: World Health Organization; 2024
668
- 669 3. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert
670 Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. WHO Technical
671 Report Series No. 957, Annex 2. Geneva: World Health Organization; 2010
672 (<https://www.who.int/publications/m/item/annex-2-trs-957> accessed on 28 March 2024)
673
- 674 4. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert
675 Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report. WHO Technical
676 Report Series, No. 986, Annex 2. Geneva: World Health Organization, 2014
677 (<https://www.who.int/publications/m/item/trs986-annex2> accessed on 28 March 2024)
678
- 679 5. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for
680 Pharmaceutical Preparations: forty-seventh report. WHO Technical Report Series No. 981, Annex
681 2. Geneva: World Health Organization; 2013 ([https://www.who.int/publications/m/item/trs981-
682 annex2](https://www.who.int/publications/m/item/trs981-annex2) accessed on 28 March 2024)
683
- 684 6. WHO Guidelines on good manufacturing practices: validation. Appendix 3: Cleaning validation. In:
685 WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO
686 Technical Report Series No. 1019, Annex 3. Geneva: World Health Organization; 2019
687 (<https://www.who.int/publications/m/item/trs1019-annex3> accessed on 28 March 2024)
688
- 689
- 690 7. WHO good practices for research and development facilities of pharmaceutical products. In: WHO
691 Expert Committee on Specifications for Pharmaceutical Preparations: fifty-sixth report. WHO
692 Technical Report Series No. 1044, Annex 6. Geneva: World Health Organization; 2022
693 (<https://www.who.int/publications/m/item/trs1044-annex6> accessed on 28 March 2024)

694

695 8. ICH Q11 Development and Manufacture of Drug Substances. Geneva: The International Council
696 for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2012

697 (<https://www.ich.org/page/quality-guidelines>)

698

699 9. ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to
700 Limit Potential Carcinogenic Risk. Geneva: The International Council for Harmonisation of
701 Technical Requirements for Pharmaceuticals for Human Use; 2023

702 (<https://www.ich.org/page/multidisciplinary-guidelines>)

703

704 10. Guidance on nitrosamine impurities in Medications: Evaluating and managing the risks of N-
705 nitrosamine impurities in human pharmaceutical, biological and radiopharmaceutical products.
706 Ottawa: Health Canada; 2024

707

708 11. The Lhasa Carcinogenicity Database (LCDB), 2024.

709

710

711 **Further reading**

712 • ICH Q9 quality risk management. Geneva: The International Council for Harmonisation of
713 Technical Requirements for Pharmaceuticals for Human Use; 2005

714 (<https://www.ich.org/page/quality-guidelines>)

715 • ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle
716 Management. Geneva: The International Council for Harmonisation of Technical Requirements
717 for Pharmaceuticals for Human Use; 2019 (<https://www.ich.org/page/quality-guidelines>)

718 • WHO Information Note: Update on Nitrosamine impurities. Geneva: World Health
719 Organization; 2019 ([https://www.who.int/news/item/20-11-2019-information-note-](https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities)
720 [nitrosamine-impurities](https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities) accessed on 28 March 2024)

721 • Zhong, H., Chan, G., Hu, Y., Hu, H. and Ouyang, D., 2018. A comprehensive map of FDA-
722 approved pharmaceutical products. *Pharmaceutics*, 10(4), p.263.

723 • Fukuda, S., Kondo, K., Fukumoto, S., Takenaka, N., Uchikawa, O. and Yoshida, I., 2023. N-
724 Nitrosodimethylamine Formation in Metformin Drug Products by the Reaction of
725 Dimethylamine and Atmospheric NO₂. *Organic Process Research & Development*, 27(11),
726 pp.2123-2133.

- 727 • Galande A., Pazhayattil A., and Sharma S. 2021. A Checklist For Risk Assessment Of
728 Nitrosamine Impurities In Oral Solid Dose Drugs. Outsourced Pharma
729 ([https://www.outsourcedpharma.com/doc/a-checklist-for-risk-assessment-of-nitrosamine-](https://www.outsourcedpharma.com/doc/a-checklist-for-risk-assessment-of-nitrosamine-impurities-in-oral-solid-dose-drugs-0001)
730 [impurities-in-oral-solid-dose-drugs-0001](https://www.outsourcedpharma.com/doc/a-checklist-for-risk-assessment-of-nitrosamine-impurities-in-oral-solid-dose-drugs-0001) accessed on 28 March 2024)
- 731 • Boetzel, R., Schlingemann, J., Hickert, S., Korn, C., Kocks, G., Luck, B., Blom, G., Harrison, M.,
732 Francois, M., Allain, L. and Wu, Y., 2023. A nitrite excipient database: a useful tool to support
733 N-nitrosamine risk assessments for drug products. Journal of Pharmaceutical Sciences, 112(6),
734 pp.1615-1624.
- 735 • Health Canada. Nitrosamine impurities: Information for health product manufacturers.
736 ([https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-](https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html)
737 [enforcement/information-health-product/drugs/nitrosamine-impurities.html](https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html) accessed on 28
738 March 2024)
- 739 • Therapeutic Goods Administration (TGA). Nitrosamine impurities in medicines.
740 ([https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/industry-](https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/industry-information-about-specific-safety-alerts-recalls-and-shortages/nitrosamine-impurities-medicines#origin-of-nitrosamine-impurities)
741 [information-about-specific-safety-alerts-recalls-and-shortages/nitrosamine-impurities-](https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/industry-information-about-specific-safety-alerts-recalls-and-shortages/nitrosamine-impurities-medicines#origin-of-nitrosamine-impurities)
742 [medicines#origin-of-nitrosamine-impurities](https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/industry-information-about-specific-safety-alerts-recalls-and-shortages/nitrosamine-impurities-medicines#origin-of-nitrosamine-impurities) accessed on 28 March 2024)
- 743 • European Medicines Agency (EMA).. Nitrosamine impurities.
744 ([https://www.ema.europa.eu/en/human-regulatory-overview/post-](https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines/nitrosamine-impurities)
745 [authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-](https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines/nitrosamine-impurities)
746 [medicines/nitrosamine-impurities](https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines/nitrosamine-impurities) accessed on 28 March 2024)
- 747 • United States Pharmacopeia (USP). Nitrosamine impurities.
748 (<https://www.usp.org/impurities/nitrosamine-impurities> accessed on 2 April 2024)
- 749 • European Pharmacopoeia (Ph. Eur). General chapter on N-nitrosamines.
750 ([https://www.edqm.eu/en/-/ph-eur-commission-adopts-a-new-general-chapter-for-the-](https://www.edqm.eu/en/-/ph-eur-commission-adopts-a-new-general-chapter-for-the-analysis-of-n-nitrosamine-impurities)
751 [analysis-of-n-nitrosamine-impurities](https://www.edqm.eu/en/-/ph-eur-commission-adopts-a-new-general-chapter-for-the-analysis-of-n-nitrosamine-impurities) accessed on 2 April 2024)
- 752 • U.S. Food and Drug Administration (FDA). Liquid Chromatography-High Resolution Mass
753 Spectrometry (LC-HRMS) method for the Determination of six nitrosamine Impurities in ARB
754 Drugs. (<https://www.fda.gov/media/125478/download> accessed on 2 April 2024)
- 755 • U.S. Food and Drug Administration (FDA). Test methods for ranitidine and nizatidine
756 (<https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine> accessed
757 on 2 April 2024)
- 758 • U.S. Food and Drug Administration (FDA). Test methods for metformin
759 (<https://www.fda.gov/drugs/spotlight-cder-science/rigorous-detection-nitrosamine->

- 760 [contaminants-metformin-products-balancing-product-safety-and-product](#) accessed on 2 April
- 761 2024)
- 762 • Swissmedic. Limit test for the determination of Nitrosamines by GC-MS/MS
- 763 • Health Sciences Authority (HSA; Singapore). Test methods for metformin
- 764 ([https://www.hsa.gov.sg/docs/default-source/announcements/safety-alerts/determination-of-](https://www.hsa.gov.sg/docs/default-source/announcements/safety-alerts/determination-of-ndma-in-metformin-products-by-hram-gcms.pdf)
- 765 [ndma-in-metformin-products-by-hram-gcms.pdf](https://www.hsa.gov.sg/docs/default-source/announcements/safety-alerts/determination-of-ndma-in-metformin-products-by-hram-gcms.pdf) accessed on 2 April 2024)
- 766 • Health Sciences Authority (HSA; Singapore). Test methods for ranitidine
- 767 ([https://www.hsa.gov.sg/announcements/safety-alert/updates-on-impurities-in-ranitidine-](https://www.hsa.gov.sg/announcements/safety-alert/updates-on-impurities-in-ranitidine-products)
- 768 [products](https://www.hsa.gov.sg/announcements/safety-alert/updates-on-impurities-in-ranitidine-products) accessed on 2 April 2024)
- 769 • Taiwan Food and Drug Administration. (n.d.). Methods for testing for N-nitrosamines in
- 770 medicines. (<https://www.fda.gov.tw/ENG/siteList.aspx?sid=10360> accessed on 2 April 2024)
- 771 • European Directorate for the Quality of Medicines & HealthCare (EDQM). Ad hoc projects-
- 772 OMCL network. (<https://www.edqm.eu/en/ad-hoc-projects-omcl-network> accessed on 2 April
- 773 2024)
- 774
- 775
- 776
- 777
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784 **Appendix 1: Examples of Interim allowable daily intake**
785 **limits for a selection of N-nitrosamine impurities.**

786

Impurity (Abbreviation)	Chemical name	Allowable daily intake
NDMA	N-nitrosodimethylamine	96.0 ng/day
NDEA	N-nitrosodiethylamine	26.5 ng/day
NMBA	N-nitroso-N-methyl-4-aminobutryric-acid	96.0 ng/day
DIPNA	N-nitroso-diisopropylamine	26.5 ng/day
EIPNA	N-nitroso-ethylisopropylamine	26.5 ng/day

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