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6 June 2024

Dr. Steve Estevao Cordeiro
Technical Officer
Norms and Standards for Pharmaceuticals
World Health Organization

Reference: Working Draft- Good Manufacturing Practices Considerations for the Prevention and Control of Nitrosamine Contamination in Pharmaceutical Products (Working Document QAS/24.943)

Dear Sir,

PDA appreciates the opportunity to provide feedback to the World Health Organization (WHO) on the working draft of Good Manufacturing Practices Considerations for the Prevention and Control of Nitrosamine Contamination in Pharmaceutical Products. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important guidance.

PDA is a non-profit international professional association of more than 10,000 individual members who are industry professionals having an interest in fields of pharmaceuticals, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Consultation on behalf of PDA's Science Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

cc. Josh Eaton,PDA; Carrie Horton,PDA; Jessie Lindner, PDA; Danielle Bretz, PDA

TEMPLATE FOR COMMENTS

World Health Organization

Norms and Standards for Pharmaceuticals (NSP)
Health Products Policy and Standards (HPS)

COMMENTS ON WHO WORKING DOCUMENT: QAS/24.943

TITLE OF THE DOCUMENT: …GOOD MANUFACTURING PRACTICES CONSIDERATIONS FOR THE PREVENTION AND CONTROL OF NITROSAMINE CONTAMINATION IN PHARMACEUTICAL PRODUCTS

Name:	Parenteral Drug Association
Employer:	
Position, Title:	
City, Country:	Bethesda, Maryland, USA and Berlin, Germany

*Kindly complete the table **without modifying the format** of the document - thank you.*

Comments			
Please don't add any personal information as the comments might be published			
Line number(s)	**Comments**	**Suggested text**	**Justification**
N/A	Unclear what is meant by “finished pharmaceutical products (FPPs)”. International readers may have different interpretations of what is included in the term and could therefore impact the readers understanding of the scope of the guidance.	Add “Finished Pharmaceutical Product (FPP)” to the glossary.	By providing a definition for Finished Pharmaceutical Product, it will clarify for the reader what types of products are covered under the scope of this guidance (e.g., primary packaging material, medical devices, licensed products, non-licensed/Over-the-Counter products, compounded products, etc.).
48-61	Section headers in the table of contents do not match the section headers in the document.	Harmonize table of content headers with the headers provided in the document.	By harmonizing the listed headers, it will eliminate possible reader confusion.

72-76	PDA proposes to delete “significantly’ and to add “overall” before cancer risk to clarify intent of statement.	“Nitrosamine impurities may increase the risk of cancer in case of exposure above acceptable levels and over long periods of time (i.e., lifetime intakes below acceptable limit is not expected to **increase overall** cancer risks).”	By stating “not expected to significantly increase”, the statement might be understood as there is always a higher risk, but not significantly. PDA feels this new wording would clarify the intent for the reader.
76-79	PDA suggests using the term “pharmaceutical product” in place of “medication” and “finished product”. PDA also recommends removing the second bullet “how long the medication is taken”.	“The risk further depends on several factors, such as: • the daily dose of the **pharmaceutical product**; • ~~how long the **pharmaceutical product** is taken;~~ • the level of the nitrosamine impurity in the **pharmaceutical product**.”	Changing “medication” and “finished product” to use the term “pharmaceutical” will align terms with the document title and harmonize the language. By using the term from the guidance title consistently in this listing, PDA feels it will eliminate possible confusion/misinterpretation that “medication” and/or “finished product” has a different connotation than the scope of the document. The second bullet may lead to confusion regarding the duration of time a person is prescribed the medication versus the duration of the drug product administration. How a pharmaceutical product is prescribed is out of the control of the manufacturer. If not feasible to remove bullet point, it would be beneficial to clarify how the drug product is intended to be used. See below for proposed language for consideration: “How long the pharmaceutical product is taken **(e.g., lifetime, intermittent, ad hoc)**”

93-95	PDA proposes to add language addressing storage concerns in this section of the document.	"Some can arise from recycled solvents or reused catalysts from different processes or across manufacturing lines with inadequate control and inappropriate monitoring, **or during storage."**	This additional verbiage provides more context to manufacturing risks that will be further discussed in text in Section 6: Root Cause Analysis.
97-102	Unclear what is meant by "probable human carcinogen". Using probable could potentially lead to misinterpretation of the application of this guidance to certain nitrosamines and could therefore impact the reader's understanding of the scope of the guidance.	Provide clarification of nitrosamine definition regarding "probable human carcinogen".	By providing clarity on the intent of "probable human carcinogen" regarding the definition of nitrosamines, it will clarify for the reader the scope of substances covered by this guidance. In addition to clarifying the nitrosamine definition, could also direct reader to the Food and Drug Administration guidance document "Control of Nitrosamine Impurities in Human Drugs" (2021) for additional information, if appropriate.

101-102	PDA proposes adding a reference that provides guidance on risk management plans (RMP).	"A comprehensive risk management plan should be established and implemented. **(Reference #)"**	Providing a reference would direct the reader to a document that provides guidance on how to create and implement a risk management plan (RMP). Potential references examples are: - International Organization for Standardization (ISO) 14971:2019: Conformity for Medical Devices - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline Q9 (R1) on Quality Risk Management - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) topic E 2 E: Pharmacovigilance Planning

104-108	PDA suggests adding clarification regarding the manufacturing task(s) being addressed in this statement. Also, it is suggested to highlight the burden of importers and distributors to ensure their manufacturers are performing and providing documentation of such risk assessments. Finally, PDA suggests adding the statement "but is not limited to" so the reader is directed to considerations for the risk assessment beyond those listed.	"Manufacturers should perform risk assessments to determine whether their products are at risk of containing nitrosamine impurities, and to ensure that the levels of impurities in the **finished pharmaceutical products (FPP)** do not exceed the acceptable limits. **Importers and distributors need to ensure that their manufacturers have provided such risk assessments.** Risk assessment should include **but is not limited to,** the assessment of information relating to excipients, active pharmaceutical ingredients (APIs) and finished pharmaceutical product manufacture."	In scope of the document, manufactures could be producing excipients, active pharmaceutical ingredients (APIs) and/or finished pharmaceutical products (FPPs). A risk assessment should be done by all manufacturers, but only for those manufacturing FPPs does it need to be ensured that nitrosamine impurity concentration is not exceeding acceptable limits. The presence of nitrosamine in released raw material should be removed and/or reduced to its minimum. The application of the acceptable intake does not relate to this portion of the process. Storage of pharmaceuticals at the premises of importers/ distributors may contribute to the formation of nitrosamine impurities. In these situations, a manufacture's risk assessment should address environment storage considerations (i.e., temperature and moisture contents) to ensure safety/quality of the finished pharmaceutical product. By adding the statement "but is not limited to", the reader will be able to assess the unique considerations applicable to their specific manufacturing process.

112-120	PDA suggests adding references which provide extensive listings of nitrosamine impurities.	"New impurities of concern may be identified on an ongoing basis. The following nitrosamine impurities are currently of concern: (Note: This not an exhaustive list) • N-nitrosodimethylamine (NDMA) • N-nitrosodiethylamine (NDEA) • N-nitrosodiisopropylamine (NDIPA) • N-nitroso-N-methyl-4-aminobutanoic acid (NMBA) • 1-methyl-4-nitrosopiperazine (MNP) • N-nitrosoethylisopropylamine (NEIPA) • N-nitrosodibutylamine (NDBA **For a comprehensive list, please refer to the following:** - **European Medicines Agency (EMA)-** ***Appendix 1: Acceptable Intakes Established for N-nitrosamines*** **(2004)** - **U.S. Food and Drug Administration-** ***Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)*** **(2023**)"	By providing reference documents such as those proposed, readers will have a more comprehensive reference for a more comprehensive listing of nitrosamine impurities.
155-156	PDA proposes to expand nitrosamine definition in order to provide a link between carcinogens and the nature of nitrosamines.	**"Nitrosamine.** Nitrosamines are organic compounds with the chemical structure $R_2N{-}N{=}O$, where R is usually an alkyl group. They feature a nitroso group bonded to a deprotonated amine. **Nitrosamines are toxic compounds, and some are known carcinogens."**	This addition will provide a link to carcinogenicity of nitrosamines. This proposed verbiage is aligned with the definition of nitrosamines used by the United States Food and Drug Agency, Health Canada and the European Medical Association.

158-159	PDA suggests addition of the reactions of tertiary and quaternary amines.	**"Nitrosamine impurities.** Undesired substances which are formed by the reaction of secondary, **tertiary or quaternary** amines, amides, carbamates, derivatives of urea with nitrite or other nitrogenous agents"	The formation of nitrosamines is not limited to secondary amines (see also point 1.4). It is recommended to either add tertiary or quaternary amines as well or to add an "e.g." to demonstrate it is not an exhaustive listing.
171-173	PDA proposes to expand the listing of standards that should be met by manufacturers. Additionally, PDA proposes to add a reference to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Scientific Guideline Q10: Pharmaceutical Quality System.	"Manufacturers should ensure that a pharmaceutical quality system consisting of e.g. procedures, instructions and specifications is in place to ensure the production and control of materials and products that meet safety, quality, **identity,** purity and **potency standards, to ultimately meet expected product efficacy. (Reference #)"**	While efficacy has a clinical connotation, identity and potency are related to the safety, quality, identity, purity and potency). (SQuIPP) elements of good manufacturing processes and should be ensured as part of the pharmaceutical manufacturing process. By providing a reference to the internationally accepted guidance ICH Q10 it will direct readers to a practical guidance that discusses guidelines to be implemented by all manufactures.
175-177	PDA suggests defining "PQS" and adding references to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) Scientific Guideline Q9: Quality Risk Management (R1) and Q10: Pharmaceutical Quality System.	"Quality risk management should be an important component of the **pharmaceutical quality system (**PQS**)**. Manufacturers should identify risks, assess those risks (harm) and implement appropriate controls to eliminate or mitigate those risks. **(Reference #)"**	By providing a reference to the internationally accepted guidance ICH Q9 and ICH Q10 it will direct readers to practical guidance documents that discuss guidelines to be implemented by all manufactures.
185-188	PDA proposes to clarify that under "production process" both manufacturing and packaging processes should be covered by the risk assessment. Additionally, PDA proposes to add storage as a component of the risk assessment.	"The risk assessment should be comprehensive and include but not be limited to the premises, equipment, materials, route of synthesis, production (**manufacturing and packaging processes), storage,** interaction between chemicals, excipients, solvents, APIs, packaging components as well as the intended use of the product, and route of administration."	By clarifying the scope of "production process" and adding storage components, this will direct the reader to additional, necessary elements to consider in the risk assessment.

210-216	PDA recommends to move figure to Section 6: Root cause analysis. PDA also recommends to update figure clarifying inputs/contributors for nitrosamine impurities and clarify or remove the footnote. Additionally, PDA suggests to move away from the use of an Ishikawa diagram for this visual representation.	Figure 1. Ishikawa diagram (Example) • Remove stability and replace with storage, shipment distribution conditions • Remove raw material-replace solvents • Remove environment and replace with utilities • Add Cleaning • Add manufacturing/ packaging process • Add compatibility	This figure would be used as a tool for root cause analysis for determining the inputs/contributors for nitrosamine impurities. By moving the figure to after line 291, it would clarify for the reader that this tool should be considered for use during their root cause analysis. By making the inputs more specific, it will provide clarity for the reader of which inputs/contributors to evaluate for nitrosamine impurities. It is unclear in the footnote if “primary, secondary and tertiary causes” is referring to inputs/contributors for nitrosamine impurities or the amines (primary, secondary, tertiary amines) that can be formed as a result of them. It would be helpful to the reader to clarify this intent. Ishikawa diagrams are traditionally used for investigation purposes and there are several tools available to identify probable causes of nitrosamine contamination. By using a different visual representation, it will reduce potential confusion on the intended purpose of this figure.

224	PDA recommends updating the leading sentence to give the reader more flexibility in their root cause analysis.	**"The following questions should be considered as appropriate to the processes and materials:"**	The listing provided is comprehensive, so PDA suggests moving away from stating "As a minimum" to reduce potential reader confusion. By modifying the wording to include "as appropriate to the processes and materials" this will give readers the flexibility to perform risk management assessments that are unique and tailored to their processes.
249	PDA suggests expanding the statement to include equipment treatment considerations for potential nitrosamine contamination.	"Is peroxide present in any of the excipients, processing aids **or equipment treatment (e.g. Vaporized Hydrogen Peroxide, VHP) during production or manufacturing?**"	In the case of the finished pharmaceutical products (FPPs) filled in isolators, Vaporized Hydrogen peroxide is generally used for isolator biodecontamination and should be evaluated as a potential contributor to nitrosamine impurities in the pharmaceutical product.
273-274	PDA proposes to update this question to include other drug classes that are known sources of nitrosamine impurities.	"**Are other pharmaceutical products produced in this facility, a known source of nitrosamine impurities (ex: sartans, H2 blockers, etc.)?**"	Nitrosamine impurities have been identified/ detected in APIs and/or finished pharmaceutical products other than "sartan" products, such as ranitidine, nizatidine, pioglitazone and metformin. This proposed wording would direct the reader to consider additional sources of contamination other than "sartan" products. It might also be helpful to define what is meant by "sartan" in the glossary.

278-279	PDA suggests clarifying this statement to distinguish between general cleaning validation practices and cleaning with regard to nitrosamine impurities. PDA also proposes to add a reference to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) scientific guidance Q7:Good manufacturing practice for active pharmaceutical ingredient.	**"Do cleaning procedures and validation protocols ensure that nitrosamine contaminates are assessed? (Reference #)"**	The notion of worst-case product consideration (solubility, potency, toxicity and cleanability) are general cleaning validation concepts. By modifying the statement, the focus will be on Nitrosamine risk assessment. ICH Q7 provides recommendations for ensuring that contamination or cross-contamination with nitrosamine or nitrosamine precursors can be prevented.
283-284	PDA recommends modifying question to specific storage step considerations."	**"Have you evaluated nitrosamine formation during storage steps (exp: raw materials, solvents and finished products)?"**	If your process does not have a manufacturing step that can mitigate impurities (ex: Tangential Flow Filtration (TFF)or Purification) then the raw material storage should be considered.
287-288	PDA suggests expanding this question to encompass process typically used for biologics.	"Have the **Solvent and Detergents used in the S/D treatment,(or other processes)** been assessed for nitrosamine or nitrosamine precursor risk?"	For plasma-derived medicinal products, the manufacturing process usually includes a step called the Solvent/Detergent Treatment (anti-viral S/D treatment). By adding this, additional processes applicable to biologicals will be covered by this question.
292	PDA proposes the addition of another question for Section 6.2.	"**Have you considered the stability of product in dry form where there is residual moisture present?**"	Even if water is not added to the finished pharmaceutical product, residual water present in the product should be considered because it could lead to the generation of nitrosamine impurities.

351-355	PDA recommends correcting the typographic error in this sentence.	"The nature and composition of the cleaning solvents used for the cleaning of reactors used during API synthesis/purification and for the cleaning of finished dosage form equipment should be considered as cleaning solvents (e.g. amines) could react to form nitrosamines under certain conditions if the equipment is not perfectly dry prior to its **use** for subsequent manufacture and/or if there are residues remaining."	By correcting this error, it will clarify the meaning.
371	PDA proposes to add a statement regarding the considerations of potential nitrosamine contamination due to derouging and/or other chemical treatments.	"Where required, water should be purified to remove unacceptable impurities before use. **Consideration should be given for potential nitrosamine contamination through system treatment (e.g., derouging through passivation using nitric acid or other chemical treatments used on stainless-steel surfaces, other components or utilities)."**	The reader should be directed to consider the operational risks associated with chemical treatments, in particular that of stainless-steel maintenance which requires the use of harsh chemicals.
387-388	PDA recommends defining "quenching step".	"The risk of nitrosamine formation when a quenching step (**e.g., nitrous acid used to decompose residual azide)** is performed directly in the main reaction mixture should be avoided or controlled."	By defining what is mean by "quenching step" it will provide further clarification for reader.
402-403	PDA suggests adding "primary packaging materials" and a subsequent reference to the International Organization for Standardization document 15378: Primary packaging materials for medicinal products (Education 4, 2017) and/or the World Health Organization Technical Report Series, No. 902: Guidelines on Packaging for Pharmaceutical products (2002).	"Excipients **& primary packaging materials** should be manufactured in compliance with WHO GMP for excipients used in pharmaceutical products **(reference #)**."	Primary packaging materials should also be manufactured in compliance with WHO GMP guidelines. By providing references to the ISO and WHO, readers will be given documents that give practical guidance documents related to primary packaging materials.

410-411	PDA suggests rewording the statement to include other potential sources for packaging material source contamination. Additionally, PDA suggest supplier qualification be added.	"Packaging materials may be a source of contamination. For **example, nitrocellulose in PTP aluminium printing ink, PVC container material etc. The supplier qualification program should cover the verification of controls over the possibility of nitrite impurities or the presence of Nitrosating agents.**"	By expanding the examples of packaging material source contamination, readers will not incorrectly assume that nitrocellulose is the only agent of consideration. Supplier qualification on primary packaging materials manufacturers is crucial to the control Nitrosamines impurities.
413-416	PDA proposes to add a statement regarding purge factor and provide reference to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) scientific guidance M7 (R2) Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.	"Where the excipient is identified as a probable cause for formation of nitrosamine impurities, appropriate controls should be implemented. **For example**, **the calculation of purge factor is helpful to assess the Nitrosamines risk in the manufacturing process**. This may include consideration to change the supplier of the excipient or the change of the excipient to reduce the risk of nitrosamine impurities formation."	The manufacturing process of excipients should be assessed by excipient suppliers to consider a purge factor that may reduce and/or eliminate nitrosamines impurities. Discussion of the purge of nitrosamine impurities is present in another section (8.8), but not here in the excipients and packaging material section. This addition will tie the sections together for the reader. Addition of the ICH M7 (R2) reference will provide readers access to guidelines on how to assess the effectives off the purge produces of the excipient supplier.
414-416	PDA recommends removing this statement.		Supplier changes have many implications which require risk mitigation consideration before immediately changing suppliers. These are compliance strategies that have business risks that need to be fully assessed.

473-474	PDA suggests adding “based on justified and documented decisions” to the statement.	“API batches containing nitrosamine impurities may be reprocessed or reworked **based on justified and documented decisions** under oversight of the quality unit. Records should be kept.”	To ensure quality, a proper risk assessment should be carried out before initiating the reprocessing and/or reworking.
476-477	PDA suggests providing clarification on intended meaning of “recommend limits” in the case of API. Additionally, PDA proposes clarifying scope regarding blood and plasma products.		Currently recommended or acceptable limits are defined for FPP, not for API. The Finished pharmaceutical product contains API, leachables, etc., so there is a need to have lower limits set on the API. Clarification on acceptable API limits is needed to ensure the FPP does not exceed final limitations. Blood and Plasma products usually contain various levels of nitrosamines. The same might also apply to other biological material sources. Do we have specific norms for Biologics, and should it be included as part of this guidance?
503-505	PDA proposes to expand statement to include changes to materials used in addition to changes in the manufacturing process.	“If a nitrosamine impurity is detected, the root cause should be determined. Where appropriate, changes in the manufacturing process **or materials used** to mitigate or reduce the nitrosamine impurities should be made.”	In some cases, the root cause of nitrosamine impurities is not always the manufacturing process so changes in excipients, APIs or other materials used maybe required.
518-520	PDA suggests removing the last sentence of this note and adding a sentence that addresses considerations regarding biologic products.	“Note: Purification steps during the production of an API may assist in mitigating risks of the presence of nitrosamine impurity in the API. **Other mitigating steps during finished product steps, such as the use of filtration during purification steps in biologics products, can also be considered.”**	Mitigation steps may be present in the manufacturing of the pharmaceutical product itself. This is particularly true for biologics (purification and TFF are good examples).

532-533	PDA recommends providing clarification on the intended meaning of “greater than 1 g.”		Unclear if “greater than 1 g” is referring to 1 g of active ingredient(s) or 1 g of the final drug product. For injectables, the weight of the dosage can be high, especially in the case of large volume infusion. In the case of reconstituted lyophilized product, unclear if the 1 g applies to the added solution or if it should be assumed the solution is nitrosamine free. Additional clarification regarding intent would be beneficial.
552-555	PDA recommends providing a reference to the European Medicines Agency (EMA) guidance: Q&A: Good Clinical Practice (GCP).	“If N-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as described above, the Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines should be used to establish the AI, unless other robust data are available that would override this AI; **(Reference #)**”	The Carcinogenic Potency Categorization Approach (CPCA) is a useful technique for calculating AIs for nitrosamines. Providing reference to the EMA Q&A document, readers will be given a resource to know how to conduct such a technique.
590	PDA recommends adding guidance on how to proceed if more than one nitrosamine is present.	“These limits are applicable only if a drug product contains a single nitrosamine (1). **If more than a single nitrosamine is present, see the reference.”**	It would be beneficial to the reader to provide a reference to a guidance that can be used when multiple nitrosamines are present in the drug product.
595-597	PDA encourages directing the reader to use pharmacopeial or validated analytical procedures.	**“Pharmacopeial** or validated **(in the case of non-pharmacopeial)** analytical procedures should be used when testing for the presence of nitrosamines. The procedure should be sensitive for the determination of the specific nitrosamine(s) in the product.”	Pharmacopeial methods are more effective for the separation of nitrosamine impurities. In case of non-pharmacopeial methods, a validated analytical method should be used.
602-603	PDA suggests rewording this statement to include other Health Authorities as applicable.	**“Changes should be submitted to Health Authorities per local guidance.”**	Amended text will allow for global considerations.

644-649	PDA recommends removing “benefits” and reference to “NMRA”.	“The risks of products with levels of nitrosamines exceeding acceptable limits **and/or** more than one nitrosamine should be submitted to **Health Authorities according to regulatory requirements and as appropriate**. **Drug shortage should be assessed via a health risk assessment and** impact on the patient if the product will no longer be available. This could involve determining the availability of alternative products or treatments on their own market and the clinical impact of stopping or switching to a different treatment.”	As currently written, could be interpreted that some pharmaceutical products have enough “benefits” that they can exceed acceptable nitrosamine levels. Updating the text from “NMRA” to “Health Authorities” makes the guidance more suitable for global considerations.