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PSEHB/PED Notification No. 1008-1

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October 8, 2021

To Commissioners of Prefectural Health Departments (Bureaus):

Director, Pharmaceutical Evaluation Division,  
Pharmaceutical Safety and Environmental Health Bureau,  
Ministry of Health, Labour and Welfare

Director, Pharmaceutical Safety Division,  
Pharmaceutical Safety and Environmental Health Bureau,  
Ministry of Health, Labour and Welfare

Director, Compliance and Narcotics Division,  
Pharmaceutical Safety and Environmental Health Bureau,  
Ministry of Health, Labour and Welfare

## Self-inspection on Risks of Contamination with Nitrosamines in Drugs

In recent years, nitrosamines, which are carcinogens, have been detected in some sartan drugs, ranitidine, nizatidine, metformin, etc. in Japan and overseas, and some products have been voluntarily recalled.

Possible causes of nitrosamines contaminated in drugs include generation during the synthesis process, cross-contamination from shared facilities, contamination in recovered solvents or reagents, use of some packaging materials, and generation during storage. Therefore, the possibility that nitrosamines may be present even in drugs other than those in which nitrosamines have been detected cannot be denied, and it is important to reduce the risk of contamination as much as possible. For these reasons, we have now established the procedures for self-inspection on risks of contamination with nitrosamines in drugs as shown in the appendix.

Commissioners of Prefectural Health Departments are requested to instruct the marketing authorization holders (hereinafter referred to as "MAHs") under their jurisdiction to conduct self-inspection on risks of contamination with nitrosamines, in cooperation with manufacturers involved in the manufacture of drug substances or drug products, or their

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packaging, suppliers of excipients, reagents, container closure systems, etc., as well as administrators of active ingredients in Japan.

Questions and answers will be prepared separately in order to facilitate the self-inspection, and we will later issue an administrative notice.



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(Appendix)

## Self-inspection on Risks of Contamination with Nitrosamines in Drugs

### 1. Target drugs

The target drugs shall be the following (1) and (2). However, this does not apply to drugs that are indicated only for the treatments of advanced cancers which are defined in the scope of the application of ICH S9 Guideline (Guideline for Nonclinical Evaluation for Anticancer Pharmaceuticals) and drugs that are not directly used in human bodies.

- (1) Chemically synthesized prescription drugs, guidance-mandatory drugs, and over-the-counter drugs
- (2) Among Biologics, etc., those with high risks of contamination with nitrosamines as follows.
  - Biologics, etc. that contain chemically synthesized fragments and have risk factors equivalent to those of chemically synthesized active ingredients.
  - Drugs that are manufactured using the process of intentionally adding nitrosation reagents
  - Drugs that are packaged using specific primary packaging materials (blister packs, etc. containing nitrocellulose)

### 2. Basic concepts for self-inspection

- (1) In terms of the known root causes of contamination with nitrosamines (including those with potential risks), methods for the evaluation of contamination risks, and principles for the development of analytical methods, please refer to EMA or FDA guidance.
- (2) The limit values of nitrosamines contaminated in drugs shall be as follows.

[1]. When a single known nitrosamine is identified

For the limits of N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitroso-N-Methyl-4-Aminobutyric Acid (NMBA), N-Nitrosomethylphenylamine (NMPA), N-Nitrosoisopropylethylamine (NIPEA), N-Nitrosodiisopropylamine (NDIPA), Methylnitrosopiperazine (MeNP), N-



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Nitrosodibutylamine (NDBA), and N-Nitrosomorpholine (NMOR), the acceptable intake shown in the table should be applied.

Nitrosamines	Acceptable intake* (ng/day)
NDMA	96.0
NDEA	26.5
NMBA	96.0
NMPA	34.3
NIPEA	26.5
NDIPA	26.5
MeNP	26.5
NDBA	26.5
NMOR	127

\* Calculated based on TD 50 (dosage that causes tumor incidence to be 50%) in rodents, etc. A daily intake of carcinogenic impurities equivalent to a theoretical carcinogenic risk of 1 in 100,000.

[2]. When a single new nitrosamine is identified

The limits should be set in a scientifically valid manner, such as by setting limits assuming lifetime exposure with reference to ICH M7 (R1) when carcinogenicity study data using rodents are available, or by setting limits based on structure-activity relationships or genotoxicity study when carcinogenicity study data are not available.

[3]. When two or more nitrosamines are identified

The limits should be set in a scientifically valid manner not to exceed the carcinogenic risk of 1 in 100,000. For example, the following two methods can be considered.

- A method to set the total daily intake of all detected nitrosamines so that it does not exceed the acceptable intake of the most potent carcinogen among the detected nitrosamines
- A method to set the total carcinogenic risk of all detected nitrosamines so that it does not exceed the lifetime excess carcinogenic risk of 1 in 100,000

When setting limits in the cases of [2] and [3] above, the validity of such limits should be discussed with the Ministry of Health, Labour and Welfare (dedicated email address: nitrosamines@mhlw.go.jp).



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3. Items to be confirmed, implementation deadline, etc.
  - (1) As for items marketed by the company, the risks of contamination with nitrosamines shall be evaluated by April 30, 2023 with reference to the known root causes of contamination with nitrosamines.
  - (2) As a result of (1) above, for items that have a risk of contamination with nitrosamines, the amount of nitrosamines contained in the relevant drugs shall be measured in an appropriate number of lots. Items that are found to be contaminated with nitrosamines exceeding the limit shall be promptly reported to the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, the Ministry of Health, Labour and Welfare.
  - (3) As a result of (2) above, items that are found to be contaminated with nitrosamines exceeding the limit shall be subject to risk reduction measures such as setting an acceptance criteria or changing the manufacturing process to reduce the amount of nitrosamines. The measurement of the amount of nitrosamines in (2) above and the measures shown in this section shall be taken by October 31, 2024. In addition, if an application for approval of partial change or a notification of minor change is required due to the measures taken, such application or notification shall be made by October 31, 2024.
  
4. Items under application for approval or before filing an application for approval
  - (1) Items that are under application for approval of marketing (including applications for approval of partial change requiring risk evaluation for contamination with nitrosamines) and items whose applications for approval will be filed by April 30, 2023 shall be as follows.
    - [1]. The same kind of risk evaluation as in 3 (1) shall be conducted whenever possible. In the case where an application for approval is filed by April 30, 2023, the application for approval may be made prior to the risk evaluation described in 3 (1).
    - [2]. If there is a risk of contamination as a result of the evaluation in 3 (1), the measures in 3 (2) and (3) shall be taken.
    - [3]. These actions shall be treated as unrelated to the approval review, and the actions described in 3 (1) (when the approval is obtained by April 30, 2023)



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through (3) may be taken after approval. However, for ingredients (sartan drugs, ranitidine, nizatidine, metformin, etc.) that have already been identified as having a contamination risk or for items that have a known route of generation or contamination of nitrosamines in the manufacturing process, the results of risk evaluation and the appropriateness of risk reduction measures shall be confirmed in the approval review.

- (2) Items that will be filed for application for approval on or after May 1, 2023 shall be subject to the risk evaluation described in 3 (1) by the time of the application for approval. And necessary risk reduction measures shall be taken by October 31, 2024.

Note that in both cases (1) and (2) above, there may be cases that require the submission of materials related to risk evaluation results and risk reduction measures for ingredients, etc. that are newly identified as a risk in the future. Items under the approval review that are found to be contaminated with nitrosamines exceeding the limit shall be promptly reported to the Ministry of Health, Labour and Welfare (dedicated email address: nitrosamines@mhlw.go.jp) and the responsible review department of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA").

## 5. Responses by companies other than MAHs

- (1) Manufacturers involved in the manufacture of drug substances or drug products, or their packaging, and suppliers of excipients, reagents, container closure systems, etc. shall cooperate with this self-inspection by evaluating the risk of contamination with nitrosamines and providing information to the MAHs as much as possible.
- (2) Administrators of active ingredients in Japan shall have the manufacturers of drug substances, etc. registered in the drug master file (MF) conduct self-inspection in accordance with this notification, and provide information to the MAHs appropriately without delay. When taking the risk reduction measures described in 3 (3), the administrators shall make adjustments so that the MAHs can apply for the necessary application for approval of partial change or the notification of minor change, and shall make the necessary application for registration of MF changes or notification of minor changes, and report to the MAHs.



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## 6. Others

Please refer to the special website (<https://www.pmda.go.jp/safety/info-services/drugs/0371.html>, only in Japanese) for this self-inspection on the PMDA's website for related information as appropriate.

### References:

- EMA Guidance <sup>Note</sup>
  - Assessment report: Nitrosamine impurities in human medicinal products.
  - Questions and answers for MAHs /applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.
  
- FDA Guidance <sup>Note</sup>
  - Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs.

Note: For the latest guidance, please check the relevant regulatory authorities' websites (EMA: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities>, FDA: <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>).