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Past, Present (& Future) Regulation on Nitrosamines in Japan

240911
USP-MHLW/PMDA Joint WS

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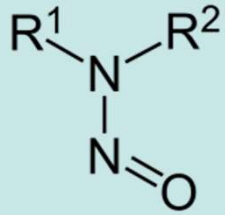
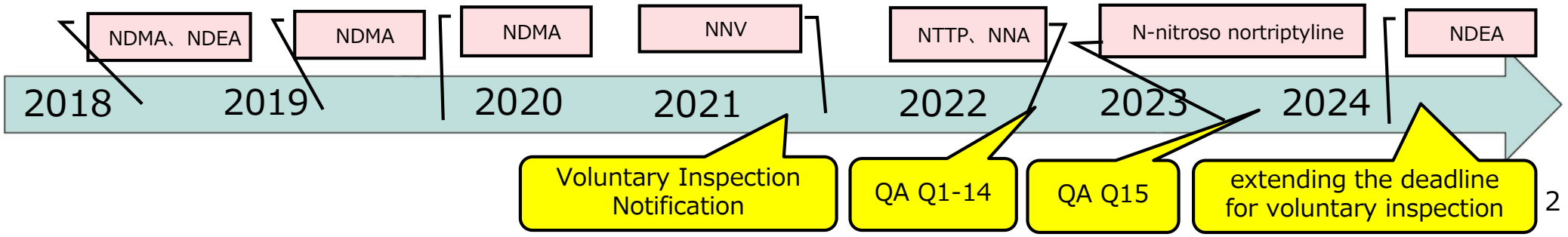
Response to Risk of Contamination with Nitrosamines (Summary)

- In recent years, nitrosamines*, potentially carcinogenic substances, have been detected in sultan-based pharmaceuticals, ranitidine, nizatidine, and metformin in Japan and overseas, leading to a voluntary recall of some products.
- Possible causes of contamination of pharmaceutical products with nitrosamines include generation during the synthesis process, cross-contamination from shared facilities, contamination in recovered solvents and reagents, use of certain packaging materials, and generation during storage.
- **In October 2021**, a notice was issued regarding the handling of **voluntary inspections on the risk of contamination of nitrosamines in pharmaceutical products**. In establishing the handling of voluntary inspections, the guidance of the EMA and the U.S. FDA was referred to.
- **In December 2022**, **Q&A (Q1-14) was issued** as an administrative communication to facilitate voluntary inspections.
- **In August 2023, Q&A (Q15) was issued** as an administrative communication to facilitate voluntary inspections.
- **In July 2024, a notice was issued extending the deadline (to 2025/8/1) for voluntary inspection.**



*Refers to a group of compounds that have a chemical structure in which a nitroso group is attached to an amine. (See figure above).Mainly formed by the nitrosation reaction of amine and nitrous acid.

Major drugs and substances detected with nitrosamines



- **Cases of Nitrosamines Detection and Response**
- Handling of Voluntary Inspections
- Risk Communication Guidance
- Voluntary Inspection Questionnaire for Nitrosamines

Detection cases and responses in sultan-based drugs (1)

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Case Summary

- On July 6, 2018, a MAH announced that N-nitrosodimethylamine (NDMA) had been detected in bulk Valsartan produced at a manufacturing facility in China, and a voluntary recall was issued. In addition, on September 13, the EMA, the U.S. FDA, and Health Canada announced that N-nitrosodiethylamine (NDEA) was newly detected in some lots of the said API.
- The MHLW instructed the MAH to analyze for NDMA and NDEA.
- **NDMA was presumed to have been formed as a byproduct in the synthesis process** of the tetrazole ring of Valsartan.

Responses

- In addition to the announcement by the MAH, a press release regarding the voluntary recall by the MAH was also issued on the MHLW's website. In addition, on September 7, 2018, an administrative communication (“Response to Detection of Carcinogen in Valsartan Preparation”) was issued **to inform the public of the status of response (analysis results by the MAH, etc.) since the announcement and the measures to be taken by those taking the drug**.
- On September 25, the case was reported to the Council* of the MHLW. **A health effects assessment was conducted in cooperation with the National Institute of Health Sciences (NIHS).** The results of the evaluation were announced in an administrative communication (“Results of Deliberations at the FY2018 8th Meeting of the Drug Safety Measures Subcommittee on Safety Measures Concerning the Detection of Carcinogens in Valsartan Preparations”) on October 5. * https://www.mhlw.go.jp/stf/shingi2/0000206683_00001.html

Detection cases and responses in sultan-based drugs (2)

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Case Summary

- NDMA and NDEA were detected in bulk Valsartan manufactured at a Chinese plant, and formulations using the API were recalled worldwide (previous slide).
- Furthermore, in the U.S and Europe, NDMA and NDEA were also detected in bulk Valsartan and other bulk sultan products manufactured by other drug substance manufacturers, and these products were recalled.
- In light of these international trends, on November 5, 2018, control indicators for NDMA and NDEA in sultan-based pharmaceutical products were established based on discussions* at the MHLW's Council. ※ https://www.mhlw.go.jp/stf/shingi2/0000183979_00001.html

Responses

- The program is intended for businesses, etc. that manufacture and sell sultan-based pharmaceutical products in which the risk of generation of NDMA and NDEA is assumed in the manufacturing process.
- **The concept of internationally harmonized guidelines (ICH-M7) is applied to the management of impurities with carcinogenic potential, and control indicators for NDMA and NDEA are set.** Control values for individual drug ingredients are calculated based on the maximum daily dose.
- On November 9, 2018, an administrative communication ("Establishment of Control Indicators for Carcinogenic Substances in Sultanate Medicines (Request)") was issued, requesting business operators that manufacture and sell sultanate medicines with a risk of generating NDMA and NDEA **to implement manufacturing and quality control based on the control indicators.**

Detection cases and responses in Ranitidine and Nizatidine

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Case Summary

- On September 13, 2019, the EMA and the U.S. FDA announced that trace amounts of NDMA had been detected in the drug substance of Ranitidine Hydrochloride.
- On September 17, MHLW instructed the MAH of Ranitidine and Nizatidine to analyze NDMA in the API of both drugs and the formulations containing them, and to consider recalling the products if it cannot be denied that the levels exceed the provisional standard values. As a result, all Ranitidine products on the market were voluntarily recalled because it could not be denied that they exceeded the provisional standard values. As for Nizatidine, a lot in which NDMA exceeding the provisional standard was detected was voluntarily recalled.
- It was estimated that **NDMA may have been formed in Ranitidine due to degradation of Ranitidine itself.**

Responses

- On September 17, 2019, an administrative communication ("Response to Detection of Carcinogen in Ranitidine Hydrochloride") was issued. **The MAH are instructed to analyze the drug substance and formulation for NDMA and to consider recalling the product if it cannot be ruled out that the concentration exceeds the provisional standard value.**
- On July 27, 2020, the case was reported to the Council* of the MHLW. A health impact assessment was conducted in cooperation with the NIHS. The results of the evaluation were announced in an administrative communication ("Results of Health Effects Assessment of Ranitidine Hydrochloride or Nizatidine Preparations in which N-nitrosodimethylamine was detected") on September 1. * https://www.mhlw.go.jp/stf/newpage_12568.html

Detection cases and responses in Metformin

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Case Summary

- On December 4, 2019, the Health Sciences Authority of Singapore announced that trace amounts of NDMA had been detected in preparations containing Metformin Hydrochloride.
- On December 9, MHLW ordered domestic MAH of Metformin products to analyze their formulations and APIs for NDMA. On April 27, 2020, NDMA exceeding the provisional standard was detected in some lots of the formulation, and two MAHs voluntarily recalled the product.
- **It was suggested that NDMA may have been generated by the reaction between an ingredient (nitrocellulose) in the printing ink on the PTP sheet and an ingredient (dimethylamine) derived from the API, or during the formulation process.**

Responses

- On December 9, 2019, an administrative communication ("Response to Detection of Carcinogen in Metformin Hydrochloride") was issued. **The MAH are instructed to analyze the API and formulation for NDMA.**
- On July 27 and September 30, 2020, the case was reported to the MHLW's Council*. Conducted a health impact assessment in cooperation with the NIHS. The results of the evaluation were announced in an administrative communication ("Results of Health Effects Assessment of Metformin Preparation in which N-nitrosodimethylamine was detected") on October 19. * https://www.mhlw.go.jp/stf/newpage_12568.html & https://www.mhlw.go.jp/stf/newpage_13767.html

Detection cases and responses in Sitagliptin Phosphate Hydrate

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Case Summary

- On August 9, 2022, the U.S. FDA announced that NTTP (7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3-a] pyrazine) had been detected in a Sitagliptin Phosphate Hydrate formulation.
- NTTP was thought to be formed by nitrosation of the raw materials of Sitagliptin Phosphate Hydrate formulation or degradation products during the manufacturing process.
- In general, nitrosamines are potentially carcinogenic, but it is not known at this time whether NTTP is carcinogenic in animals.
- The U.S. FDA recommends continued use of the drug when clinically appropriate to prevent a period of no treatment, as it is potentially dangerous for patients to stop taking the drug without consulting a health care professional at this time.

Responses

- On September 1, 2022, the MHLW issued an administrative communication ("Response to Detection of Nitrosamines in Sitagliptin Phosphate Hydrate Preparation").
- Report on the case to the MHLW's Council*. * https://www.mhlw.go.jp/stf/newpage_28092.html
- Currently, the MAH are considering conducting additional non-clinical studies and evaluating safety, and the results will be made known as soon as they are finalized.

Detection cases and responses in Amoxapine

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Case Summary

- On August 31, 2022, a MAH announced that N-nitrosoamoxapine was detected in an Amoxapine preparation as a result of a voluntary inspection.
- **N-nitrosoamoxapine was thought to be formed by nitrosation of the active ingredient in Amoxapine preparations.**
- In general, nitrosamines are potentially carcinogenic, but it is currently unknown whether N-nitrosoamoxapine is carcinogenic in animals.
- **Withdrawal symptoms may occur with rapid dose reduction or discontinuation of the drug.**

Responses

- On September 1, 2022, an administrative letter ("Response to Detection of N-nitrosamines in Amoxapine Preparations") was issued.
- On September 27 and October 25, the case was reported to the MHLW's Council*. Conducted a health impact assessment in cooperation with the NIHS. The results of the evaluation were announced in an administrative communication ("Results of Health Effects Assessment of Amoxapine Preparations in which N-nitrosoamoxapine was detected") on November 9, 2022.
  * https://www.mhlw.go.jp/stf/newpage_28092.html & https://www.mhlw.go.jp/stf/newpage_28762.html
- **The MAH voluntarily recalled the drug after a certain transitional period, based on the fact that withdrawal symptoms may appear and that the risk of cancer caused by the drug cannot be completely ruled out.**

Detection cases and responses in Nortriptyline

Case Summary

- On June 7, 2023, a MAH announced that N-nitrosonortriptyline was detected in a Nortriptyline Hydrochloride preparation as a result of a voluntary inspection.
- **N-nitrosonortriptyline was thought to be formed by nitrosation of the active ingredient in the Nortriptyline Hydrochloride formulation.**
- In general, nitrosamines are potentially carcinogenic, but it is currently unknown whether N-nitrosonortriptyline is carcinogenic in animals.
- **Withdrawal symptoms may occur with rapid dose reduction or discontinuation of the drug.**

Responses

- On June 7, 2023, the case was reported to the MHLW's Council*. Conducted a health impact assessment in cooperation with the NIHS. On June 8, an administrative communication ("Response to Detection of N-nitrosamines in Nortriptyline Hydrochloride Preparation") was issued. * https://www.mhlw.go.jp/stf/newpage_33471.html
- **In light of the results of the health assessment and the fact that withdrawal symptoms may appear, the immediate response is to provide information on the results of the health effects assessment and inform the public to consider switching to other drugs, etc. (No voluntary recall was conducted).** In addition, since it is necessary to prevent excessive exposure to N-nitrosonortriptyline, **provisional control values have been set and shipments are being controlled.**
- MHLW will continue to consider further measures as necessary in light of overseas trends, etc.

Detection cases and responses in Entacapone

Case Summary

- On March 22, 2024, a MAH announced the detection of NDEA in an Entacapone preparation as a result of a voluntary inspection.
- Entacapone has a diethylamide structure [-CO-N(CH2CH3)2] in its structure, and there is a possibility that NDEA is formed by nitrosation of diethylamine generated in the manufacturing process in the presence of nitrite.
- Based on the results of the follow-up survey of the prescription continuation status of patients treated with Entacapone using the domestic medical database, it was considered that Entacapone has been administered for less than 10 years. Therefore, the acceptable daily intake of 177.55 ng*, calculated by applying the LTL approach of the ICH M7 guideline, was set as the control value for NDEA in Entacapone.

Responses

- Voluntarily recalled lots of single dosage form of Entacapone that exceeded the control value in the already shipped dosage form.
- On March 26, 2024, the Health Effects Assessment was conducted by the MHLW's Council*, and on March 29, an administrative communication (Results of the Health Effects Assessment of the use of a preparation containing Entacapone in which N-nitrosodiethylamine was detected) was issued. * https://www.mhlw.go.jp/stf/newpage_38855.html
- When discontinuing the drug, patients are cautioned not to discontinue the drug solely on their own judgment, as malignant syndromes and rhabdomyolysis, which are seen in patients with Parkinson's disease, may occur.

- Cases of Nitrosamines Detection and Response
- **Handling of Voluntary Inspections**
  2021/10/8 Voluntary Inspection
  2022/12/22 QA
  2023/8/4 Revised QA
  2024/7/30 Extension
- Risk Communication Guidance
- Voluntary Inspection Questionnaire for Nitrosamines

1. Eligible drugs

The following are eligible drugs. However, drugs that are indicated only for the treatment of advanced cancer as defined in the scope of application of the ICH S9 Guidelines (Guidelines for the Nonclinical Evaluation of Antineoplastic Agents) and drugs that are not used directly on the human body are not covered.

a. Chemically synthesized ethical drugs, drugs requiring special instructions and over-the-counter drugs

b. Biological preparations, etc., which have a high risk of contamination with the following nitrosamines

- Biologics, etc., containing chemically synthesized fragments that have risk factors equivalent to those of chemically synthesized active ingredients
- Manufactured using a process in which nitrosating reagents are intentionally added
- Packaged using certain primary packaging Packaged using materials (e.g. blister packs containing nitrocellulose)

1. Eligible drugs (excerpts from the Q&A)

Q1 Attachment 1 (1) of "Voluntary Inspection of Risk of Contamination of Nitrosamines in Drugs" (October 8, 2021, Hereafter referred to as the "Voluntary Inspection Notice") states "chemically synthesized ethical drugs, drugs requiring special instructions, and OTC drugs", but does this only apply to those whose active ingredients are chemically synthesized?

A1 The term basically refers to drugs that contain synthetic or semi-synthetic APIs as active ingredients. However, even for pharmaceutical products manufactured by methods other than synthesis by artificial chemical reactions, it is not always possible to say that the risk of contamination with nitrosamines is lower for such pharmaceutical products than for those containing synthetic or semi-synthetic APIs as active ingredients. The manufacturer/distributor shall appropriately determine the necessity of the risk assessment of contamination. Note that MAH are required to take appropriate measures even for pharmaceutical products not included in the scope of the Voluntary Inspection Notice, because of the need to conduct proper evaluation of the effects on the quality, efficacy, and safety of pharmaceutical products and their effects on human health.

Q2 Is it correct to consider inorganic salts to be outside the scope of this voluntary inspection?

A2 Basically, it is not covered, but appropriate measures should be taken based on the manufacturing method.

Q3 Can crude drugs and their preparations (including Chinese herbal extracts) be considered to be outside the scope of this voluntary inspection?

A3 It is acceptable. However, combination products of active pharmaceutical ingredients and crude drugs and their preparations (including Chinese herbal extracts) are subject to self-inspection. For such combination products, evaluation should be based on information on the active pharmaceutical ingredients, packaging, additives, reagents, container closure system, etc.

2. Basic Concept of Voluntary Inspection

A) Refer to EMA or FDA guidance on known (including potential risk) root causes of adulteration of nitrosamines, methods for assessing the risk of adulteration, and principles for developing analytical methods.

B) The limits for nitrosamines in pharmaceutical products should be as follows

① One known nitrosamines identified

Nitrosamines	AI (ng/day) AI : acceptable intake
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

② One new nitrosamines identified

If data on carcinogenicity tests using rodents are available, limit values should be set based on the assumption of lifetime exposure with reference to ICH M7(R1), etc. If data on arcinogenicity tests are not available, limit values should be set based on structure-activity relationships or genotoxicity tests, or in other scientifically valid ways.

③ When two or more nitrosamines are identified

A limit value should be set in a scientifically valid manner so that the carcinogenic risk of 1 in 100,000 is not exceeded. For example, the following two methods may be considered.

- Setting the limit so that the sum of the daily intake of all detected nitrosamines does not exceed the allowable intake of the most carcinogenic of the detected nitrosamines
- Setting the limit so that the sum of the carcinogenic risks of all detected nitrosamines does not exceed the lifetime excess carcinogenic risk of 1 in 100,000

When setting the abovementioned limits, consult with the MHLW regarding the appropriateness of the limits.

2. Basic Concept of Voluntary Inspection (excerpts from the Q&A)

Q 5　Attachment 2 (1) of the Voluntary Inspection Notice states "Guidance from EMA or FDA should be referred to for root causes of contamination, methods for evaluating the risk of contamination, principles for developing analytical methods, etc." Please indicate the specific part of the guidance to be referred to.

A 5

	FDA "Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs"	EMA "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products."
root causes of contamination	II. BACKGROUND	4.What are the currently identified root causes for presence of nitrosamines?
methods for evaluating the risk of contamination	III. RECOMMENDATIONS	7. How should the risk evaluation be performed?
principles for developing analytical methods	III.RECOMMENDATIONS	8. How should confirmatory tests be conducted by MAHs and manufacturers? 9. What are the requirements of the analytical method(s)?

The main reference should be to the FDA Guidance and the EMA Guidance. The PMDA's website (https://www.pmda.go.jp/safety/info-services/drugs/0371.html) provides links to these guidance documents. In addition, Japanese translations of the FDA and EMA guidance are available in the "Notices" section of the website of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ), and should be referred to as necessary.

2. Basic Concept of Voluntary Inspection (excerpts from the Q&A)

Q11　What determines that the risk of contamination with nitrosamines is not confirmed? The basic concept of Voluntary Inspection states "refer to the guidance of the EMA or FDA", however, since the interpretation may differ, is there any plan from MHLW to present a list of evaluation items, etc.?

A11　For the evaluation method of contamination risk, refer to the ICH-Q9 Guideline on Quality Risk Management. Although there is no plan to provide a list of evaluation items, the evaluation should be conducted with reference to either "III. RECOMMENDATIONS" of the FDA guidance or "7. How should the risk evaluation be performed?". (Please refer to the latest information on the FDA and EMA guidance.)

For nitrosamines for which a limit value is indicated in Attachment 2 (2) of the Voluntary Inspection Notice regarding the limit value of nitrosamines that can be mixed in the drug product, the limit value should be followed.

When setting a limit value in cases where nitrosamines for which no limit value is indicated are identified, or where multiple nitrosamines are identified, consult with the MHLW regarding the appropriateness of the limit value. In explaining the reasonableness, if the limit value is set as described in the EMA or FDA guidance, this should also be stated. 。

2. Basic Concept of Voluntary Inspection (excerpts from the Q&A)

Q15 Attachment 2 (2) of the Voluntary Inspection Notice states, "If carcinogenicity test data are not available, limit values should be set using scientifically valid methods such as structure-activity relationships or genotoxicity tests". However, the EMA guidance has recently been updated and The Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines (Annex 2) has been presented. Is it acceptable to use this approach in setting the limit values in Japan?

A15 For nitrosamines for which there is no sufficient carcinogenicity test data, it is acceptable to set the limit value using the CPCA presented by the EMA this time. In the case of setting the limit value using the CPCA in the case of Attachment 2 (2) ② of the Voluntary Inspection Notice, consultation with the MHLW regarding the validity of the limit value is not required.

In cases where the limit value can be considered scientifically valid, setting the limit value based on the conventional structure-activity relationship is not denied.

3. confirmation items, implementation deadlines, etc.

1. Evaluate the risk of contamination with nitrosamines **by April 30, 2023**, with reference to known causes of contamination with nitrosamines for items manufactured and sold by the MAH.
2. As a result of 1., for items with a risk of contamination with nitrosamines, the amount of nitrosamines contained in the drug product in question should be measured in an appropriate number of lots. Any item found to be contaminated with nitrosamines exceeding the limit value shall be promptly reported to the MHLW.
3. For items that are found to be contaminated with nitrosamines exceeding the limit as a result of 2., risk reduction measures, such as setting a specification value or changing the manufacturing method to reduce the amount of nitrosamines, should be taken. The measurement of the amount of nitrosamines mentioned in 2. and the measures indicated in this section must be conducted **by October 31, 2024**. If an application for partial change approval or notification of a minor change is required in conjunction with these measures, such application or notification must be submitted **by October 31, 2024**.

In accordance with the "Extension of the Implementation Deadline for Voluntary Inspection of the Risk of Contamination of Nitrosamines in Pharmaceutical Products" (dated July 30, 2024), the implementation deadline for the risk reduction measures was **extended to August 1, 2025**.

3. confirmation items, implementation deadlines, etc. (excerpts from the Q&A)

Q８　If nitrosamines exceeding the limit values are detected and need to be reported to the MHLW, how should they be reported?

A８　The report may be in any format, but should include the following information;

- Name and content of nitrosamines exceeding the limit
- Necessity of recall
- Evaluation of impact of nitrosamines exceeding the limit on product quality (including specific evaluation method, criteria, lots measured, lots exceeding the limit, distribution status of each lot, etc.)
- Distribution status in the market
- Impact on the market due to recall
- status of overseas measures
- Proposed response schedule (timeline)　,etc.

Q10　If the risk assessment results show that there is no contamination risk or the measurement results are below the limit, is it necessary to report this to the MHLW? Also, how should we handle reports on risk assessment and measurement results internally?

A10　Although reporting is not required, it is the responsibility for the MAH to document and retain the reports on risk assessment and measurement results for an appropriate period of time. It should be noted that such reports may be required to be submitted at the time of application for partial change approval, GMP investigation, etc.

4. For items for which an application for approval is ongoing or has not yet been filed

（1） The following is a list of items for which an application for approval for manufacturing and marketing (including an application for partial change approval requiring risk assessment of contamination with nitrosamines) is ongoing and for which an application for approval will be submitted **by April 30, 2023**.

① The same risk assessment as in 3(1) should be performed as much as possible. If an application for approval is to be submitted **by April 30, 2023**, it is acceptable to submit the application for approval prior to the risk assessment in 3(1).

② If the assessment in 3(1) indicates that there is a risk of contamination, the measures in 3(2) and 3(3) should be taken.

③ This action should be treated as unrelated to the approval review, and actions 3(1) (if the approval was obtained **by April 30, 2023**) through (3) may be taken even after approval. However, for ingredients for which the risk of contamination has already been identified (e.g., sartans, ranitidine, nizatidine, metformin, etc.) or for items with a known generation or contamination route of nitrosamines in the manufacturing process, the results of risk assessment and appropriateness of risk reduction measures shall be confirmed in the approval review.

4. For items for which an application for approval is ongoing or has not yet been filed

（2）For items for which an application for approval is to be submitted **on or after May 1, 2023**, the risk assessment described in 3(1) should be conducted by the time of the application for approval. Necessary risk reduction measures should be taken **by October 31, 2024**.

Note

- In both cases (1) and (2) above, please note that the MHLW may request the submission of risk assessment results and risk reduction measures for newly identified risk components in the future.
- In addition, for items that are found to be contaminated with nitrosamines exceeding the limit values during the approval review, the MAH shall promptly notify the MHLW/PMDA.

In accordance with the "Extension of the Implementation Deadline for Voluntary Inspection of the Risk of Contamination of Nitrosamines in Pharmaceutical Products" (dated July 30, 2024), the implementation deadline for the risk reduction measures was **extended to August 1, 2025**.

5. response of the manufactures other than MAH

1. Manufacturers involved in the manufacture or packaging of APIs or drug products and suppliers of additives, reagents, container closure systems, etc. should evaluate the risk of contamination with nitrosamines and cooperate with this voluntary inspection by providing as much information as possible to MAHs.
2. The In-Country Custodian for Active Pharmaceutical Ingredients (INPI) should have manufacturers of APIs registered in the MF register conduct voluntary inspections in accordance with this notice, and provide information to the MAH appropriately without delay. In addition, when implementing the risk reduction measures in 3 (3), the INPI should coordinate to file an application for partial change approval or a notification of minor change as necessary, and should promptly file an application for registration of change or notification of minor change in the MF as necessary, and report to the MAH.

- Cases of Nitrosamines Detection and Response
- Handling of Voluntary Inspections
- **Risk Communication Guidance**
- Voluntary Inspection Questionnaire for Nitrosamines

Future Responses in Light of the Risk Communication Guidance Based on the Systematic Risk Assessment Methodology for Nitrosamines

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Past Initiatives

- Information has been provided to the medical community and patients based on the health impact assessment by the MHLW's Council.
- On the other hand, the introduction of CPCA has enabled rapid and simple risk assessment through a systematic risk assessment method.
- Guidance developed by the FY2023 MHLW's study contributed to prompt and high quality risk communication, and the categorization of items for which information should be provided and how to cooperate with related organizations were organized. In particular, a draft model for the provision of information was prepared and disseminated in a notice.

Future correspondence

- Based on the above efforts, from the viewpoint of providing information to the medical community more promptly, it was decided that, in principle, information will be provided to the medical community by the MAH without going through the discussion at the MHLW's Council.
- However, in the following cases, health effects assessment of each drug product is necessary, and therefore, the information to be provided to the medical community will be organized after the evaluation by the MHLW's Council.
  - ✓ For new nitrosamines, limit values are set based on toxicity data of compounds with similar structure instead of CPCA, and safety control measures such as recall and provision of information are taken
  - ✓ Due to circumstances such as limited period of drug administration, Less-than-lifetime (LTL) approach is applied
  - ✓ When careful consideration of safety control measures is required.

Positioning of this guidance

- Based on the current state of knowledge, this document indicates items to be considered by MAH when providing information to the medical community, etc. regarding the contamination of pharmaceuticals with nitrosamines in excess of the limit values.
- However, it should be noted that further action may be required depending on the circumstances of individual pharmaceutical products.

Risk Communication Guidance Based on a Systematic Risk Assessment Methodology for Nitrosamines

Items for which information should be provided to medical institutions

- Background of the information provided. In addition to a general description of the nitrosamines, include a description of the health risks due to adulteration.
- Names of nitrosamines detected
- Potential health effects
  - ✓ Whether or not the detected nitrosamines are mutagenic or carcinogenic (including unknown)
  - ✓ Acceptable daily intake (AI) of the detected nitrosamines
  - ✓ Whether or not the measurement results of the detected nitrosamines exceed the AI
    Example 1: "The theoretical cancer risk is equivalent to an excess risk of cancer in approximately 1 in X million people“
    Example 2: "The value detected here is up to X times higher than this acceptable intake.
- Measures to be taken
  - ✓ Whether or not the shipment of the product can continue (recall or not) and the reason
  - ✓ Risks to patients who have taken the product in the past
  - ✓ Recommendations for discontinuation or continuation of prescriptions for patients currently taking the product
  - ✓ Prospects for future supply
- If there are any changes in the risk assessment or the measures taken for the drug product in light of the latest findings, information should be provided promptly.

- Cases of Nitrosamines Detection and Response
- Handling of Voluntary Inspections
- Risk Communication Guidance
- **Voluntary Inspection Questionnaire for Nitrosamines**

Summary of Results of the First Questionnaire on Voluntary Inspection of Nitrosamines (1)

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Conducting Surveys

- With the cooperation of related industries, a survey was conducted from February 8 to March 1, 2024. Although the responses did not cover the detailed number of items, the general situation was as follows.

Result Summary

<Progress of voluntary inspections>

- 80-90% of the risk assessment of contamination has been completed, of which 10% have risk and 70-80% do not have risk.
- 20-30% of the items to be measured have been actually completed.
- Many items are still considering whether risk management measures are necessary.
- Risk management measures currently under consideration include setting specifications at the stage of APIs and intermediates, setting shipping specifications for final products, controlling nitrous acid at the time of receiving additives, and relatively many other measures that do not involve changes to the approval documents.

<Factors hindering voluntary inspections (partial list)>

① Relationship with setting of specifications

- It is difficult to set the allowable intake when CPCA is not applicable. Setting by the lead-across method is difficult.
- Lack of clear guidelines for setting acceptable intake levels (setting of values exceeding 1500 ng/day, availability of Enhanced Ames test, etc.)
- Late response from the MHLW

Summary of Results of the First Questionnaire on Voluntary Inspection of Nitrosamines (2)

Result Summary

② Risk assessment and measurement of contamination

- Insufficient information obtained from manufacturers of additives, raw materials, materials, containers, etc. makes it difficult to identify the nitrosamines generated, etc.
- There is a lack of analytical equipment and analysts for in-house measurement of nitrosamines. In the case of outsourcing, there are a limited number of analysis institutions that can perform the analysis, and outsourcing also requires time.
- Synthesis or acquisition of standard products is difficult, and measurement costs are high.
- Development of analytical methods is difficult in cases such as formulations containing many foreign substances, formulations with low limit values, and cases where nitrosamines are decomposed or generated during measurement operations.

③ Risk reduction measures

- Difficult to identify the formation pathway of nitrosamines.
- When changing raw materials or manufacturing methods, there are many parameters to consider and much time is required.
- When changing raw materials, differences in manufacturers and model numbers have a significant impact on physical properties, requiring much time to study.
- Raw materials with low risk cannot be changed because they are not distributed in Japan. Difficult to ask the manufacturer of the raw material that is the source of contamination to make improvements.

Summary of Results of the Second Questionnaire on Voluntary Inspection of Nitrosamines

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Ministry of Health, Labour and Welfare

Conducting Surveys

- Based on the results of the first questionnaire, it became necessary to reconfirm the risk management measures taken by each company, so a second questionnaire was conducted from April 19 to May 20, 2024, and the results were as follows.
- We plan to present the points to be noted in the pharmaceutical procedures regarding risk management measures in near future.

Result Summary

<Ethical pharmaceuticals>

- 95% of the risk assessment of contamination was completed. (14% risk, 81% without risk.)
- Of the items to be measured, 30% have been measured, and many items are being measured or will be measured in the future.
- Of the items that have been measured, 61% are below the detection limit, 31% are above the detection limit to below the limit, and 8% are above the limit.
- As for planned risk management measures, 58% will not set a specification value to the final product and will manage it in other ways (no change in the approval document), 29% will add a specification value (including cases where control measures other than adding a specification are also taken), and 13% will add a specification value to the final product but will skip testing.

Thank you for your attention.