Control of organic impurities in marketed products in Japan
- current status and perspectives

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Today's Agenda

1. JP General information : Concept on impurities in chemically synthesized Drug Substances and Drug Products
2. Current status of the ICH M7-based control options in Japan

1. JP General information : Concept on impurities in chemically synthesized Drug Substances and Drug Products

The purpose of “Concept on impurities in chemically synthesized Drug Substances and Drug Products”

- This General Information presents an overview of the control of impurities in drugs currently distributed in Japan and products listed on the Japanese Pharmacopoeia (both chemically synthesized), and outlines the concepts of ICH Q3A/B and the control of impurities in products listed on the Japanese Pharmacopoeia, with a focus on organic impurities.
- With such a comprehensive reference, the basic principles of purity testing and analogous substance setting shown in each article of pharmaceutical products will be clarified, and what the Japanese Pharmacopoeia expects from impurity control will be clearly stated.

The agenda of “Concept on impurities in chemically synthesized Drug Substances and Drug Products”

1. Classification of impurities found in chemically synthesized pharmaceuticals and the guidance to comply with for their control

2. The concept of ICH Q3A and Q3B guidelines for the control of organic impurities

3. Principles for controlling organic impurities in the articles listed in the JP

Classification of impurities found in chemically synthesized pharmaceuticals and the guidance to comply with for their control

- New drug substances
  - ➢ Specified
- Generic drugs
  - ➢ The drug substance is identical to that of the brand name drug.

    The drug product has equivalent bioavailability.
- Drugs listed in the JP
  - ➢ Official specifications available
  - ➢ Note that time of listing may largely differ.

- Organic impurities

Starting materials, by-products, intermediates, degradation products, reagents, etc.

- Inorganic impurities (elemental impurities)

Reagents, etc., heavy metals, and other materials (filter aids, charcoal, etc.)

- Residual solvents

Control of organic impurities in new drug substances : Reference guidelines

- Q3A: Impurities in New Drug Substances (PAB/ED Notification No. 877 dated September 25, 1995)
- Q3B: Impurities in New Drug Products (PAB/ED Notification No. 539 dated June 23, 1997)

  - DNA Reactive (mutagenic) impurities
    - ✓ M7: Assessment and Control of DNA Reactive(Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015)
  - Optical enantiomers
    - ✓ Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (PMSB/ELD Notification No. 568 dated May 1, 2001)

Control of organic impurities in drugs other than new drug substances

- Even for drugs other than new drug substances, control of organic impurities is required in accordance with the above guidelines from the viewpoint of ensuring the quality.

→ These guidelines apply as appropriate for marketing application (application for partial change).

- Any generic drug is required to have the quality identical to and comparable to that of the brand name drug by review. Q3A/B guidelines apply to brand name drugs.

→ Even to generic drugs, concepts of the Q3A/B guidelines apply for control.

Principles of control of organic impurities in products listed in the JP (1)

- Drugs in which impurities have been controlled in accordance with the ICH Q3A and Q3B guidelines
  - Specified impurities, unspecified impurities, and total impurities established in accordance with the ICH Q3A and Q3B guidelines at the time of JP listing.
- Drugs listed in the JP long before application of these guidelines
  - Some drugs are not required to have impurities controlled in accordance with Q3AB.
  - Even such old drugs listed in the JP, however, may be required to have impurities controlled in accordance with the ICH Q3A and Q3B guidelines where necessary when a new marketing application is submitted.
- The acceptance limits will be established based on the analysis data at the development stage submitted by a company preparing the draft monograph (draft preparing company) and analysis data on impurities in production batches after stabilization of the manufacturing process.
- Because the safety has been evaluated at the time of approval, it will not be evaluated again at the time of JP listing.

Principles of control of organic impurities in products listed in the JP (2): Corrections in the JP in view of Q3AB: 1

- When organic impurities evaluated in accordance with the ICH Q3A and Q3B guidelines are included in the JP monograph by defining procedures for the purity test, original corrections are made to ensure consistent and reasonable handing of the impurities in the JP.
  - Unless otherwise exclusively specified, impurity reference standards will not be established, and identification of the impurities by liquid chromatography, if applicable, will be performed based on relative retention times of the impurities with respect to the drug substance.
  - If the drug is highly purified, and only unspecified impurities (not more than 0.1%) are included, the acceptance limit for the total impurities may not be established in general.
  - If the acceptance limit is established based on measured values only, resulting in assignment of slightly different acceptance limits to many impurities, consideration should be given so that the test includes the small number of representative acceptance limits.
  - Neither chemical structure nor name of any impurity will be disclosed.
  - These measures allow control of impurities without the impurity reference standards and establishment of a simplified system suitability test for highly purified drugs where applicable.

Principles of control of organic impurities in products listed in the JP (3): Corrections in the JP in view of Q3AB: 2. Current actions

- Identification based on relative retention times depends on column; analysis would be difficult without an appropriate column.
  - The JP 17 additionally accepts analysis methods using impurity reference standards for the purity test of the drug substance.
- In principle, information about impurities including the chemical name and structural formula will be disclosed in the JP as well.
- When special consideration is given to the purity test for organic impurities in a drug product at the time of JP listing
  - Impurities in a drug product are defined as substances derived from reaction products of the drug substance with an excipient and/or immediate container closure system. These impurities can differ depending on the formulation, and even some may not be generated in a different formulation. Because the JP accepts various formulations, it may not be appropriate to establish uniform acceptance limits in the monograph, and in such a case, the monograph may include a statement “separately established,” allowing the establishment at the time of approval.

Principles of control of organic impurities in products listed in the JP (4): Concept of reinvestigation of acceptance limits for impurities during review of the specifications for impurities when the new monograph of a drug is listed in the JP

- The ICH Q6A guideline points out that data submitted in marketing application are limited, potentially affecting establishment of the acceptance criteria, and thus consideration should be given to such an impact.
- For impurities, the profile obtained at the manufacturing stage is different from that at the development stage in some cases, and thus consideration should be given to the change in impurity profile at the manufacturing stage where necessary.
- Regarding impurities to be specified at the time of JP listing, consideration should be given to not only information obtained at the development stage but also that about the change in impurity profile at the manufacturing stage, if any, and that at the stage where the product manufacture has been stabilized (stable manufacturing stage).

Principles of control of organic impurities in products listed in the JP (5): Handling of impurities that have been adequately reduced or no longer detected at the stable manufacturing stage

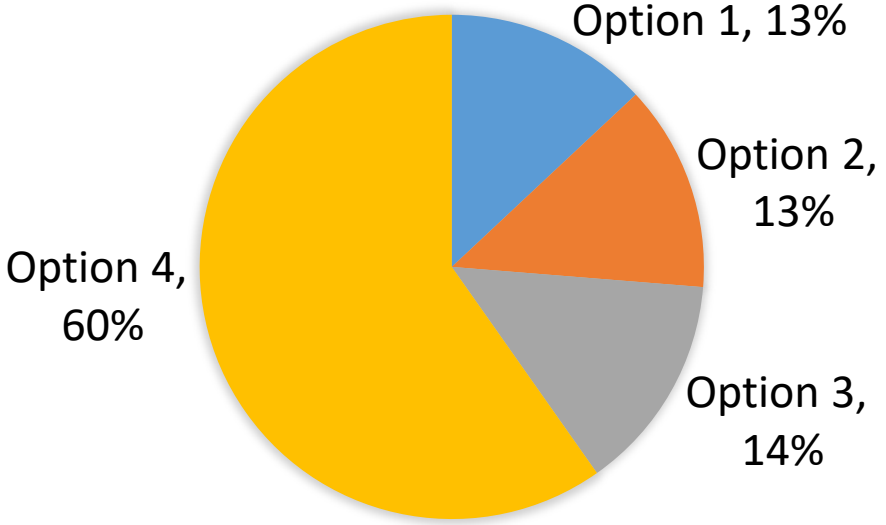
- It is not desirable to remove impurities that have been adequately reduced or no longer detected at the stable manufacturing stage from a list of chemical compounds to be potentially specified.
- Of a drug listed in the JP, products conforming to specifications in the monograph will be accepted for marketing, but for a generic drug of which the manufacturing process is not identical to that of the drug substance at the draft preparing company, the impurity profile may be different and contain these impurities. The information based on detection results at the development stage, if provided at the time of JP listing, will lead to the monograph that comprehensively covers impurities contained in the drug substance and product distributed as JP drugs.
- Accordingly, careful consideration should be given to removal of impurities that have been adequately reduced or no longer detected at the stable manufacturing stage from a list of potentially specified impurities in the JP in view of the safety based on concepts of the ICH Q3A and Q3B guidelines.
- Impurities during manufacture can be controlled by establishing an appropriate control strategy, which covers release tests, in-process tests, and process parameters.

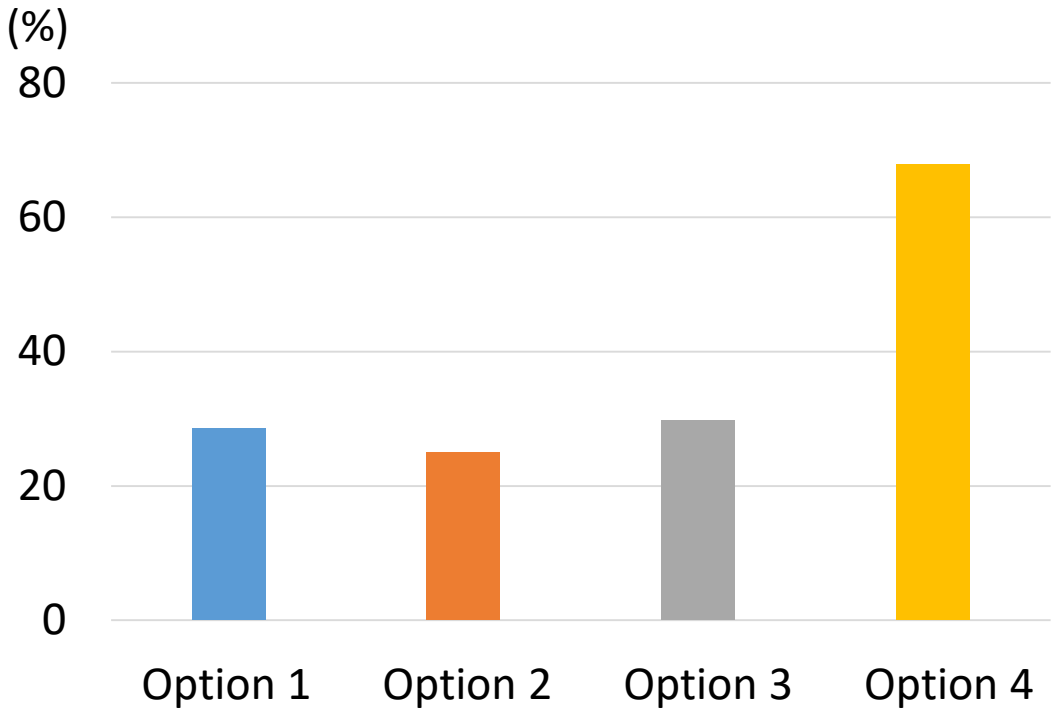
2. Current status of the ICH M7-based control options in Japan

Introduction : ICH M7 guideline provides the control options for mutagenic impurities

- Option 1 : drug substance specification
- Option 2 : raw material, starting material, or intermediate specification/ in-process control
- Option 3 : raw material, starting material, or intermediate specification/ in-process control, coupled with understanding process parameters, knowledge of the fate and purge
- Option 4 : Understanding process parameters, knowledge of the fate and purge, no analytical testing

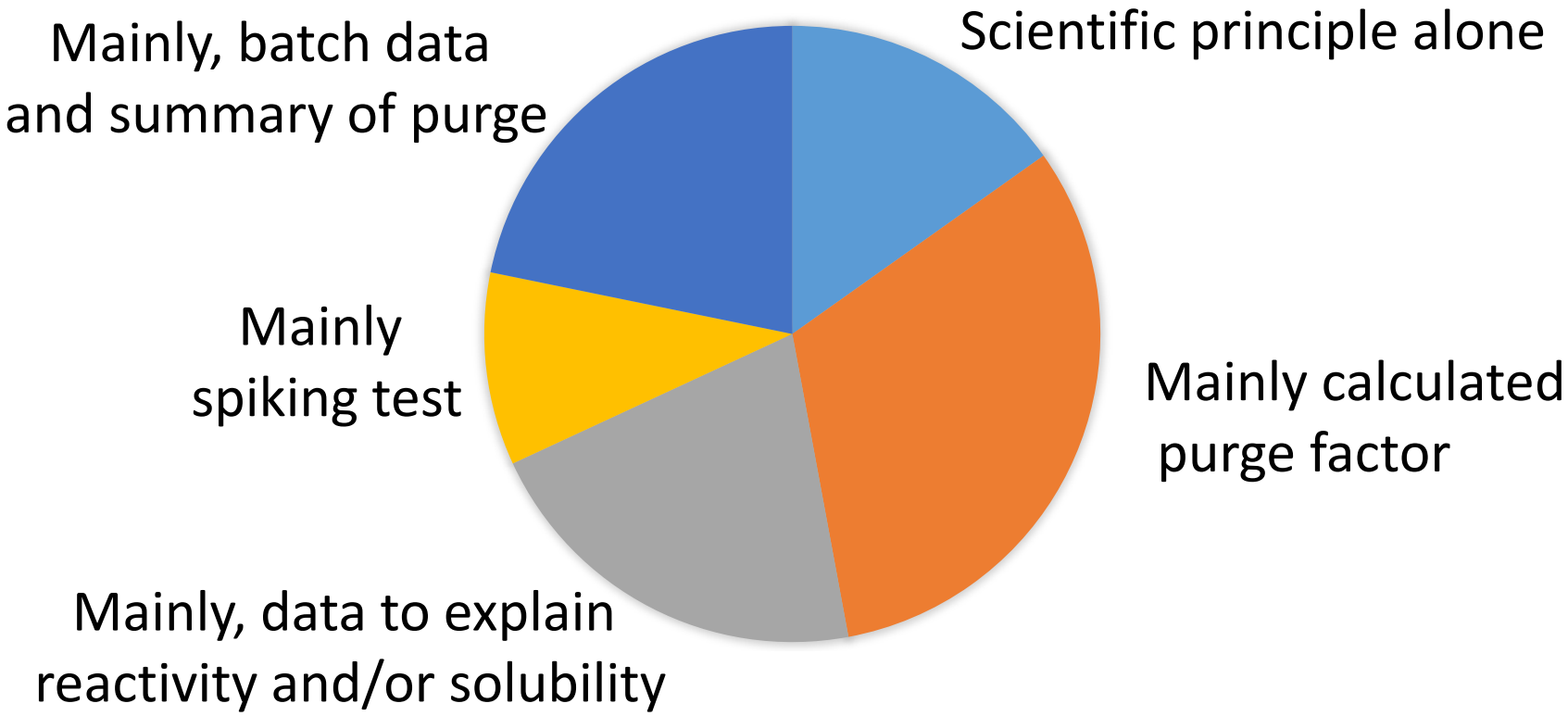
ICH M7-based Control options for the new drug products approved in Japan from Apr. 2016 to Sep. 2020





Reference: Nagato Y. et al. PDA Journal of GMP and Validation in Japan Vol. 23, No. 1 (2021), in press.

The classification of the main reasons used to explain the justification of the option 4



Reference: Nagato Y. et al. PDA Journal of GMP and Validation in Japan Vol. 23, No. 1 (2021), in press.

Conclusion

- The current status of the control of organic impurities in Japan prescription drug products is outlined in the JP General Information : Concept on Impurities in Chemically synthesized Drug Substances and Drug Products.
- The current status of the ICH M7-based control strategy for mutagenic impurities in Japan marketed products as new drug substances and new drug products.
- It is expected that this information will bring up the opportunity to discuss the development of more rational management of organic impurities in Japan marketed drug products.

Thank you for your attention.