IMPLEMENTATION OF ICHQ3D IN JAPAN

4th PQRI Workshop
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(IPEC JAPAN)

Outline

- About Japanese Pharmacopoeia (JP)
  - Legal status in Japan
  - Revision Procedure of the Japanese Pharmacopoeia (JP)
- Implementation of ICH Q3D to the JP 18th edition
  - Timeline of ICH Q3D related matters
  - IPEC Japan Survey
  - Exchange of Opinion between Authorities and Industrial Associations
  - Final Draft of General Tests 2.66 - Elemental Impurities issued by PMDA
  - Final Draft of General Notices 34. issued by PMDA
  - Full-fledged revisions of JP18 for Public comments from MHLW
  - What's the NEXT?

About Japanese Pharmacopoeia

Legal Status of the Japanese Pharmacopoeia (JP)

Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, revised Pharmaceutical Affairs Law (Act No.145 of 1960) in 2014.

Chapter VIII. Standards and Official Verification of Pharmaceuticals, etc.

(The Japanese Pharmacopoeia)

Article 41-1

To standardize and control the properties and quality of drugs, the Minister shall establish and publish the Japanese Pharmacopoeia (JP), after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC).

That is,
The JP is stipulated by Law (Act No.145) and is set forth and made public notice by the Minister of Health, Labour and Welfare.
So, if materials listed in the JP do not comply with the requirements, they must not be manufactured and distributed as the JP material in Japan. If manufactured and distributed non-conforming products, then it will be a violation of the law.

➔ **The JP is directly linked to the law !**

Revision Procedure of the Japanese Pharmacopoeia

MHLW

1. The JP Committee of PAFSC* at Ministry of Health, Labour and Welfare (**MHLW)** determines **Basic policies and New and/or Revised monographs/others** to be listed in the next JP revision.

*PAFSC: Pharmaceutical Affairs and Food Sanitation Council

PMDA

2. Based on results of discussions at the JP Expert Committees, the Office of Review Management at the **PMDA** **prepares the drafts of new and revised items** that are intended for inclusion in the JP revision.

PMDA: Pharmaceuticals Medical Devices Agency

3. Proposed revisions are quarterly published **for Public comments**.

4. After further review of those drafts with the comments by the JP Expert Committees, the **Final draft is submitted to the MHLW**.

Pharma Industry & Other Stakeholders

MHLW

5. After public comments, official texts are adopted and promulgated by the MHLW (by name of Minister of HLW).

Implementation of ICH Q3D to the Japanese Pharmacopoeia 18th edition

Timeline of ICH Q3D related matters

Year	Month	Subject	Issued by
2016	Apr.	The JP 17th was published	MHLW Ministerial Notification No. 64
2016	Oct.	The basic policies for the preparation of the JP 18th Edition • ICH Q3D will be formulated a roadmap for incorporation into the JP 18th Edition and work on its implementation.	**MHLW Announcement**
2017	Apr.	ICH Q3D was effective for new-drug applications	MHLW Notification
2018	Sep.	IPEC Japan Questionnaire Survey	IPEC Japan
2018 – 2020		Meetings for Exchange of Opinion between Authorities and Industrial Associations	(Hosted by the MHLW)
2019	Jun.	Notification of JP 17th Suppl. II • General Tests - 2.66. Elemental Impurities – Procedures • General Information – G1. Physics and Chemistry - Control of Elemental Impurities in Drug Products	Minister of HLW Notification No. 49
2019	Nov.	Published "JP 18 General Tests 2.66. Elemental Impurities (Draft)"	**PMDA** (Public comment)
2020	Mar.	Published "JP 18 General Notices 34 (Draft)"	**PMDA** (Public comment)
2020	Jun.	ICH Q3D(R1) Guideline (in Japanese) was notified.	MHLW Notice No. 0626-1
2020	Oct.	Published the full-fledged JP 18 revision for Public comments	**MHLW**
2021	(2Q)	The JP 18th Edition will be published in 2Q 2021.	

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IPEC Japan Survey:

Survey of the Preparation status for the implementation of ICH Q3D guideline

Date of the survey: **11th – 30th September, 2018**

Survey to: **IPEC Japan member companies and other excipient manufacturers**

Key Questions:

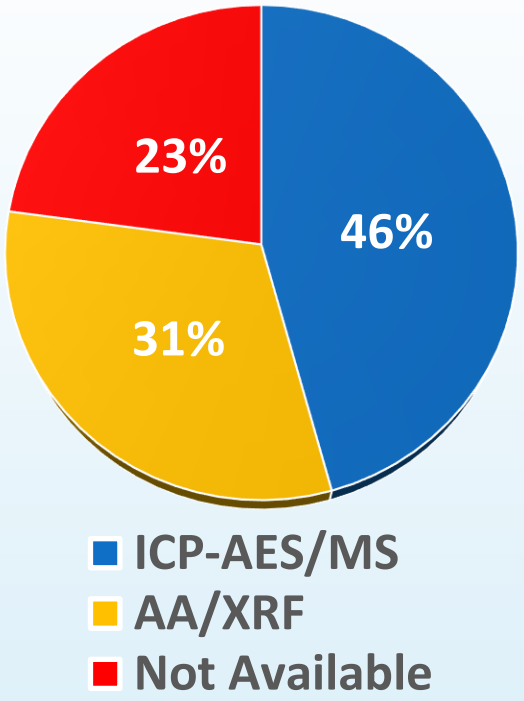
- Ownership status of Analytical Equipment for elemental impurities
- Status of Elemental Impurities analysis and Provision of the Information to the pharmaceutical excipient users
- Needs for Heavy Metal specification in each monograph
- Others

Results of IPEC Japan Survey I

1. Companies who replied to the Questionnaire

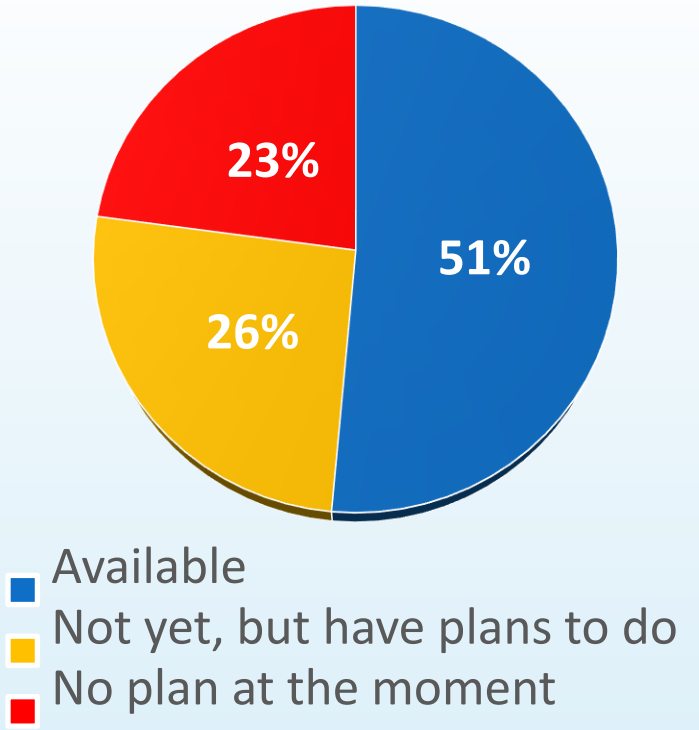
Companies responded	No.	%
Excipient Manufacturer	34	85.0%
Excipient Distributer	1	2.5%
Drug Manufacturer	5	12.5%
Total	40	100%

2. Ownership status of Analytical Equipment

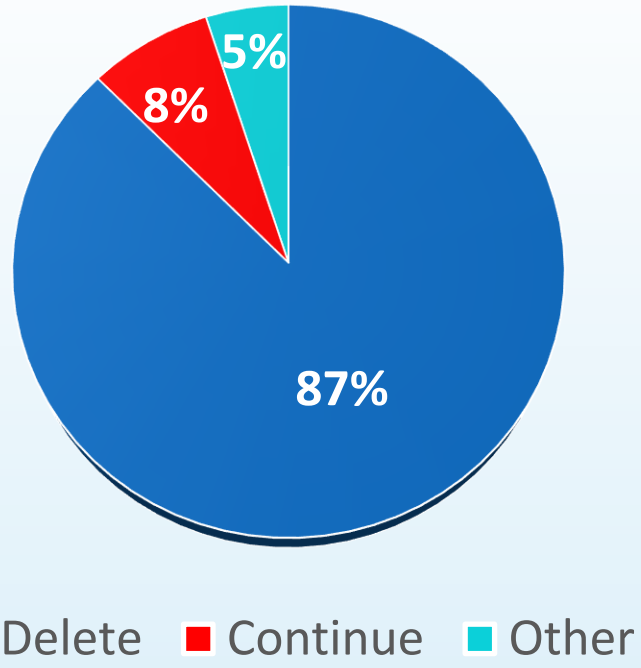


Results of IPEC Japan Survey II

3. Provision of the Information



4. Needs for Heavy Metal test



Exchange of Opinion between Authorities and Industrial Associations

- This meeting was set up as a place for the government and the industry to exchange opinions on ICH Q3D implementation to the JP.
- Government basic policy:
  - ✓ ICH Q3D will be applied to the JP 18 (2021) with a grace period before the full implementation.
  - ✓ During this period, Q3D and Heavy metal test can be selected.
  - ✓ Requirements of Q3D will be put in the General Notices section rather than General Rules for Preparations section in the JP.
- The meeting participants are as follows;

The Pharmaceutical Manufacturers' Association of Tokyo (PMAT) - Innovator -	Kansai Pharmaceutical Industries Association (KPIA) - Innovator -
Japan Generic Medicines Association (JGA)	Japan Self-Medication Industry (JSMI)
Japan Kanpo Medicines Manufacturers Association (JKMA)	Japan Bulk Pharmaceutical Manufacturers Association (JBPMA)
Japan Pharmaceutical Traders' Association (JAPTA)	International Pharmaceutical Excipients Council Japan (IPEC Japan)
Asian Society of Innovative Packaging Technology	National Institute of Health Science (NIHS)
Pharmaceutical and Medical Devices Agency (PMDA)	Ministry of Health, Labour and Welfare (MHLW)

Exchange of Opinion between Authorities and Industrial Associations

◆ Key Comments from Industrial Associations for Implementation of ICH Q3D to the JP18/Existing drug products

- **Innovator (PMAT, KPIA) :**
  It should be implemented as soon as possible from the viewpoint of International harmonization.
- **Generic Medicines Association (JGA):**
  As there are a lot of drug products to do risk assessment, sufficient preparation period will be required.
- **OTC company (JSMI)**
  Concerned about longer period and cost increase to do risk assessment because OTC drugs are usually formulated many ingredients. If possible, please avoid targeting all OTC drugs.
- **APIs manufacturer (JBPMA/JAPTA)：**
  No particular objection, but to delete Heavy Metal tests as soon as possible
- **Excipients manufacturers (IPEC Japan)：**
  Should be the same as the USP and the Ph. Eur, especially Heavy metal test.

Implementation of ICH Q3D to the JP18

PMDA Final Draft of General Tests 2.66. Elemental Impurities

PMDA's Final Draft of General Tests 2.66. Elemental Impurities

Posted on 1st Nov. 2019

http://www.pmda.go.jp/files/000231271.pdf

This includes two sections,

2.66. Elemental Impurities

I. Control of Elemental Impurities in Drug Products

⇒ ICH Q3D Guideline for Elemental Impurities

II. Elemental Impurities – Procedures

⇒ PDG G-07 Elemental Impurities - Procedures (Stage 2)

IMPLEMENTATION OF ICH Q3D TO THE JP18

PMDA Final Draft of General Tests 2.66 Elemental Impurities

PMDA Final Draft of General Tests 2.66 Elemental Impurities	ICH Q3D (R1) GUIDELINE FOR ELEMENTAL IMPURITIES
I. Control of Elemental Impurities in Drug Products	
1. Introduction	1. INTRODUCTION
2. Scope	**2. SCOPE**
	3. SAFETY ASSESSMENT OF POTENTIAL ELEMENTAL IMPURITIES
3. The PDEs for Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration, and Element Classification	4. ELEMENT CLASSIFICATION
4. Risk Assessment and Control of Elemental Impurities	5. RISK ASSESSMENT AND CONTROL OF ELEMENTAL IMPURITIES
	6. CONTROL OF ELEMENTAL IMPURITIES
5. Converting between PDEs and Concentration Limits	7. CONVERTING BETWEEN PDES AND CONCENTRATION LIMITS
6. Speciation and Other Considerations	8. SPECIATION AND OTHER CONSIDERATIONS
7. Analytical Procedures	9. ANALYTICAL PROCEDURES
8. Lifecycle Management	10. LIFECYCLE MANAGEMENT

IMPLEMENTATION OF ICH Q3D TO THE JP18

PMDA Final Draft of General Tests 2.66 Elemental Impurities

PMDA Final Draft of General Tests 2.66 Elemental Impurities	PDG G-07 Elemental Impurities -Procedures (Stage 2)
Ⅱ. Elemental Impurities — Procedures	
	Introduction
1. Sample Preparation	Sample Preparation
2. Analytical Procedures 1 and 2	Analytical Procedures 1 and 2
3. Requirements for Procedure Validation	Requirements for Procedure Validation
3.1. Procedure for Limits Tests	• Procedure for Limits Tests
3.2. Procedures for Quantitative Tests	• Procedures for Quantitative Tests
4. Glossary	Glossary

IMPLEMENTATION OF ICH Q3D TO THE JP18
A difference in "Scope"

- **Draft of General Tests <2.66> Elemental Impurities**

2. Scope

The acceptable limit of elemental impurities apply to drug products, and also……..

It does not apply to **crude drugs**, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellar blood components, blood derivatives including plasma and plasma preparations, dialysate solutions not intended for systematic circulation, and ……

- **ICH Q3D (R1) GUIDELINE FOR ELEMENTAL IMPURITIES**

2. SCOPE

The guideline applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products containing existing drug substances. ……..

This guideline does not apply to **herbal products**, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and ……

IMPLEMENTATION OF ICH Q3D TO THE JP18
Crude Drugs in the current JP

- No. of Crude Drugs in the current JP Official Monographs (JP 17 Suppl. II)

No. of Chemical Drugs	No. of Crude Drugs	Total
1,683	325	2,008

- Many of Crude drugs and Related Drugs have Heavy Metals and Arsenic limits in each monograph.

	No. of Crude Drugs
Heavy Metal (+ Arsenic tests)	162

- These Crude drugs are **excluded from** the Scope of Elemental Impurities Control.

Therefore,
<1.07> Heavy Metals Limit Test and <1.11> Arsenic Limit Test will not be deleted from "General Tests, Process and Apparatus" section in the JP.

Implementation of ICH Q3D to the JP18

PMDA Final Draft of General Notices 34

PMDA's Final Draft of General Notices 34

Posted on 3rd March 2020

https://www.pmda.go.jp/files/000234145.pdf

34. In principle, the JP Drug Products are controlled appropriately according to the direction under the Elemental Impurities of the General Tests. When elemental impurities in the drug products are appropriately controlled in accordance with the direction, it is not necessary to perform the tests on elemental impurities such as heavy metals and arsenic in the monographs including but not limited to those of drug products, drug substances and excipients.

Interpretation of the final draft of General Notices 34. - I -
(including my personal point of view)

- **Scope**
  - Drug products (same as ICH Q3D Guideline 2. SCOPE)
  - Crude drugs (≈ Herbal products) are excluded

- **Required control of Elemental impurities**
  - Drug products should be controlled appropriately in accordance with the direction of General Tests 2.66 I/ICH Q3D Guideline).
  - APIs, Excipients and Packing materials are expected to conduct appropriate control based on risk assessment of elemental impurities and provide information as much as possible to contribute to the control of elemental impurities at drug product manufacturers.

Interpretation of the final draft of General Notices 34. - II -
(including my personal point of view)

- **Handling of elemental impurities specified in each monograph**
  - Heavy Metal/Arsenic specifications in each monograph will remain during a certain period (a grace period before the full implementation).

  However,

  - If a required control of elemental impurities would be conducted appropriately in drug products, drug substances or excipients, then Heavy Metals, Arsenic and others specified elemental impurities in each monograph are not necessary to perform the test. Because these are overlapped with the purpose based on the General Notices 34.

IMPLEMENTATION OF ICH Q3D TO THE JP18
MHLW Full-fledged revisions of JP18 for Public comments

- Full-fledged revision for JP 18 for public comments was published and posted on the **MHLW** website **on 14th Oct. 2020 (in Japanese).**

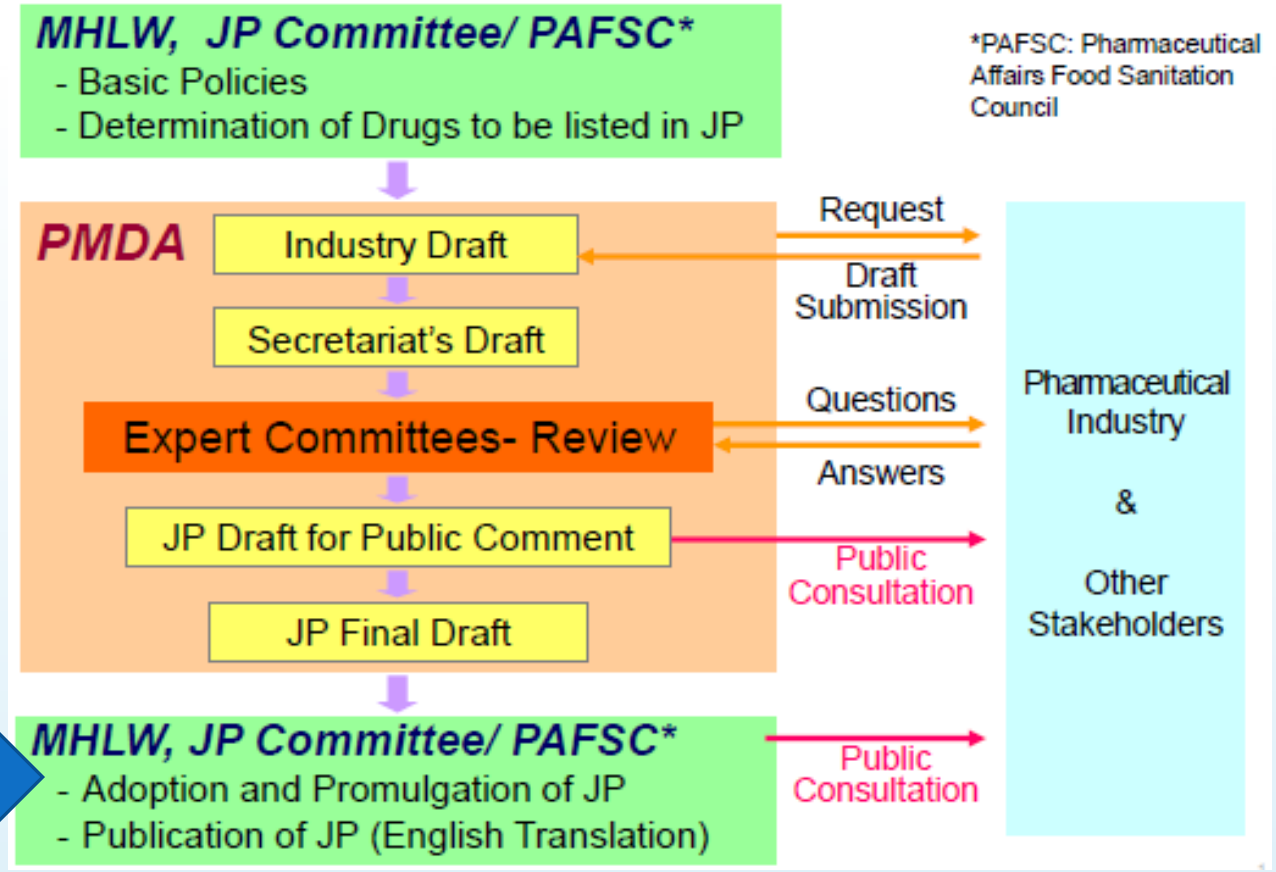
  https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066530.html

- Period for the comments : Oct. 14 – Nov. 15, 2020

- General Notices 34 and General Tests 2.66 Elemental Impurities are not amended by the MHLW (same as the Final Drafts of PMDA).

Revision Procedure of the Japanese Pharmacopoeia

https://www.pmda.go.jp/files/000234419.pdf



Current status of ICH Q3D Implementation in the JP

IMPLEMENTATION OF ICH Q3D TO THE JP18
What's the Next ?

- Issue the MHLW Notice regarding "Handling of elemental impurities in pharmaceutical products"
  ⇒ **Ongoing and soon-to-be-published**
- O&A on the "Handling of Elemental Impurities in Pharmaceutical products"
  ⇒ **Ongoing and soon-to-be-published**
- Publication of the JP 18 in 2Q, 2021

Complete the Implementation of ICH Q3D Guideline in Japan !!

Thank you for your attention