USP-MHLW/PMDA Joint Workshop
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Session 2: Excipient Quality

Current Regulatory Landscape of Pharmaceutical Excipients in Japan

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*This presentation reflects the views of the author and should not be construed to represent MHLW/PMDA's views.

Outlines

1. Regulatory Status of Pharmaceutical Excipients in the Japanese Pharmacopoeia (JP)

2. Potential Adulteration Risks : Diethylene glycol (DEG) and Ethylene glycol (EG)

3. Summary

What is a Pharmaceutical Excipient?

JP18 General Notices for Preparations (6)

- Pharmaceutical Excipients are substances **other than** active substances (API) contained in preparations.

API + Excipients = Drug product

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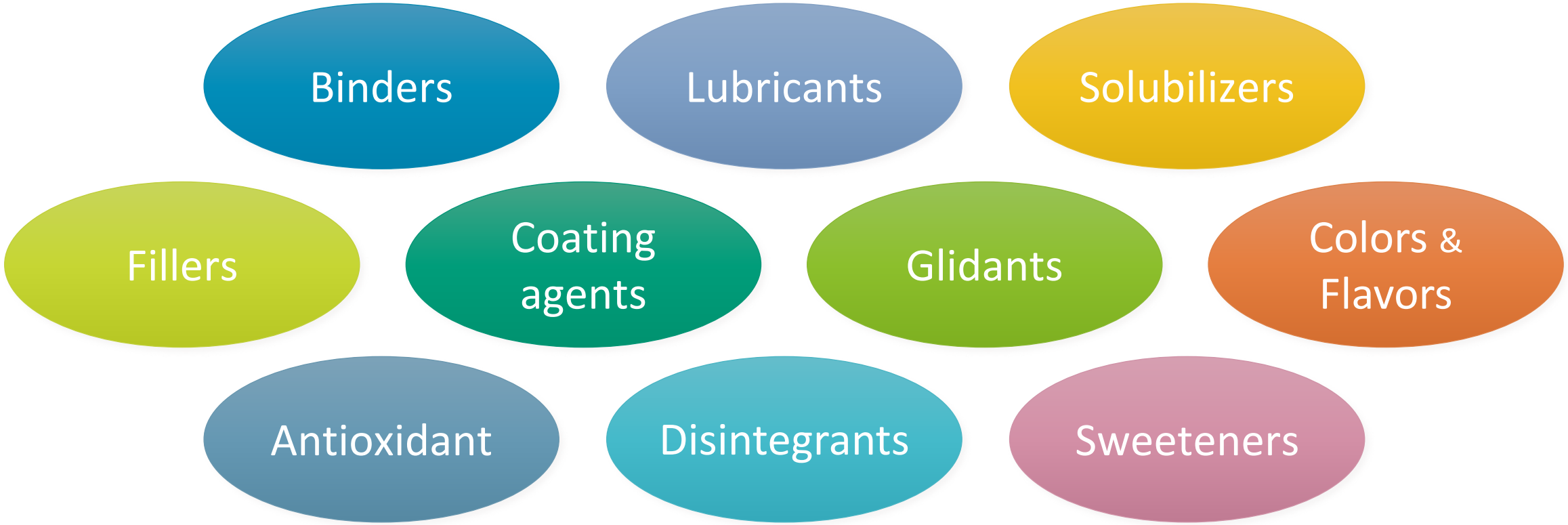
- The excipients must be pharmacologically **inactive** and harmless in the administered amount and must not interfere with the therapeutic efficacy of the formulation.

Roles of Pharmaceutical Excipients

- Excipients should be **inactive**, but are not limited to “inert diluents”.
- Excipients are essential for enhancing the **manufacturability**, **stability**, and **bioavailability** of the API.

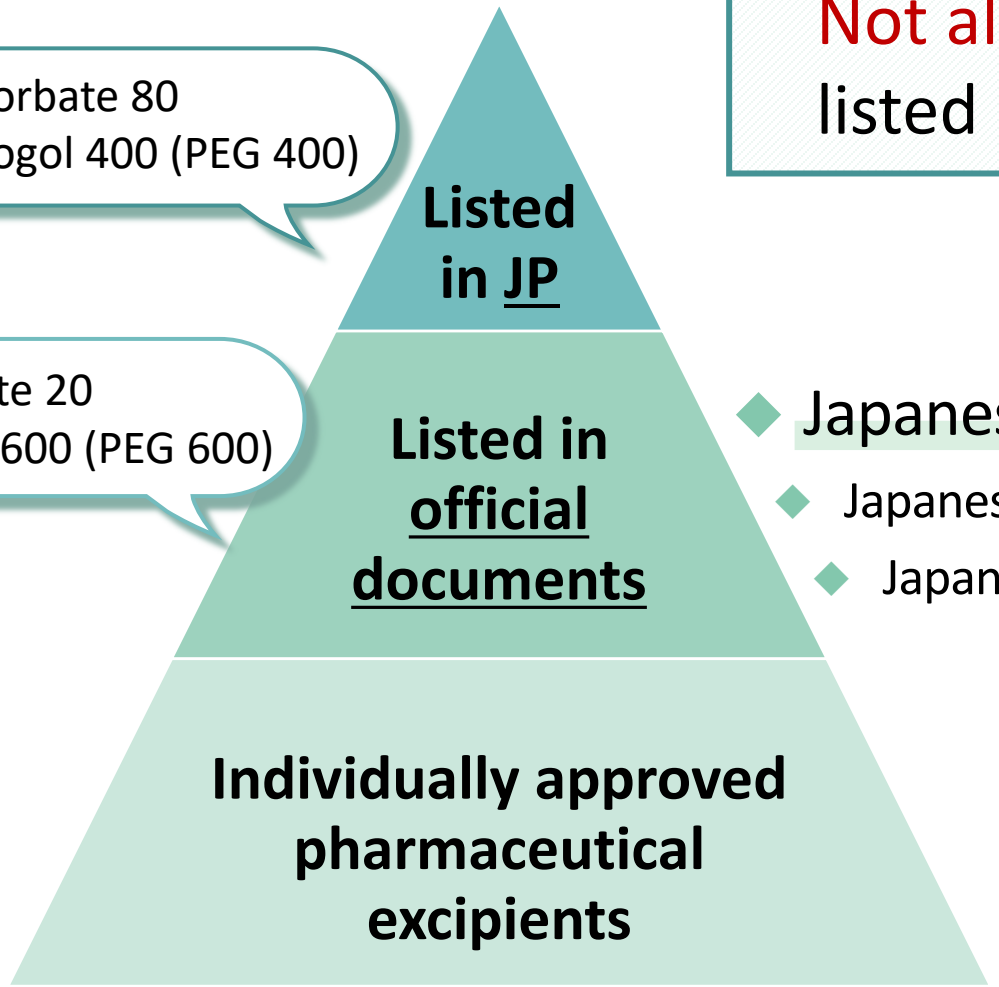


Excipients for Drug Products

Not all pharmaceutical excipients are listed in Japanese Pharmacopoeia (JP)

- Polysorbate 80
- Macrogol 400 (PEG 400)

- Polysorbate 20
- Macrogol 600 (PEG 600)



- Japanese Pharmaceutical Excipients (JPE)
- Japanese Pharmaceutical Codex
- Japanese Standards of Quasi-drug Ingredients

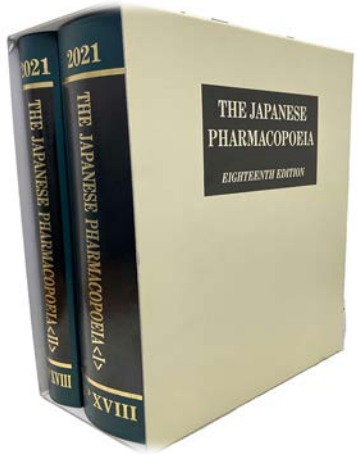
・Japanese Pharmaceutical Excipients: 医薬品添加物規格　（薬添規）
・Japanese Pharmaceutical Codex: 日本薬局方外医薬品規格（局外規）
・Japanese Standards of Quasi-drug Ingredients: 医薬部外品原料規格（外原規）

Japanese Pharmacopoeia (JP)

- Notified by Minister of Health, Labour and Welfare (MHLW), based on **Law** on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices

MHLW
Ministry of Health, Labour and Welfare of Japan

- Publication:
  - First Edition : published in 1886
  - Current Edition : JP18th Supplement 2 (June 6, 2024)



- JP is revised every 5 years and two supplements are released between each revision.

- FREE download from PMDA website (English Ver.)
  https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0010.html

Organization of JP Expert Committees

Standing Committee

- Sub-Standing Com.
- Com. On Manufacturing Process-related Matter

- Chemicals (1), (2)
- Antibiotics
- Biologicals
- Crude Drugs (A), (B)
- **Pharmaceutical Excipients**
- Nomenclature for Pharmaceuticals
- Reference Standards
- Drug Formulation
- Physical Methods
- Biological Methods
- Physico-Chemical Methods
- International Harmonization

15 Expert committees

Number of experts
Approx. 290

Expert Com. Members

- PMDA (secretariat)
- Research institute (NIHS)
- University
- Pharmaceutical company
- Excipients manufacturer

Typical Excipient Monographs

Monograph (Mandatory)

- **Identification tests**
- **Specific physical/chemical values**
- **Purity tests**
- **Potential adulteration** (added following the adulteration incident with DEG)
- **Loss on drying, Residue on Ignition, Water**
- **Other specific tests** (e.g. Bulk density of Microcrystalline Cellulose)
- **Assay**
- **Containers and storage**

General Information (Non-mandatory)

- **Functional-related characteristics** (e.g. Consistency of Yellow/White petrolatum)

Basic Principles for Preparation of JP19 -Five pillars

1. Enriching monographs by incorporating essential drugs for healthcare
2. Making qualitative improvement by introducing the latest science and technology
3. Promoting internationalization in response to globalization of pharmaceuticals
4. Making prompt partial revision as necessary and facilitating smooth administrative operation
5. Ensuring of transparency regarding the revision, and disseminating the JP to the public

Potential Risks and Regulatory Challenges

- Pharmaceutical excipient supply chain is globalized.

➢ Complex global supply chains heighten risks of quality control failures, adulteration, mislabeling, and supply instability.

- Chemical manufactures produce primarily for industrial and food applications, with pharmaceutical applications comprising on a small part of their business…
- Many small Japanese excipient manufacturers face budget limitation, making it difficult to install the latest analytical equipment.

➢ Financial challenges hinder the promotion of international harmonization

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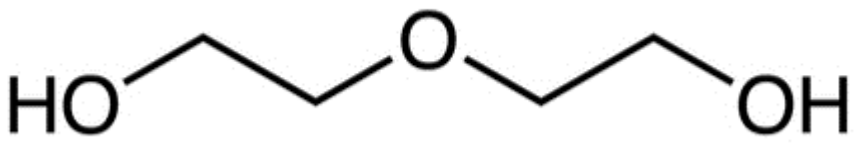
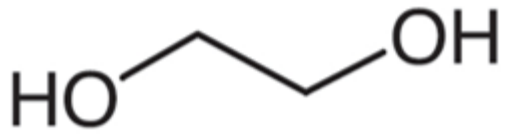
2 Potential Adulteration Risks :
Diethylene glycol (DEG) and Ethylene glycol (EG)

3 Summary

Diethylene glycol (DEG) and Ethylene glycol (EG)



Diethylene glycol (DEG)



Ethylene glycol (EG)

- **Widely used in industry :** Common in antifreeze solvent and inks
- **Highly toxic to kidneys :** Even small amounts can cause acute renal failure
- **Sweet taste and viscous :** Can be easily mistaken for glycerin or syrups

➢ **Global incidents : Adulteration of glycerin with cheaper, more toxic DEG**

Recent Incidents of DEG Adulteration

Adulteration Cases

1995 — **Haiti**
Acetaminophen syrup: 85 deaths

2006 — **Panama**
Cough & anti-allergy syrup: 46+ deaths

2008 — **Nigeria**
Teething formula: 84+ deaths

2020 — **India**
Cold syrup : 12 deaths

2022 — **Gambia/Indonesia/Uzbekistan**
Cough syrup : 300+ deaths

Regulatory Actions

2008 — **JP15 partial revision**
Glycerin/Concentrated Glycerin
- Purity test for **DEG** and related substances

2009 — **USP proposed impurity test to PDG**
Glycerin/Propylene glycol
- Purity test for **DEG and EG**

2014 — **JP16-2**
Glycerin/Concentrated Glycerin/Propylene glycol
- Purity test for **DEG, EG** and related substances

2023 — **WHO developed "two-level approach"**
Liquid Preparations for Oral Use
- TLC / GC methods for **DEG and EG**

JP16-2：Purity Test for DEG and EG

Monograph	Method	Acceptable criteria	
Glycerin	GC	NMT 0.1% : DEG, EG, other peaks, respectively NMT 1.0% : Total amount of peaks other than API	Adulteration
Concentrated Glycerin			
Propylene Glycol			
Macrogol 400 (PEG 400)	GC	NMT 0.25% : Sum of DEG and EG	raw material-derived Impurities
Macrogol 1500 (PEG 1500)	UV*	NMT 0.25% : Sum of DEG and EG	

GC: Gas Chromatography, *Color reaction using cerium (IV) diammonium nitrate

WHO: Test for DEG and EG (two-level approach)

Level 1 **Screening for non-compliance by TLC** (thin-layer chromatography)

Detection level: about 0.2%

- **Limitation:** Cannot distinguish between DEG and EG.
- **Low sensitivity:** Risk of false negatives due to semi-quantitative
- **Cost effective:** Accessible method for resource-limited countries
- **Benefit:** Enhances the chance of detecting adulterated products

Level 2 **Confirmatory testing for DEG/EG using GC**

Detection level: 0.1%

- **Quantitative :** More sensitive and well-validated method

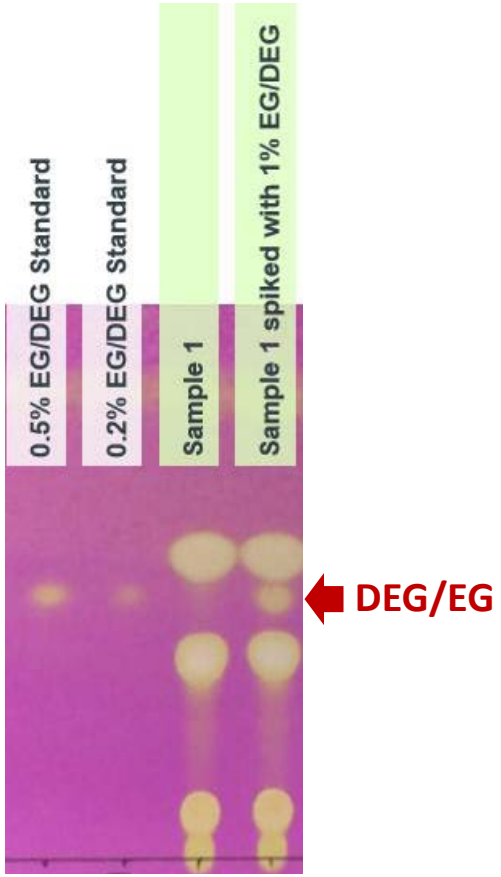


Image 3, Working document QAS/23.922/rev3, WHO (2023)

➢ This approach will be included in the next edition of the *International Pharmacopoeia*

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Global Supply Chain Challenges

- Complex networks increase risks in quality control
- Rigorous inspection of incoming excipients is critical to prevent adulteration or contamination
- Supporting developing countries in strengthening regulatory systems

Promoting International collaboration

- Reduces duplicate testing by harmonizing procedures and criteria
- Saves resources and time for both industry and regulators
- Encourages global standards for supplier qualification and auditing

Thank You

For Your Attention

Appendix Slides

Content of the Japanese Pharmacopoeia (JP)

Main body (Legally binding parts)

1. **General Notices** – specification of general rules: 49 paragraphs
2. **General Rules for Crude Drugs** – 10 paragraphs
   General Rules for Preparations – general notices for preparations, packaging of preparations, monographs for preparation, monographs for preparations related to crude drugs
3. **General Tests** – 8 categories (General tests: 90)
   Chemical methods, Physical methods, Powder property determinations, Biological/Microbial tests, Tests for crude drugs, Tests for preparations, Tests for containers and packing materials, Reference standards/standard solutions, Reagents, Test solutions
4. **Official Monographs** - 2048 articles (APIs, **Excipients**, Preparations, Crude drugs)
5. **Reference Spectra** - Ultraviolet-visible: 565 articles, Infrared: 649 articles
6. **General Information** – 71 chapters
7. **Appendix**

(As of September, 2024)

Pharmacopoeial Discussion Group (PDG)

History

- 1989 : The PDG was founded by EP  , USP  , and JP  .
- 2001 : WHO  joined as an observer.
- 2023 : Indian Pharmacopoeia Commission (IPG)  joined as a member.

Activities

- The purpose of PDG is to harmonize **pharmacopeial excipient monographs** and general chapters, such as physicochemical test and test for preparations.

➢ To reduce manufacturer's burden of performing tests in different ways, using different acceptance criteria

➢ To establish a standardized specification for excipients that can be used for a number of drug products

➢ To maintain an optimal level of science consistent with protection of public health

Harmonization Status for Excipient Monographs (PDG)

Sign-off: 49 items, Under discussion : 13 items , Revision on going: 15 items (As of April 2023)

No.	PDG Harmonization item
E-01	Alcohol
E-02	Dehydrated Alcohol
E-03	Benzyl Alcohol
E-04	Calcium Disodium Edetate
E-05	Calcium Phosphate Dibasic
E-06	Calcium Phosphate Dibasic Anhydrous
E-07	Carmellose Calcium
E-08	Carmellose Sodium
E-09	Croscarmellose Sodium
E-10	Microcrystalline Cellulose
E-11	Cellulose, Powdered
E-13	Cellulose Acetate Phthalate
E-14	Citric Acid, Anhydrous
E-15	Citric Acid, Monohydrate
E-16	Crospovidone
E-17	Ethylcellulose

No.	PDG Harmonization item
E-18	Hydroxyethylcellulose
E-19	Hydroxypropylcellulose
E-20	Hydroxypropylcellulose, Low Substituted
E-21	Hypromellose
E-22	Hypromellose Phthalate
E-23	Lactose, Anhydrous
E-24	Lactose, Monohydrate
E-25	Magnesium Stearate
E-26	Methylcellulose
E-27	Methyl Paraben
E-28	Petrolatum
E-29	Petrolatum, White
E-30	Polyethylene Glycol
E-31	Polysorbate 80
E-32	Povidone
E-36	Silicon Dioxide

https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0026.html

Harmonization Status for Excipient Monographs (PDG)

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No.	PDG Harmonization item
E-37	Silicon Dioxide, Colloidal
E-38	Sodium Chloride
E-39	Sodium Starch Glycolate
E-40	Starch, Corn
E-41	Starch, Potato
E-42	Starch, Rice
E-43	Starch, Wheat
E-44	Stearic Acid
E-45	Sucrose
E-46	Talc
E-48	Ethyl Paraben
E-49	Propyl Paraben
E-50	Butyl Paraben
E-51	Glycerin
E-52	Carmellose
E-54	Copovidone

No.	PDG Harmonization item
E-55	Gelatin
E-56	Glucose Monohydrate/Anhydrous
E-58	Mannitol
E-59	Propylene Glycol
E-60	Sodium laurylsulfate
E-61	Starch, Pregelatinized
E-62	Sterile Water For Injections in Containers
E-64	Isomalt
E-65	Isostearyl Alcohol
E-66	Myristyl Myristate
E-68	Polysorbate 65
E-69	Calcium Silicate
E-70	Polysorbate 20
E-71	Purified water
E-72	Water for Injection

https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0026.html