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Kansai Pharmaceutical Industries Association
関西医薬品協会

Current Situation and Request for Pharmaceutical Excipients

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Activities of the Kansai Pharmaceutical Industries Association

Introduction

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- **Pharmacopoeial Discussion Group (PDG)**
  - ✓ European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopoeia (JP) and United States Pharmacopoeia (USP).
  - ✓ Three-pharmacopoeial conference that carries out harmonization for test methods and monographs of excipients

- The specifications and test methods for about 80 excipients have been harmonized.

- Pharmaceutical companies strongly expect for even more harmonization as globalization in drug development and drug manufacturing would be getting expanding in the future.

- **Topics** - Current situation and requests on the harmonization of specifications and test methods for excipients

Current Situation and Trend for Harmonization of Excipients

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- **Setting and revising monograph for an excipient**
  - ✓ The monograph for an excipient should be based on scientific evidence and real measurements.
  - ✓ There are cases when enough data are not available for setting and revising the monograph in Japan.
  - ✓ Difficult to discuss and understand the monograph scientifically.

- **Proposal of test methods with uncommon analytical equipment and inexperienced test methods**
  - ✓ Purchase a new analytical equipment.
  - ✓ Outsource to an external laboratory which can perform the test under the GMP.
  - ✓ Take time to learn skills and know-how to be performed.

Example of uncommon analytical equipment and inexperienced test methods

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Monograph/attribute	Current situation
Hydroxyethylcellulose Purity (2) Nitrate	• Checking whether the test can be carried out with the following condition in the existing equipment. Indicator electrode: Nitrate ion selective electrode Reference electrode: silver-silver chloride electrode Reference electrolyte: Diluted ammonium nitrate TS (1 in 30) • Need to be installed newly or outsourced in case that there are no available equipment. • Ion selective electrodes are in the direction of becoming composite electrodes. • Limited combination of a reference electrode with a reference electrolyte.
Hydroxyethylcellulose Assay	Improvement of safety and analytical equipment is necessary for the operation of "Add hydroiodic acid, stopper tightly, and heat in an oven at 165±2 ºC or with stirring with an appropriate heater for 150 minutes".
D-Mannitol Related substances Assay	Since laboratories do not have refractive index detector for HPLC, a new detector has to be purchased. The column used for the test - sensitive to deterioration (weak to pressure fluctuation). - expensive
Gelatin Jelly strength	A new equipment has been purchased for gelatin testing only. - Texture analyzer (small tabletop testing machine) - Controllable water bath within 0.1 ºC for sample preparation under Low-temperature.

Issues and Requests (1)

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- **Monograph using uncommon analytical equipment**
  - ✓ Pharmaceutical companies need to deal with concerned methods.
  - ✓ Investigation and consideration are required during harmonization process.
- **Inexperienced test procedure in Japan**
  - ✓ Technical information (e.g. test system/measured data at harmonization)
  - ✓ Such information should be disclosed in the home page of PMDA.
  - ✓ Japanese Pharmacopoeia is user-friendly.
- **Even if monographs are harmonized between pharmacopeias, test results cannot be utilized in the worldwide.**
  - ✓ Local requirements and non-harmonized items
- **Difference between harmonized procedure and pharmacopoeia procedure**
  - ✓ Possible to unify the both procedures?

Issues and Requests (2)

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- **Rapid uptake of harmonized specifications and test methods in JP**
  - ✓ Certain time lug between harmonization and revision of the JP (tree times in five years)
  - ✓ According to JP, USP and Ph. Eur., all tests sometimes need to be performed separately due to the time lug.
- **Difficult to procure excipients meeting with the harmonized specification in Japan**
  - ✓ Excipient manufacturers have been withdrawn increasingly.
  - ✓ Difficult to deal with harmonized specifications and test methods in JP.
- **Harmonize reagent/test solution among JP, USP and Ph. Eur.**
  - ✓ JIS grade for JP and ACS grade for USP
- **Harmonize excipient standard specified in the monograph among JP, USP and Ph. Eur.**

Conclusion

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- **Harmonization for excipient monographs among JP, USP and Ph. Eur.**
  - ✓ Globalization in drug development and drug manufacturing
  - ✓ Pharmaceutical companies' further expectation
- **Situation at pharmaceutical companies**
  - ✓ Purchase of new analytical equipment and outsource of concerned tests
  - ✓ Take time to learn skills and know-how of harmonized method
    - ➢ Pharmaceutical companies should deal with harmonization earlier.
- **Making use of harmonization for excipients to development and manufacture of pharmaceuticals**
  - ✓ Necessary to accelerate the incorporation of harmonized results into the pharmacopoeias
  - ✓ Sharing of technical information
  - ✓ Harmonization of reagents/test solutions and standard materials