Expectation for PDG from pharmaceutical industries

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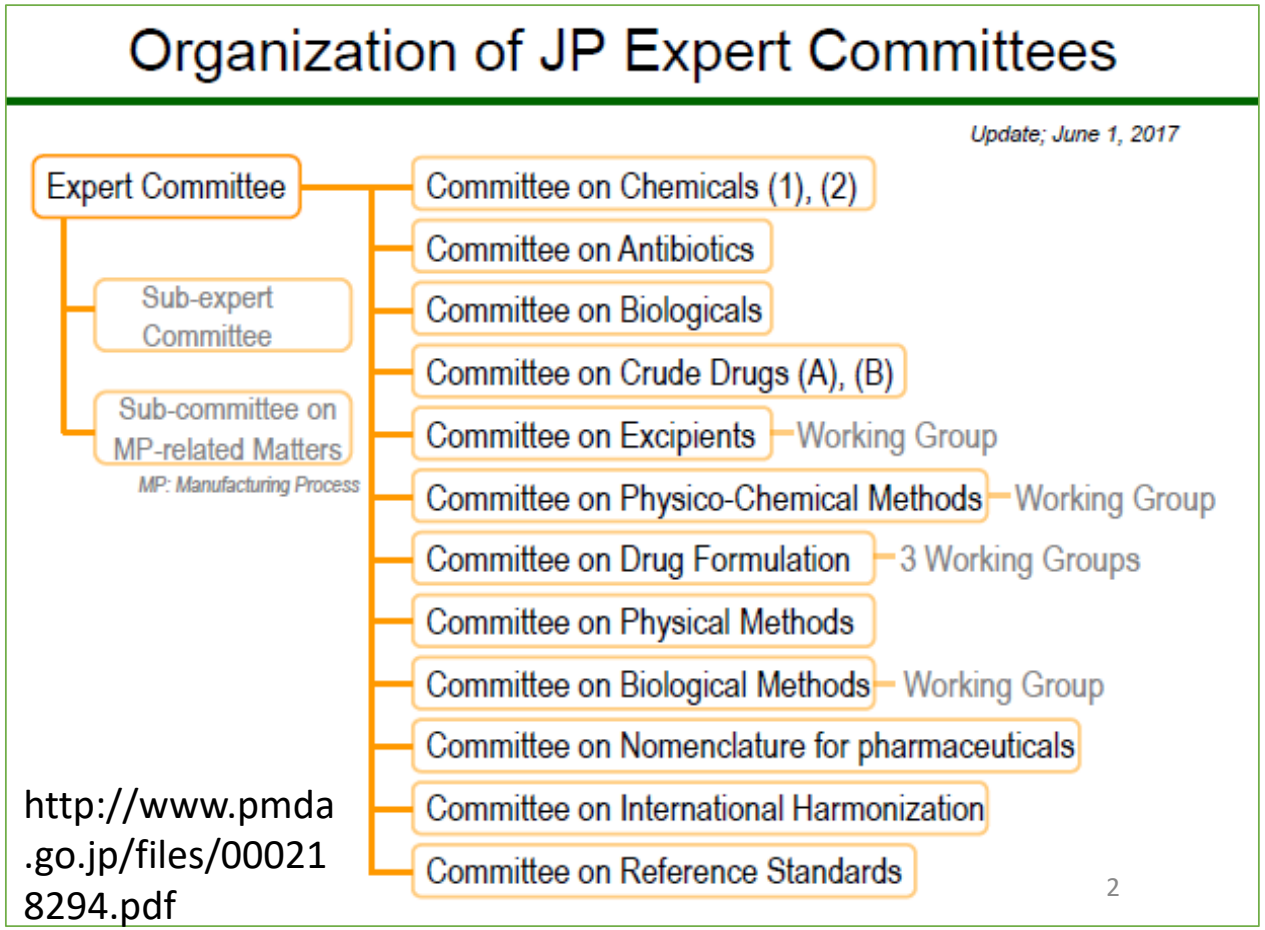
PMAT is a member of JP expert committee as a representative of pharmaceutical industries.

PMAT is organized with 216 companies of MAHs and Manufacturers of medicinal products.



http://www.pmda.go.jp/files/000218294.pdf

Expectations for G-20 Chromatography

■ G-20 Chromatography (Stage 2)

Discussion for harmonization started from 2009

Based on:

- 2.2.46 Chromatographic separation techniques in Ph. Eur.
- 2.01 Liquid Chromatography and System Suitability of General Information in JP
- <621> Chromatography in USP

Content:

- Definition and calculations of common parameters : Chromatogram, Distribution constant (K_0), Resolution (Rs) , Signal-to-noise ratio (S/N)…
- Requirements for system suitability : Repeatability, Sensitivity, Peak symmetry
- Adjustment of chromatographic conditions
- Quantification : External standard method, Internal standard method, Normalization procedure...

G-20 Chromatography (Stage 2) in PDG

Adjustment of chromatographic conditions

- The chromatographic conditions described have been validated during the elaboration of the monograph. The extent to which the various parameters of a chromatographic test may be adjusted to satisfy the system suitability criteria without fundamentally modifying the methods are listed below. Changes other than those indicated require revalidation of the method.
- since the stationary phases are described in a general way and there is such a variety available commercially, with differences in chromatographic behavior, some adjustments of the chromatographic conditions may be necessary to achieve the prescribed system suitability requirements.

G-20 Chromatography (Stage 2) in PDG

Adjustment of chromatographic conditions

For example:

The adjustment of following parameters within specified ranges is acceptable for isocratic elution of Liquid chromatography

✓Particle size, length of column, flow rate, temperature…

Provided that

- system suitability requirements are fulfilled
- furthermore, selectivity and elution order of specified impurities are demonstrated to be equivalent

✓Mobile phase (composition, pH, concentration of salts in buffer)

✓Injection volume

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Is it correct to understand that adjustments require no regulatory action or “do and tell” variation (minor change notification)?

2.01 Liquid Chromatography, 2.02 Gas Chromatography in JP

■7. Point to consider on changing the operating conditions (Liquid Chromatography)

Among the operating conditions specified in the individual monograph, inside diameter and length of the column, particle size of the packing material, column temperature, composition ratio of the mobile phase, composition of buffer solutions in the mobile phase, pH of the mobile phase, concentration of ion-pair forming agents in the mobile phase, ionic strength of the mobile phase, flow rate of the mobile phase, number and timing of mobile phase composition changes in gradient program, flow rate of mobile phase in gradient program, composition and flow rate of derivatizing reagents, and reaction time and chamber temperature in chemical reaction may be modified within the ranges in which the liquid chromatographic system used conforms to the requirements of system suitability.

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Adjustment of operating conditions had been considered to be a GMP matter requiring no regulatory action, however recently HA demands a prior approval (partial change application) before implementation of adjustment.

Expectations for G-20 Chromatography

Industries' concern

- Impact of harmonized G-20 Chromatography would not remain within the Pharmacopeia.
  - ✓General tests in Pharmacopoeia, such as Chromatography, are not only used for Pharmacopoeial monograph, but also for our own (non-Pharmacopoeial) products widely.
- Some adjustments of the chromatographic conditions are required for achieving the prescribed system suitability requirements in some cases.
  - ✓A certain brand of HPLC or GC equipment/column are suddenly discontinued and must be replaced by different ones
  - ✓Method transfer to other testing site using different brand of HPLC or GC equipment/column happened

Expectations for G-20 Chromatography

Industries' concern (continued)

- If the prior approval (partial change application) is required for the adjustments, it will take 0.5 to 1 year, and pose the very big risks for releases and stable supplies of our products to the Japanese market.
- ICH Q12 is also intended to provide with flexible regulatory approaches to post-approval changes. However, …
  - ✓The flexibility is based on degree of understanding of relationship between method parameters and method performance…
  - ✓Then, we are concerned that huge data might be requested to take the flexibility even for chromatography…

Expectations for G-20 Chromatography

Expectation for PDG

- We understand that PDG is not actively involved in the harmonization of regulation among the regions. However, please acknowledge that PDG's activities are having big impacts on it.
- So, we expect PDG to clearly indicate that this "Adjustment of chromatographic conditions" means regulatory flexibility for changing operating conditions.
- We hope this "Adjustment of chromatographic conditions" will be a good first step for our future collaborations between PDG and industries.