Consideration point of Post-approval change

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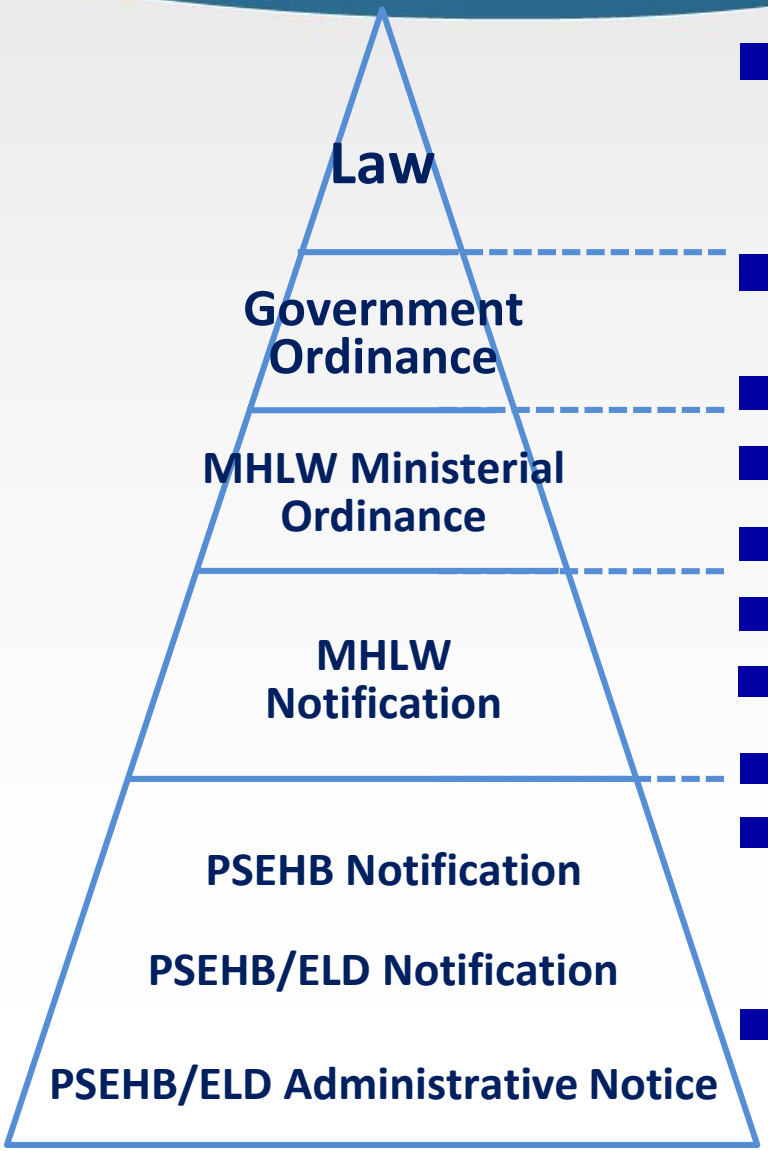
Go Yamamoto
Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Regulatory Framework in Japan



- Pharmaceuticals and Medical Devices Act (PMD. Act)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH guidelines
- Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law
- Etc.

- MHLW: Minister of Health Labour and Welfare
- PSEHB: Pharmaceutical Safety and Environmental Health Bureau
- ELD: Evaluation and Licensing Division

PMD. Act

(Marketing approval to drug etc.)

Article 14 Persons intending to market a drug …… must obtain approval of the Minister for marketing of each item.

Partial Change Application (PCA)

9 When persons who have received approval as specified in Paragraph 1 wish to make a partial change of approval items (excluding cases where such changes are minor changes as specified by MHLW Ordinance), approval of the Minister must be obtained for such cases. In such cases, the provisions of the preceding paragraphs shall apply *mutatis mutandis*.

Minor Change Notification (MCN)

10 A person who has obtained approval specified in Paragraph 1 shall submit a notification of minor changes specified by MHLW Ordinance in the preceding paragraph to the Minister as specified by MHLW Ordinance.

Enforcement Regulations of the PMD. Act

(Range of minor change in the approval items)

Article 47 The minor changes specified by MHLW Ordinance pursuant to the provisions of Article 14, Paragraph 10 of the Act shall be changes other than those specified below.

(1) Changes in the manufacturing methods, etc. that will affect the nature, properties, performance, or safety of a product

(2) Deletion of items from the specifications and changes in the specifications

(3) Changes concerning methods for the inactivation or elimination of pathogenic factors

(4) Addition, changes or deletions concerning the dosage and administration, or the indications

(5) In addition to those specified in the preceding items, any changes that could potentially affect the quality, efficacy, or safety of a product

Relationship between Application Form and ICH CTD

Approved Matters

Application Form

Extracted

Main review document

Module 2 (QOS)

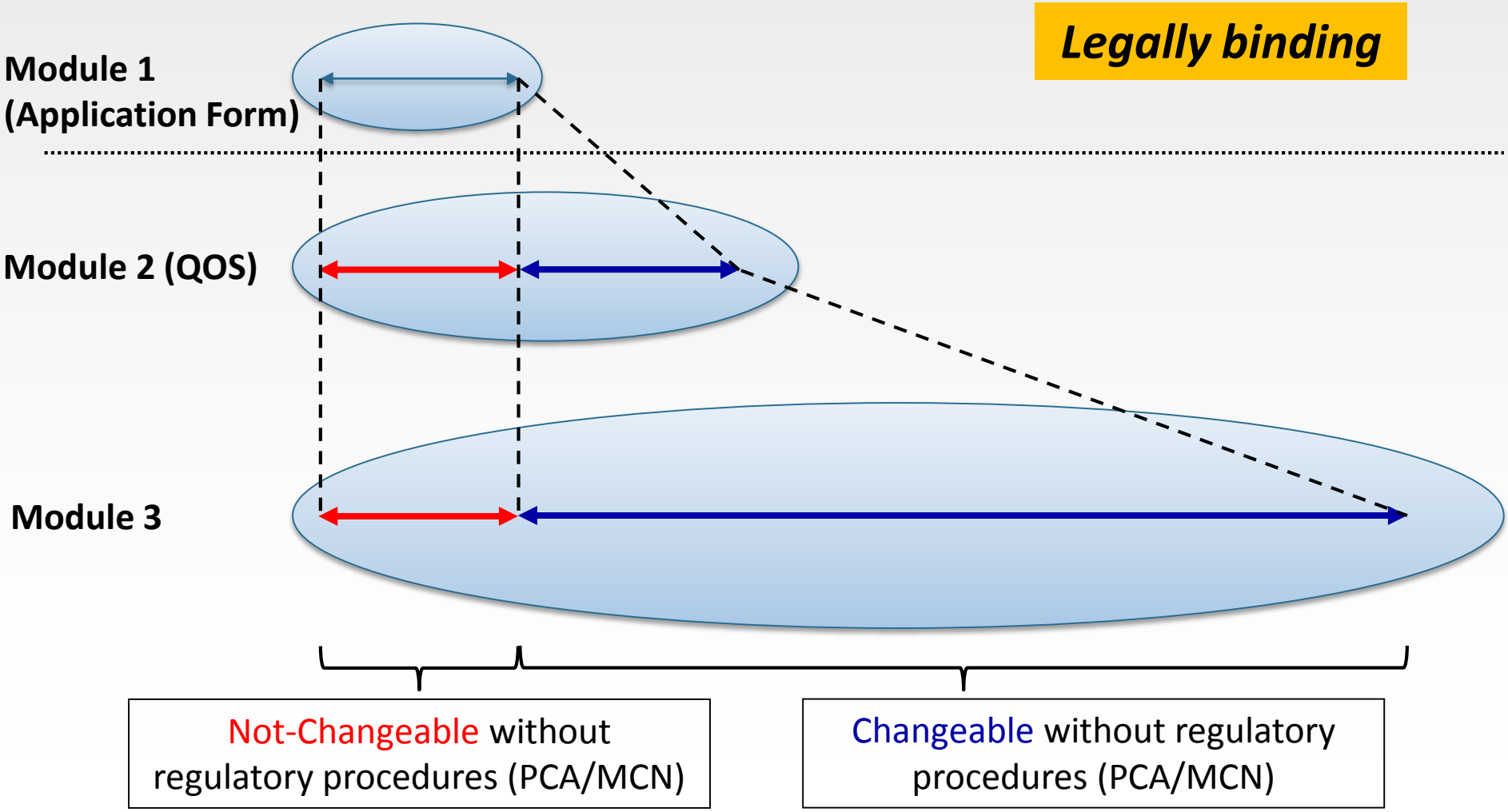
Summarized

Module 3

Section of Application Form

- General name (JAN)
- Brand name
- Composition
- Manufacturing process, incl. control of materials
- Specifications
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Manufacturing sites information

Japan's Effective/Efficient/Flexible Quality Regulation



Revision of PAL* in 2002 (enforced in 2005)

*: Pharmaceutical Affairs Law
currently Pharmaceuticals and Medical Devices Act (PMD. Act)

Revision of the Quality Regulation and Needs for Practice Development

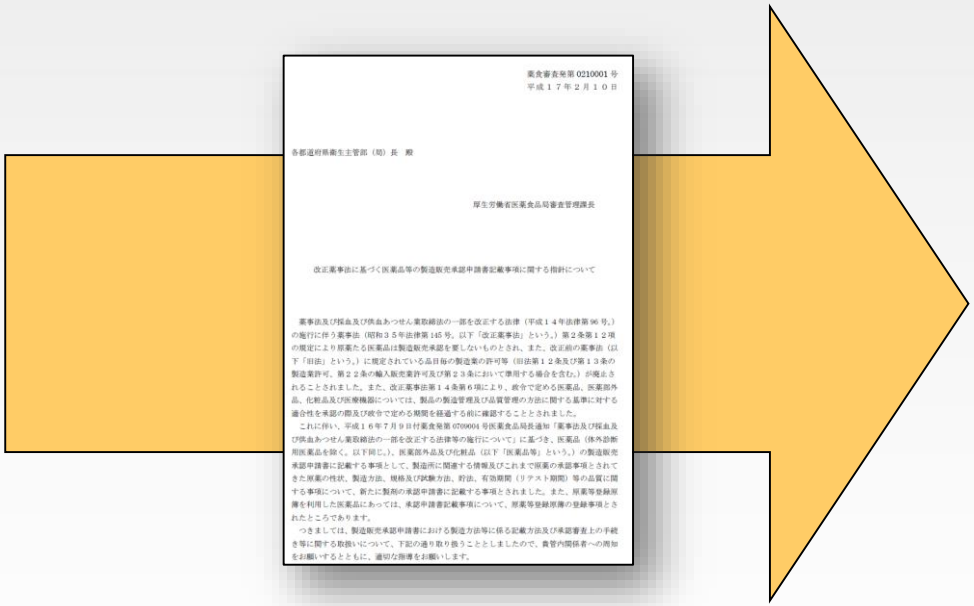
1. MAH's responsibility for the Quality management
   New Ministerial Ordinance (GQP), Guidance- ICH Q10
2. Manufacturing process commitment
   Policy Notification, Guidance- Case study, Mock
3. Drug Master File system
   Policy Notification
4. Consolidation of the Legal Positioning of GMP
   Revise GMP Ministerial Ordinance,
   Policy Notification: Pre-approval and Foreign inspections
5. Revision and Consolidation of GMP standards
   Revise GMP Ministerial Ordinance,
   Guidance: Product GMP, Change Control

Dr. Yukio Hiyama
EDQM Conference Quality of Medicines in a Globalised World: Dreams and Reality
14-15 October 2010, Prague, Czech Republic

Regulatory change in Application Form (1)

- Chemicals
  - Specifications
  - Mfg. process
- Biologics
  - Specifications
  - Mfg. process

- Mandatory for all products



薬食審査発第 0210001 号
平成１７年２月１０日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

改正薬事法に基づく医薬品等の製造販売承認申請書記載事項に関する指針について

薬事法及び採血及び供血あっせん業取締法の一部を改正する法律（平成１４年法律第９６号。）の施行に伴う薬事法（昭和３５年法律第１４５号。以下「改正薬事法」という。）第２条第１２項の規定により原薬たる医薬品は製造販売承認を要しないものとされ、また、改正前の薬事法（以下「旧法」という。）に規定されている品目毎の製造業の許可等（旧法第１２条及び第１３条の製造業許可、第２２条の輸入販売業許可及び第２３条において準用する場合を含む。）が廃止されることとされました。また、改正薬事法第１４条第６項により、政令で定める医薬品、医薬部外品、化粧品及び医療機器については、製品の製造管理及び品質管理の方法に関する基準に対する適合性を承認の際及び政令で定める期間を経過する前に確認することとされました。

これに伴い、平成１６年７月９日付薬食発第 0709001 号医薬食品局長通知「薬事法及び採血及び供血あっせん業取締法の一部を改正する法律等の施行について」に基づき、医薬品（体外診断用医薬品を除く。以下同じ。）、医薬部外品及び化粧品（以下「医薬品等」という。）の製造販売承認申請書に記載する事項として、製造所に関連する情報及びこれまで原薬の承認事項とされてきた原薬の性状、製造方法、規格及び試験方法、貯法、有効期間（リテスト期間）等の品質に関する事項について、新たに製剤の承認申請書に記載する事項とされました。また、原薬等登録原簿を利用した医薬品にあっては、承認申請書記載事項について、原薬等登録原簿の登録事項とされたところであります。

つきましては、製造販売承認申請書における製造方法等に係る記載方法及び承認審査上の手続き等に関する取扱いについて、下記の通り取り扱うこととしましたので、貴管内関係者への周知をお願いするとともに、適切な指導をお願いします。

- Discussions in research groups
- Guideline incl. mock for chemicals

- Specifications
- Mfg. process
- Specifications
- Mfg. process

Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law in 2005
http://www.pmda.go.jp/files/000153677.pdf (in English)

Regulatory change in Application Form (2)

- Minor Change Notification in mfg. process section was introduced.
- Harmonization among ICH regions was considered.
  - CBE30/Type1B, Annual Report/Type1A, Comparability Protocol were NOT introduced.
  - Information/elements classified as Annual Report/ Type1A were considered as non-Approved Matters.

Post-Approval Change Reporting Categories

Impact on quality	Japan	US	EU
High	**Partial change Application** (prior approval for change)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	**Minor change Notification** (within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	**(Non-approved matters)**	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

Review Process of MAA with document flow