Connection from ICH Q12 (ECs) to Application Form (Approved Matters)

ICH Q12 Update:
Established Conditions for Manufacturing Process
Established Conditions for Specification
Application Form: History

- **Chemicals**
  - Specifications
  - Mfg. process
  - Mandatory for all products

- **Biologics**
  - Specifications
  - Mfg. process
  - Discussions in research groups
  - Guideline incl. mock for chemicals

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)
Application Form: History

- 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

<table>
<thead>
<tr>
<th>Impact on quality</th>
<th>Japan</th>
<th>US</th>
<th>EU</th>
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| 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  
2) Supplement  
(changes being effected (CBE) | Type IB variation  
(Notification before implementation and MAHs must wait a period of 30 days) |
| Low               | (Non-approved matters) | Minor change  
(Annual report) | Type IA IN variation  
(Immediate notification) |

- **Type IA IN variation**: Immediately notification before implementation and MAHs must wait a period of 30 days.

- **Type IA variation**: Notification within 12 months after implementation.

- **Type IB variation**: Notification before implementation and MAHs must wait a period of 30 days.

- **Type II variation**: Application for approval of variation.
(My personal observation) Remaining Challenges

- Our 2005 GL has provided the basic principle of AMs in the Mfg. process and helped both regulators and the industry.

- However, there still remain some challenges, including:
  - Adverse effects of mock
    - Some just followed the mock described in the guideline to meet deadline.
    - Both regulators and the industry tend to follow the mock (?), although the description in the AF is on a product-by-product basis.
  - Document management
    - The discrepancy between the actual situation (e.g. MBR) and AF is caused by multiple factors.
  - Others
    - Some tend to lose sight of the original purpose of the AF.
    - Some tend to think MAHs manufacture and control their products only according to the AF.
    - **There had been no detailed discussion on Specification.**
Japan’s Effective/Efficient/Flexible Quality Regulation

Module 1
(Application Form)

Module 2 (QOS)

Module 3

Legally binding

Not-Changeable without regulatory procedures (PCA/MCN)

Changeable without regulatory procedures (PCA/MCN)
Japan’s Effective/Efficient/Flexible Quality Regulation

Module 1 (Application Form)

Module 2 (QOS)

Legally binding

Module 3

Not-Changeable without regulatory procedures (PCA/MCN)

Changeable without regulatory procedures (PCA/MCN)
AF and Review/Inspection

-Focus on post-approval change-

Scientific Knowledge / Knowledge Management

- Change Evaluation
  - Science & Risk-based evaluation
  - Evaluate the PAC against EC/ non-EC
  - Determine the data needed
  - Design & review PAC strategy

- Change Approval

- Implement PAC & Strategy

- Regulatory notification (if required)
- Regulatory approval (if required)

Stimulus
Driving to Change Request

Past Changes Implemented

Development / Co-Development Report

Product / Process Performance Review

Other... Management review

PQR / APR

AF and Review/Inspection

Modified from draft Q12 document