QMS (Quality Management System) for Medical Device in Japan

3rd Brazil – Japan Seminar
4 October, 2016

Naoko SATO
Office of Manufacturing/Quality and Compliance
Division of Medical Devices
First of all,
Recent Incident

During flushing blood the tip of Cannula took off. This incident resulted in the manufacturing process of cutting tip of the Cannula. As CAPA, Corrective Action and Proactive Action, reviewed are the setting process of cutting machine, the measurement, and those training.
Root causes of incidents

1. Defective products and mal durability

In order to prevent the incidents with high risk, establishing QMS (Quality Management System) in the facilities is important!!

QMS requirements are harmonized with ISO13485 and not so big difference from QSR.
And some local Japanese requirements are added to QMS.

How to register, how to apply for inspection are not the same.
So today’s topics are ・・・

7. Circumstances of using medical devices
1. Entering Japan Market
2. QMS regulation
3. QMS inspection flow
4. MDSAP update
1. Entering Japan Market
License, Registration, Approval

**Marketing license**
– All the Japan organization should have this license in order to enter Japan market in Medical devices and In-vitro Diagnostics.

**Manufacturing site registration**
– Requirements for conducting specified manufacturing processes. In the case of medical devices, the design, main assembling, sterilization and domestic (Japan) distribution site shall be registered.

**Marketing approval**
– Requirement for marketing any new medical devices and IVDs in Japan, and partial changes of authorized product.
Marketing Authorization

Marketing Authorization Holder: MAH

A Japanese organization who obtains the marketing approval. MAH should manage all the registered manufacturers to comply with Japan QMS and to release the products those specification should meet approved ones in Japan.

Foreign restrictive authorization holder: FRAH

A foreign organization who obtains the marketing approval. FRAH should designate MAH in Japan responsible for the product in Japan market.

Designated MAH

A Japanese organization designated by FRAH to conduct manufacturing and quality control duties in Japan. Designated MAH should take necessary measures for the prevention of occurrence of hazards to the public health and hygiene in Japan caused by the product.
Supply Chain in Japan

- **MAH (Japanese Manufacturer)**
- **MAH (Foreign Manufacturer)**
- **FRAH (Designated MAH)**
- **Japanese Distribution Center**
- **Wholesaler**
- **Seller / Leaser**
- **Medical Institute**
- **Repairer**

**Manufacturers’ License Requirements:**
- Manufacturer Registration
- Seller/Leaser License, Notification, or Self Declaration
- Repairer License

**Marketing License Requirements:**
- Marketing License + Marketing Approval
- Marketing Approval
- Marketing License
2. QMS regulation
Type of QMS Inspection

1. Pre-approval inspection
   Requisition of the marketing approval.
   Conducted prior to obtain the approval.

2. Pre-partial change approval inspection
   Conducted prior to obtain the partial change approval.
   ex) main assembling site change etc..

3. Periodic post-approval inspection
   Requisition of maintaining existing marketing approval.
   Conducted every 5 years after obtaining the marketing approval.

4. Additional inspection
   Conducted where appropriate.
   ex) specialized inspection for biological products, micro machine
   and medical devices utilizing nano-materials etc..
QMS Inspection (Pre-, Post-)

- **R&D**
- **Application for approval**
  - Regulatory Review
  - Pre-approval inspection
    - One of the requirements for marketing approval of medical device
    - Based on application
    - Conducted per Product Family
- **Approval**
- **Marketing**
  - Post-approval inspection
    - Conducted every 5 years after marketing approval
  - Every 5 years
# Type of QMS Inspection

1. **Pre-approval inspection**
   - Required before the marketing approval.

2. **Pre-partial change approval inspection**
   - Required before the partial change approval.
   - ex) main assembling site change etc..

3. **Periodic post-approval inspection**
   - Required for maintaining marketing approval every 5 years since the initial marketing approval.

4. **Additional inspection**
   - Required for the notified cases.
   - ex) specialized inspection for biological products, micro machine and medical devices utilizing nano-materials etc.
QMS Inspection (Partial change)

Approval

Pre-partial change Application for approval

Pre-partial change Approval

Marketing

Every 5 years

Pre-partial change Approval inspection

Post-approval inspection

- Based on application
- Inspection scope: MAH and the change-related sites.

ex) Main assembling site Change
## Authority of QMS inspection

<table>
<thead>
<tr>
<th>Product</th>
<th>Inspection Authority (Based on application)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Devices</strong></td>
<td></td>
</tr>
<tr>
<td>• Class IV</td>
<td>PMDA</td>
</tr>
<tr>
<td>• New medical devices</td>
<td></td>
</tr>
<tr>
<td>• Cell / Tissue-based medical</td>
<td></td>
</tr>
<tr>
<td>devices</td>
<td></td>
</tr>
<tr>
<td>• Class III and Class II</td>
<td>PMDA</td>
</tr>
<tr>
<td>(without CS*)</td>
<td></td>
</tr>
<tr>
<td>• Class III and Class II</td>
<td>Registered certification body</td>
</tr>
<tr>
<td>(with CS*)</td>
<td></td>
</tr>
<tr>
<td><strong>IVDs</strong></td>
<td></td>
</tr>
<tr>
<td>• New IVDs</td>
<td>PMDA</td>
</tr>
<tr>
<td>• Radioactive IVDs</td>
<td></td>
</tr>
<tr>
<td>• Products without CS*</td>
<td>PMDA</td>
</tr>
<tr>
<td>• Products with CS*</td>
<td>Registered certification body</td>
</tr>
</tbody>
</table>

*CS : Certification Standards
QMS inspection and scope

QMS inspection

1. Pre-approval inspection
2. Pre-partial change approval inspection
3. Periodic post-approval inspection
4. Additional inspection

Scope

- Marketing Authorization Holder (MAH)
- Design Facility
- Main Assembling Plant
- Sterilizer
- Domestic (Japan) Distribution Center
- Other sites
## Manufacturing site Registration

Sites listed below needs to be registered for the products.

<table>
<thead>
<tr>
<th>Site</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Facility</td>
<td>(1) maintain records of design and development</td>
</tr>
<tr>
<td></td>
<td>(2) the responsible person should work here</td>
</tr>
<tr>
<td>Main Assembling Plant</td>
<td>(1) substantially responsible for QMS or product realization of the product</td>
</tr>
<tr>
<td></td>
<td>(2) operate assembling(filling) processes.</td>
</tr>
<tr>
<td>Sterilizer</td>
<td>(1) operate sterilization process</td>
</tr>
<tr>
<td>Domestic (Japan) Distribution Center</td>
<td>(1) store products until final release of shipment to Japanese market.</td>
</tr>
</tbody>
</table>
Example of mfg. site registration

Design & Development
Supplier
Sub-Assembly
Main Assembly
Packing
Distribution

Registration

Required
N/A
N/A
Required
N/A
Required

in the Korea

in Japan

Shipping to the market
Registration of Manufacturer

<table>
<thead>
<tr>
<th>Licensing system</th>
<th>Registration (Domestic, Foreign)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authority to provide license</td>
<td>Prefecture (Domestic) MHLW (Foreign)</td>
</tr>
<tr>
<td>Requirements for licensing</td>
<td>Reasons for disqualification (Health, Crime, Revocation)</td>
</tr>
</tbody>
</table>
## Scope of Registration and Inspection

<table>
<thead>
<tr>
<th>Facility / Site</th>
<th>Registration</th>
<th>QMS Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAH</strong> Marketing Authorization Holder</td>
<td>N/A</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Design Facility</strong></td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Main Assembling Plant</strong></td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Sterilizer</strong></td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>only for sterile medical device</td>
<td></td>
<td>only for sterile medical device</td>
</tr>
<tr>
<td><strong>Domestic (Japan) Distribution Center</strong></td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Other sites</strong></td>
<td>N/A</td>
<td>Depends</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMEDA determines based on risk assessment</td>
</tr>
</tbody>
</table>
- Generic names of Medical Devices and IVDs are grouped into **“Product Families”** depending on factors such as characteristics, usage method, risk etc. QMS inspection is conducted per **“Product Families”**

- The relationship between product family and generic name is announced by notification
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General Provisions</td>
<td>1~3</td>
</tr>
<tr>
<td>2</td>
<td>Medical Devices Manufacturing</td>
<td>4~64</td>
</tr>
<tr>
<td></td>
<td>Harmonized to ISO13485:2003=&gt;2016</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Additional Requirements</td>
<td>65~72-3</td>
</tr>
<tr>
<td>4</td>
<td>Biological-origin Medical Device, etc. Manufacturers (Domestic, Foreign)</td>
<td>73~79</td>
</tr>
<tr>
<td></td>
<td>Additional requirements according to the characteristics of the products</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>In-Vitro Diagnostic Radioactive Reagents Manufacturers (Domestic, Foreign)</td>
<td>80~81</td>
</tr>
<tr>
<td></td>
<td>Additional requirements according to the characteristics of the products</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Provisions Applied Mutatis Mutandis of Medical Device, etc. Manufacturing Sites, etc.</td>
<td>82~84</td>
</tr>
</tbody>
</table>
3. QMS inspection flow
Outline of QMS Inspection

Inspection Unit

Marketing Authorization Holder

- Manufacturing Site (Design Facility)
  - Desktop Inspection
  - On-site Inspection
  - Inspection Report

- Manufacturing Site (Assembling Plant)
  - Desktop Inspection
  - On-site Inspection
  - Inspection Report

- Manufacturing Site (Contract Sterilizer)
  - Desktop Inspection

- Manufacturing Site (Domestic Distribution Center)
  - Desktop Inspection

QMS Application

Product family

Conformity of Application

QMS Compliance Certification

Summary Report
Determine on-site or desktop inspection

Determination step

Input Information:
- Submitted documents
- Reported adverse events and recalls
- Records of previous QMS inspections
- Complexity of manufacturing processes
- Risk associated with the use of products
- Previous nonconformities and recalls
- Results of the previous on-site inspections
- Certificate of ISO13485 etc.

Receive application of QMS inspection

Determine on-site or desktop inspection

On-site

Site A

Site B

Desktop

Site C

Site D

Input Information

Risk Assessment

Decision of on-site or desktop

Conformity assessment

Issue Compliance certification and inspection report

On-Site Inspection

Desktop Inspection

24
On-site inspection

- **Receive application of QMS inspection**
- **Determine on-site or desktop inspection**
- **Conformity assessment**
- **Issue Compliance certification and inspection report**

**On-site inspection flow**

1. **Notification of Inspection**
2. **Submit documents PMDA requests**
3. **On-site QMS Inspection**
4. **Issue findings report**
5. **Submit improvement Plan or Report**
6. **Accept improvement Plan or Report**

- **Site A**
- **Site B**
- **Site C**
- **Site D**

- Depending on requests from application company.
- 3~4 days
- ~14 days
- ~30 days
- Depending on requests from application company.
Desktop inspection

**Required documents for Desktop inspection**

<table>
<thead>
<tr>
<th>Documents</th>
<th>Outline of Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layout of all mfg. site building</td>
<td>- Bird’s eye-view photograph or location map of mfg. site</td>
</tr>
</tbody>
</table>
| Floor plan | - Clean room grade  
- Differential pressure  
- List or layout of representative manufacturing and test equipment |
| Organization chart | - Responsible persons and departments under QMS |
| Quality management system | - Quality Manual |
| List of documents identified with QMS | - Including name, number, and retention period of QMS control documents |

**Seihin Hyojun Sho**

- The document of *Seihin Hyojun Sho* showed all the related documents to the product under QMS. (*Device master record OK*)

**Validation status of mfg. process**

- List showing mfg. process, mfg. site, and date about the validation.
QMS inspection flow

Periodic post-approval inspection

- Receive application of QMS inspection
- Determine on-site or desktop inspection
- On-site Inspection: MAH, Mfg. site A (Assembly)
  - Conformity assessment
  - Issue QMS certification and QMS inspection report
- Desktop Inspection: Mfg. site B (Design), Mfg. site C (Distribution)
  - Conformity assessment
  - Issue QMS certification and QMS inspection report

~4 week

~4 month

~6 months
QMS Compliance Certification

Marketing Authorization Holder

- Manufacturing Site (Design Facility)
  - Desktop Inspection
- Manufacturing Site (Assembling Plant)
  - On-site Inspection
- Manufacturing Site (Contract Sterilizer)
  - Desktop Inspection
- Manufacturing Site (Domestic Distribution Center)
  - Desktop Inspection

Summary Report*

On-site Inspection

Inspection Report

QMS Compliance Certification
4. MDSAP update
Trial for MDSAP Audit Reports

- PMDA accepts MDSAP audit reports as a trial. from June 22, 2016 to December 31, 2016

- The MDSAP Audit Report can reduce the manufacturer’s burden in the inspection process.

- PMDA performs the trial acceptance without any additional fee.
## Documents for application

<table>
<thead>
<tr>
<th>No.</th>
<th>Documents</th>
<th>Normal Application</th>
<th>Application using MDSAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ISO13485 Certification, registered certification body’s Inspection report, etc</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>Outline of the site</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>A document requested by the guidance</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

OR Configuration:

- Initial/Recertification
- Surveillance
- Initial/Recertification
### Documents for desk-top inspection

<table>
<thead>
<tr>
<th>No.</th>
<th>Documents</th>
<th>Normal Application</th>
<th>Application using MDSAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Arrangement of the facility</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>Floor plan</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>Organization chart</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>Quality manual</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>List of documents used in QMS</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>Summary of medical device file</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>State of implementation of validation</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>Any documentation which indicates the confirmation result of quality of a medical device to ensure safety of it, when the device is using biologically derived raw materials etc.</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>Procedure etc. for communication with Marketing Authorization Holder in relation to adverse events</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>Agreement with Registered Manufacturing Site</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>
Summary for MDSAP documentation

- **Basically** Off-Site inspection for the facility that has the MDSAP audit report when QMS inspection application.

- Exceptions: Registered Manufacturing Site are
  a) human/animal tissues
  b) radioactive IVDs
  c) A Marketing Authorization Holder (MAH)

- On-Site inspection, when necessary.
References

PMDA / QMS (Japanese)
http://www.pmda.go.jp/review-services/gmp-qms-gctp/qms/0003.html

PMDA / QMS (English)
http://www.pmda.go.jp/english/review-services/gmp-qms-gctp/0002.html

PMDA / Notifications related to PAL Revision (Japanese)
http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0040.html

MHLW (English)
Now we are also one of MDSAP members as Brazil and we will cooperate together in MDSAP.

Also as we are getting more close in the harmonization in the requirements and audit competence, awareness, and training, we should eliminate multiple audits in the same facility in Japan and in Brazil.
Contact Address

<Compliance Office address>
gmpqms-contact@pmda.go.jp

<Medical device division address>
sato-naoko@pmda.go.jp