Quality Management System Inspection of Medical Devices and In-Vitro Diagnostics in Japan

Medical Devices / In-Vitro Diagnostics Regulation Under PAL

Marketing Regulation

License for manufacture (Accreditation for foreign manufacturers)

Standards of buildings and facilities

QMS Ordinance Compliance

License for marketing

GQP (Good Quality Practice)

GVP (Good Vigilance Practice)

Marketing approval

Review of quality, efficacy and safety according to product categories

QMS compliance

Inspection and Audit by PMDA

1 Inspection of buildings and facilities

- License for domestic manufacturers
  (cell/tissue derived devices, radioactive IVDs,etc.)
- Accreditation for foreign manufacturers

2 QMS inspection

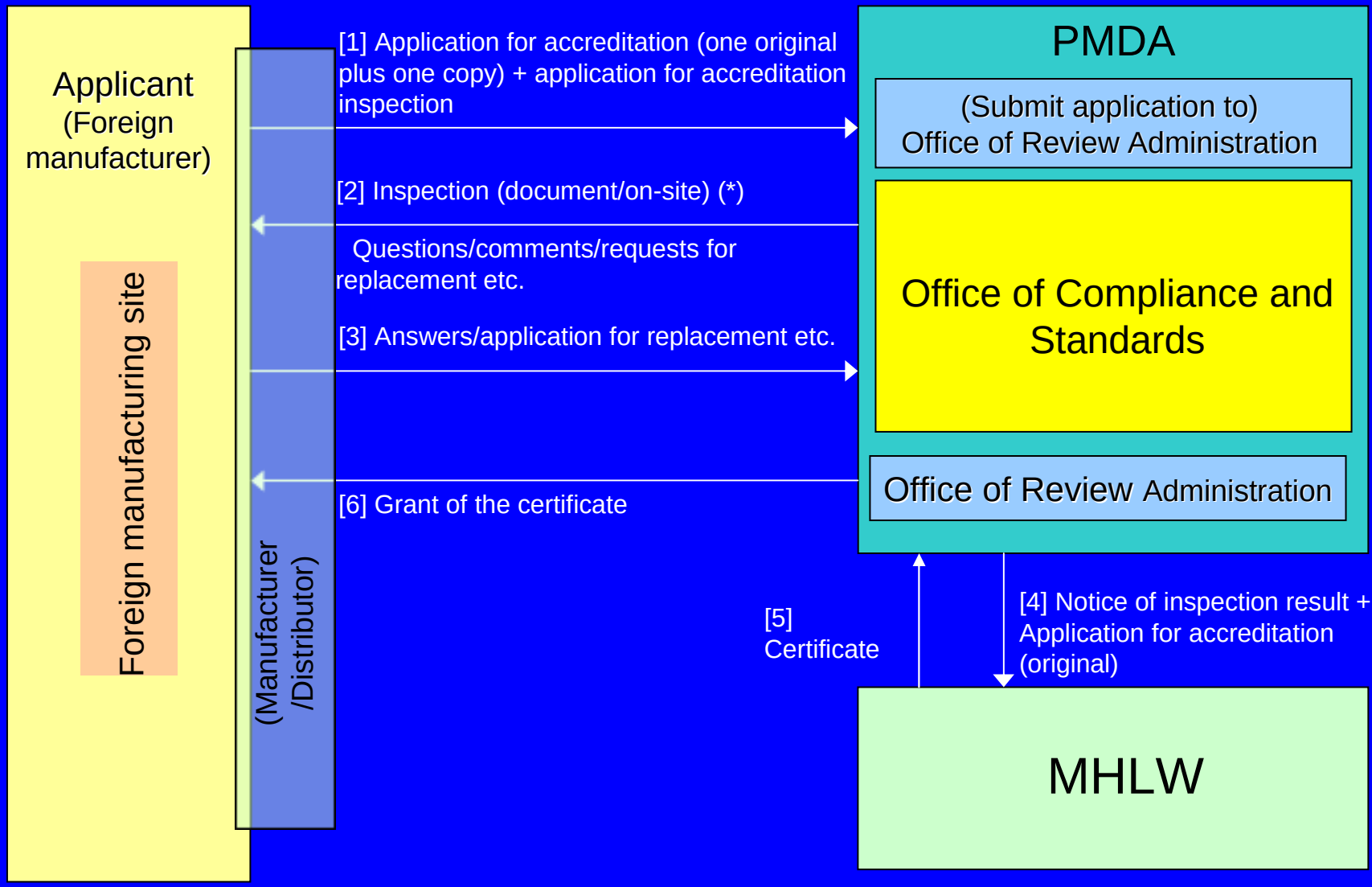
- Compliance inspection (domestic/foreign)
- Inspection of medical devices for export (domestic)
- Other Inspections

Authority of Inspection of Buildings and Facilities of Manufacturers

	Category	Domestic (License)	Foreign (Accreditation)
IVD	Radioactive	PMDA	PMDA
	Others	Prefectures	PMDA
Medical device	Cell/tissue derived	PMDA	PMDA
	Sterile	Prefectures	PMDA
	Others	Prefectures	PMDA

Flow of Foreign Manufacturer Accreditation

(*) At present, accreditation is based primarily on document review



Prerequisite for Marketing approval

1 **Review of quality, safety and efficacy**

2 **QMS Compliance**

3 **License for marketing approval holder**

4 **License for manufacturer**
(Accreditation for foreign manufacturer)

Types of QMS Inspections

Compliance inspection

1. Pre-approval inspection
2. Post-approval inspection (periodic inspection)

For cause inspection

Authority of Compliance Inspection

		Domestic establishment	Foreign establishment
IVD	New drug	PMDA	PMDA
	Radioactive drug	PMDA	PMDA
	Others	Prefectures (CB* for IVDs with certification standards)	PMDA (CB for IVDs with certification standards)
Medical device	New device	PMDA	PMDA
	Cell/tissue derived device	PMDA	PMDA
	Class IV	PMDA	PMDA
	Class III	Prefectures	PMDA
	Class II	Prefectures (CB for medical devices with certification standards)	PMDA (CB for medical devices with certification standards)
	Class I	-	-

CB: Certification body registered by Ministry of Health, Labour and Welfare

Compliance Inspections by PMDA

Target products（Medical devices and IVDs)

1. New medical devices
2. Cell-tissue-derived medical devices
3. Class IV medical devices
4. Radioactive IVDs
5. Medical devices and IVDs manufactured in foreign manufacturing sites

Target sites

Manufacturing sites (including testing laboratories, design and development Institutes)

Basic Principles of QMS Compliance Inspection

	Type of inspection	Pre-approval		Post-approval	
		The 1st time	The 2nd time and after	The 1st renewal	The 2nd renewal and after
	Subject of inspection	Overall	Product which is applied to marketing approval	Overall	Especially focused on changed parts
Subsystem	Management	○	△	○	○
	Design and development	○	△	△	△
	Product design documentation	○	○	○ (Selected product)	○ (Selected product)
	Production process	○	△	△	△
	CAPA	○	△	△	△
	Purchasing controls	○	△	△	△
	Documents and records	○	△	△	△
	Customer related process	○	△	△	△
	Findings in previous inspection	–	○	○	○

○: Major subsystems subject to inspection
△: Selective subsystems subject to inspection (can be omitted if previously inspected by PMDA, prefectures or CB)

Requirements of License/Accreditation, QMS inspection, and description in Marketing Approval Application

	License/ Accreditation	QMS inspection	Description in Marketing approval application
Manufacturing sites (sterilization facilities)*1	Necessary	Necessary	Necessary
Manufacturing sites (storage facilities)	Necessary	Necessary	Necessary
Manufacturing sites (other than above two)	Necessary	Necessary	Necessary
Design and development institutes *1, *2	Not necessary	Necessary	Necessary
Testing laboratories *1, *3	Not necessary	Necessary	Necessary

*1 QMS inspection is not necessary when the site's QMS conformity has been confirmed within the past two years.

*2 Institutes that conduct the main part of the design and development of high-risk devices called "Design and Development Controlled Medical Devices."

*3 Laboratories that conduct important tests for quality assurance of finished product and are not under the manufacturer's QMS control. Important tests for quality assurance of end products include post-EOG-sterilization tests using biological indicator, coating uniformity tests for stent-coating drugs, and precious-metal-content tests for dental metals.

Requirements of License/Accreditation, QMS inspection and description in Marketing Approval Application

	License/ Accreditation	QMS inspection	Description in Marketing Approval Application
Facilities that manufacture component parts *4	Not necessary	Not necessary	Not necessary
Facilities that conduct processes which influence the quality, performance and safety of finished product *5, *6	Not necessary	Not necessary	"Conditions of manufacture" should be described *7
Facilities that conduct processes other than above	Not necessary	Not necessary	Not necessary

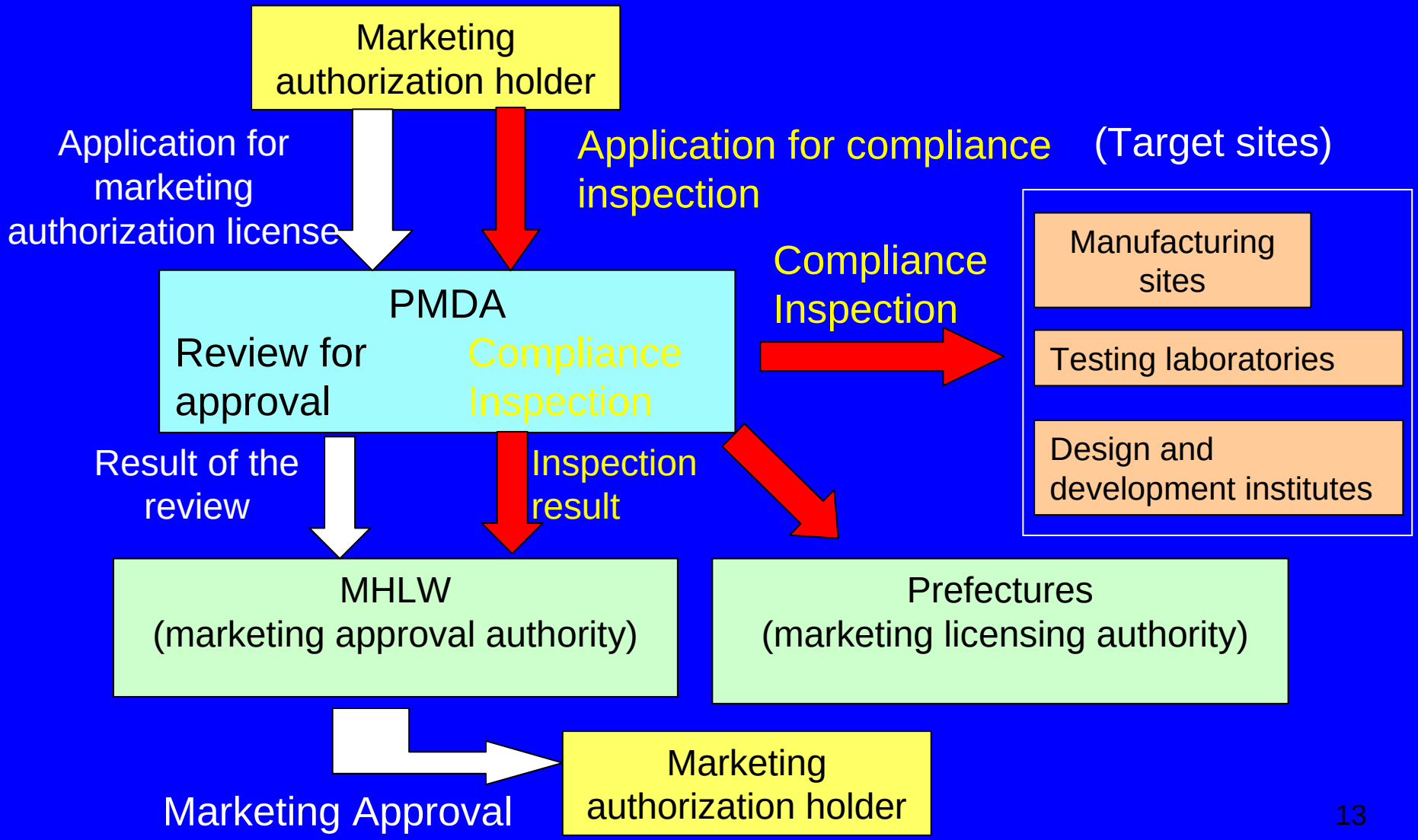
*4 Manufacturers of component parts should obtain a license (or accreditation) and have QMS inspection when they seek approvals for the component parts separately from the main unit of the medical device.

*5 For example, the processes are heparin-coating for catheters and drug-coating for stents.

*6 In principle, QMS inspection is not necessary for contracted facilities on the condition that they are under proper QMS control by the contract giver.

*7 Although the name of the facility doesn't have to be shown in the application form, conditions of important production processes should be described. If you have any question about the preparation of application forms, please ask the Office of Medical Devices, PMDA, through its consultation service.

Flow of QMS Compliance Inspection



On-site Inspection and Document Review (1)

On-site inspection is conducted in the order of sites' priority, which is determined by the comprehensive evaluation of risks associated with product, manufacturing process and others.

Risk	Product risk	Manufacturing-process risk	Other risk
Low ↓ High	Class II Class III Class IV New medical devices Cell/tissue-derived devices	- Testing - Design and development - Packaging, labeling or storage - Outsourced sterilizing - Important processes such as assembly	GHTF membership or not History of past inspections

On-site Inspection and Document Review (2)

On-site inspection is conducted in order of priority based on:

1 Complexity of manufacturing processes;
2 Risk associated with the use of products;
3 Results of the previous on-site inspections; and
4 Previous nonconformity, recall, or the contents

ex. New medical devices, cell-tissue-derived medical devices, class IV medical devices

Flow of On-site Inspection

1 Scheduling of inspection
2 Request of data prior to inspection
3 Notice of inspection date
4 On-site inspection
5 Notification of written observation items
6 Receipt of a report of corrective actions (plan)
7 Notice of the result of inspection to MHLW

QMS Inspection Schedule (Example)

Date	Time	Item
1	AM	1. Opening Meeting (1) Greeting Confirmation on the audit schedule (2) Opening of the audit (Declaration) (3) Overview of the company and the plant (Infrastructure, Main Equipments) (4) Presentation about the product 2. Overview of Quality Management System (1) Quality Manual (2) QMS Organization, Document Structure, Seihin-Hyojunsho (3) Agreement with MAH 3. Management Responsibility (1) Quality Policy and Quality Objectives (2) Management Review
	PM	4. Plant Tour
2	AM	5. Control of Design and Development (incl. risk management) 6. Control of Manufacture and Test / Inspection (incl. validation, operating procedures and records etc.) Product control (in consistency with the key specifications) 7. Control of Monitoring and Measuring Devices
	PM	8. Control of Nonconforming Product 9. Training 10. Purchasing Control (Control of Suppliers and Materials)
3	AM	11. Internal Audit 12. CAPA ・Recall and Adverse Event
	PM	13. PMDA wrap-up 14. Confirmation on findings (Site management representative and others) 15. Closing Meeting (Top management and others)

＊Timeframe and items are subject to change depending on progress.

Flow of Document Review

1. Request for the document
2. Review of the document
3. Request for additional document and the correction of flaws in the documents, as necessary
4. Receipt of additional document
5. Notification of the review result to MHLW

Points to consider in the application of QMS inspection

1. Application should be made for every facility that needs to be inspected.
2. Submission Timing; Application should be made at least six months prior to the day on which standard administrative process time of the Marketing Approval Application expires. In case the process time is less than six months, the application should be made at the same time as the Marketing Approval Application.
3. Inspection will be conducted after quality specifications and manufacturing methods are finalized in the Marketing Approval Application.
4. Facilities should be well prepared for the inspection.

Note) In principle, application of QMS inspection is not required for the application of pre-approval for partial changes regarding addition of component parts and change of product specifications→The partial changes are subjected to upcoming QMS periodic (renewal) inspection etc.

Data required for the application of pre-approval inspection

1. Copies of result notifications or reports of QMS inspections conducted on other products in last two years
2. For foreign manufacturing sites, copies of certificates or inspection reports issued in the country, certificates issued by WHO, certificates of ISO 13485 or certificates issued by the local authorities
3. Copy of the marketing approval (or approval of partial changes) application form
4. Other materials required by the inspecting organization (submission may be made after the application)

Data required by PMDA

In the case of pre-approval inspection (1/2)

<Data on manufacturing sites>

1 Outline of the sites (fill in a provided format)

2 Floor plan (including: layout drawings, dimensions of working area, material and personal flow, location or list of main manufacturing and testing equipments, and for devices that require sterilization, environment condition and pressure difference in each part of the building)

<Data on QMS>

3 Organizational structure for QMS (including the relationship with the GQP organization of the marketing authorization holder and agreements with outside contractors on quality issues)

4 Quality policies and summary of Quality Management System Standard Code (Quality Manual)

5 Structure of QMS documents of the manufacturing site including Product Standard Code(Seihin Hyojun Sho)

Seihin Hyojun Sho can be substituted by a list of documents that contain required information)

Data required by PMDA

In the case of pre-approval inspection (2/2)

<Data on Products>

6 Outline of the products (products' package inserts will be acceptable)

7 Outline of manufacturing process (flow chart) and important control points

8 (Important) specifications of the products

9 In case of foreign manufacturing sites, list of countries other than Japan to which the product is exported and its brand names in each country, if any

10 Validation of production processes
(Ex. sterilization and other processes)

(Attachment)

For medical devices

Outline of Manufacturing Site of Medical Devices

as of (date)

Name of the site:
Location of the site:
License (accreditation) number _____ Date of the first license (accreditation) _____
License (accreditation) categories
Expiry date of license (accreditation) _____
Number of employees _____(those involved in production __, those involved in testing __)
Name and position of a person in charge
Annual production output of the site ___by value in the year___(may be left blank in case of non-disclosure)

Breakdown of manufacturing items (that is; items for export to Japan, in case of foreign manufactures)

	Class I	Class II	Class III	Class IV	Total
Number of manufacturing products					

Name of the principal product (the principal product for export to Japan, in case of foreign manufactures)

Name of products exported and destinations for export (for domestic manufacturing sites only)

Area of the manufacturing site _____ m^2 Warehouse area _____ m^2
Area of production facility _____ m^2 Area of testing laboratory _____ m^2
Area of design and management institute _____ m^2 (if appropriate)
Inspected by the government or ISO certification bodies? (If yes, fill in the target items and timing of inspection)

Utilize other testing and inspection facilities ? (If yes, fill in the name ,address and items)

Data required for QMS document review of contract sterilization facilities

Current requirement	Points to consider
1. Data on manufacturing sites **(1) Outline of the sites** **(2) Floor plan**	**(1) Fill in a provided format** **(2)Shows the location of sterilizers**
2. Data on QMS **(3) Organizational structure for QMS (including outsourcing contracts)** **(4) Summary of the Quality Manual *1** **(5) QMS document architecture *1**	**(3) Submission of the QMS organization chart of the contract sterilization facility is not necessary when it is attached to the organization chart of the contract giver as a document showing a relationship between the contract giver and the contract sterilization facility.** **(4) Example: Quality policies and table of contents of the Quality Manual** **(5) Example: Documentation pyramid shown in the Quality Manual** **Example: List of top-level documents shown in the Quality Manual** **Example: List of Standard Operating Procedures required by ISO 13485**
3. Data on products (including Product Standard Code)	**Not necessary because the same information will appear in the contract giver's data *2**

***1** Not necessary when it was already submitted at the last QMS inspection conducted within the past two years and no change has been made since then

***2** Parameters of sterilization will be shown in the outsourcer's data

Note: Copy of the certificate of ISO 13485 2003 is necessary for QMS document review

(Attachment)

For outsourcing for sterilization

Outline of Manufacturing Site of Medical Devices

as of (date)

Name of the site:
Location of the site:
License (accreditation) number _____ Date of the first license (accreditation) _____
License (accreditation) categories
Expiry date of license (accreditation) _____
Number of employees _____(those involved in production __, those involved in testing __)
Name and position of a person in charge
Annual production output of the site ___by value in the year___(may be left blank in case of non-disclosure)

Breakdown of manufacturing items (that is; items for export to Japan, in case of foreign manufactures)

	Class I	Class II	Class III	Class IV	Total
Number of manufacturing products					

Name of the principal product (the principal product for export to Japan, in case of foreign manufactures)

Name of products exported and destinations for export (for domestic manufacturing sites only)

Area of the manufacturing site _____m^2 Warehouse area _____m^2
Area of production facility _____m^2 Area of testing laboratory _____m^2
Area of design and management institute _____m^2 (if appropriate)
Inspected by the government or ISO certification bodies? (If yes, fill in the target items and timing of inspection)

Utilize other testing and inspection facilities ? (If yes, fill in the name ,address and items)

(Attachment)

For IVDs

Outline of Manufacturing Site of Drugs

as of (date)

Name of the site:
Location of the site: _____License (accreditation) number _____ Date of the first license (accreditation) _____
License (accreditation) categories
Expiry date of license (accreditation) _____
Number of employees _____(those involved in production __, those involved in testing __)
Name and position of a person in charge
Annual production output of the site ___by value in the year___(may be left blank in case of non-disclosure)

Breakdown of manufacturing items (that is; items for export to Japan, in case of foreign manufactures)

	Radioactive	Non-radioactive
Number of manufacturing products		

Name of the principal product (the principal product for export to Japan, in case of foreign manufactures)

Radioactive	Non-radioactive

Name of products exported and destinations for export (for domestic manufacturing sites only)

Radioactive	Non-radioactive

Area of the manufacturing site _____m^2 Warehouse area _____m^2
Area of production facility _____m^2 Area of testing laboratory _____m^2
Inspected by the government or ISO certification bodies? (If yes, fill in the target items and timing of inspection)

Utilize other testing and inspection facilities ? (If yes, fill in the name ,address and items)

Seihin Hyojun Sho
(Product Standard Code)

The manufacturer shall establish and maintain the document defining the product specifications and QMS requirements (*Seihin Hyojun Sho*), or identifying *Seihin Hyojun Sho.* (QMS Ordinance Article 6 Para 2)

Items to be stipulated in the Product Standard Code are specified in (11), 6. Part 3, chapter4 of Notice PFSB-CND No. 0330001 dated March 30, 2005, article-by-article explanation of Ministry Ordinance for QMS of Medical Devices and In-vitro Diagnostics.
For storage facilities, the items are specified in Article 66, Chapter 3 of the Ministry Ordinance for QMS.

Product Standard Code

(Example for foreign manufacturing sites)

Items to be stipulated	**Documents containing the information**
Design, drawings and specifications of the product	Title and document ID No.
Manufacturing method and procedure	……
Labeling and packaging	……
Testing methods for the finished product, component parts and materials necessary for the production (such as adhesive)	……
And so on	……

Post-approval inspection (periodic inspection)

- Conducted every five years after the marketing approval
- In principle, application should be submitted at least six months prior to the expiration of the license for marketing
- Not required for testing laboratories and design and development Institutes
- Several foreign manufacturing sites can be applied together

  (a group of foreign manufacturing sites whose products are stored in the same facility in Japan, where the products have the final pre-shipment inspection can be submitted together in a single application)

Data required for the application of periodic inspection

1. Copies of result notifications or reports of QMS inspections conducted on other products in last two years (of all the manufacturing sites concerned)
2. For foreign manufacturing sites, copies of certificates or inspection reports issued in the country, certificates issued by WHO, certificates of ISO 13485, or certificates issued by the local authorities (of all the manufacturing sites concerned)
3. Copies of marketing approval (for representative products)
4. Copies of Approval of partial changes in approved matters, Notification of minor changes, Notification of description adjustment of approved matters due to the revision of the Pharmaceutical Affairs Law , issued in last five years (for the representative products)
5. Reasons for the selection of the “representative products”
6. Recalls in last five years, if any (for all the products)
7. Written pledge on the credibility of the application data
8. Other materials required by the inspecting organization (submission may be made after the application)

Data required by PMDA

In case of periodic inspection 1/4

<Data on manufacturing sites>

1 Outline of the sites (fill in a provided format)
→ of all the manufacturing sites (copies of ISO certificates, if any)

2 Floor plan (including: layout drawings, dimensions of working area, material and personal flow, location or list of main manufacturing and testing equipments, and, for devices that require sterilization, environment condition and pressure difference in each part of the building)
→ of manufacturing sites of the representative products

Data required by PMDA

In case of periodic inspection 2/4

<Data on QMS>

3 Organizational structure for QMS (including the relationship with the GQP organization of the marketing authorization holder and agreements with outside contractors on quality)
→ of manufacturing sites of the representative products

4 Quality policies and summary of Quality Management System Standard Code (Quality Manual)
→ of manufacturing sites of the representative products

5 QMS document architecture (including Product Standard Code)
(Product Standard Code can be substituted by a list of documents that contain required information)
→ of manufacturing sites of the representative products

Data required by PMDA

In case of periodic inspection 3/4

<Data on Products>

6 Outline of the products (products' package inserts will be acceptable) → for all the products

7 Outline of manufacturing process (flow chart) and important control points → for the representative products

8 Specifications of the products → for the representative products

9 In case of foreign manufacturing sites, list of countries other than Japan to which the product is exported and its brand names in each country, if any → for all the products

10 Implementation status of the validation in production processes (Ex. sterilization and other processes) → of manufacturing sites of the representative products

Data required by PMDA

In case of periodic inspection 4/4

<Other data>

11 Annual production volume in last three years
→ of manufacturing sites of the representative products

12 Change control procedure of the product design
→ of manufacturing sites of the representative products

13 In case that applying several foreign manufacturing sites are submitted together, the Summary Table (use a format on the next page) should be submitted

Summary Table

Information on foreign manufacturing sites *							Information on products						Remarks
Names of the site	Addresses of the site	Names of the manufacturer	Addresses of the headquarters	Category of accreditation	Accreditation number	Date of the accreditation	Categrry	Generic Name (Code)	Brand Name	Approval number	Approval date	classification	
Site A							Product a						
							Product b						
							Product c						
Site B							Product d						
							Product e						
							Product f						
							Product g						

* The domestic site which stores products that are from those foreign manufacturing sites and subject to the inspection by PMDA could also be listed here.

On-site Inspection of Domestic/Foreign Manufacturers

1. Conducted in the same manners as in Japan
2. Two inspectors in general
3. For about three days
4. Notify 3-6 weeks before inspection
5. Data submission 1-2 weeks before inspection
6. Inspection in the order of prioritized check points

Points to Consider with Regard to Overseas On-site Inspection

1. Understanding the regulations of medical affairs in Japan
2. Finding an appropriate interpreter
3. Translation of documents, as necessary
4. Efficient scheduling of inspection

Handling of Notice of Inspection Result

1 Deliver the notification of written observation items to the manufacturer concerned

2 Notify the inspection result to MHLW and marketing licensing authority

3 Deliver a copy of the notice of inspection result to the marketing authorization holder

4 Deliver a copy of the inspection report to the manufacturing site concerned