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Japan's New Regulatory Environment for Medical Devices

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Overview of Asia and Its Medical Markets

Demographics (2004)

Country	Population	Population Growth (2004 est.)	GDP (PPP)	Per Capita Income (PPP)	Life Expectancy (Years)
China	1,298,847,624	0.57%	6.449 trillion	5000	71.96
Hong Kong	6,855,125	0.65%	212.2 billion	28,700	81.39
Philippines	86,241,697	1.88%	390.7 billion	4,600	69.6
Indonesia	238,452,952	1.49%	758.1 billion	3,200	69.26
Japan	127,333,002	0.08%	3,567 trillion	28,000	81.04
Malaysia	23,522,482	1.83%	207.2 billion	9,000	71.95
Singapore	4,353,893	1.71%	109.1 billion	23,700	81.53
Korea	48,598,175	0.62%	855.3 billion	17,700	75.58
Taiwan	22,749,838	0.64%	528.6 billion	23,400	77.06
Thailand	64,865,523	0.91%	475.7 billion	7,400	71.41

Healthcare Statistics (2003)

Country	Number of Hospitals	Doctors per 1000 Persons	Per Capita Spending on Healthcare (US\$)
China	330,348	1.69	30
Hong Kong	103	1.4	N/A
Philippines	1,652	N/A	33
Indonesia	1,089	0.14	19
Japan	169,556	1.91	2,908
Malaysia	360	0.7	101
Singapore	28	1.39	4,107
Korea	21,686	1.35	584
Taiwan	18,265	7.42	677
Thailand	1,392	0.32	71

Asian Medical Device Markets (2003)

Country	Market Size (US\$)
China	\$3 billion
Hong Kong	\$500 million
Philippines	\$75 million
Indonesia	\$150 million
Japan	\$24 billion
Malaysia	\$300 million
Singapore	\$410 million
Korea	\$1.4 billion
Taiwan	\$900 million
Thailand	\$500 million

Overview of Asian Medical Device Market

- Over 30% of new expenditures on healthcare worldwide is attributable to Asia
- Spending is driven by:
 - Aging population
 - Increasing life expectancy
 - Increasing incidence of major diseases
 - Increasing health consciousness
 - Higher disposable income

Major Markets in Japan

- Southern Kanto region
 - Tokyo, Chiba prefectures
- Kansai region
 - Osaka, Kyoto, Hyogo prefectures
- Tokai region
 - Aichi, Gifu prefectures

The New Regulatory System for Medical Devices in Japan

MHLW

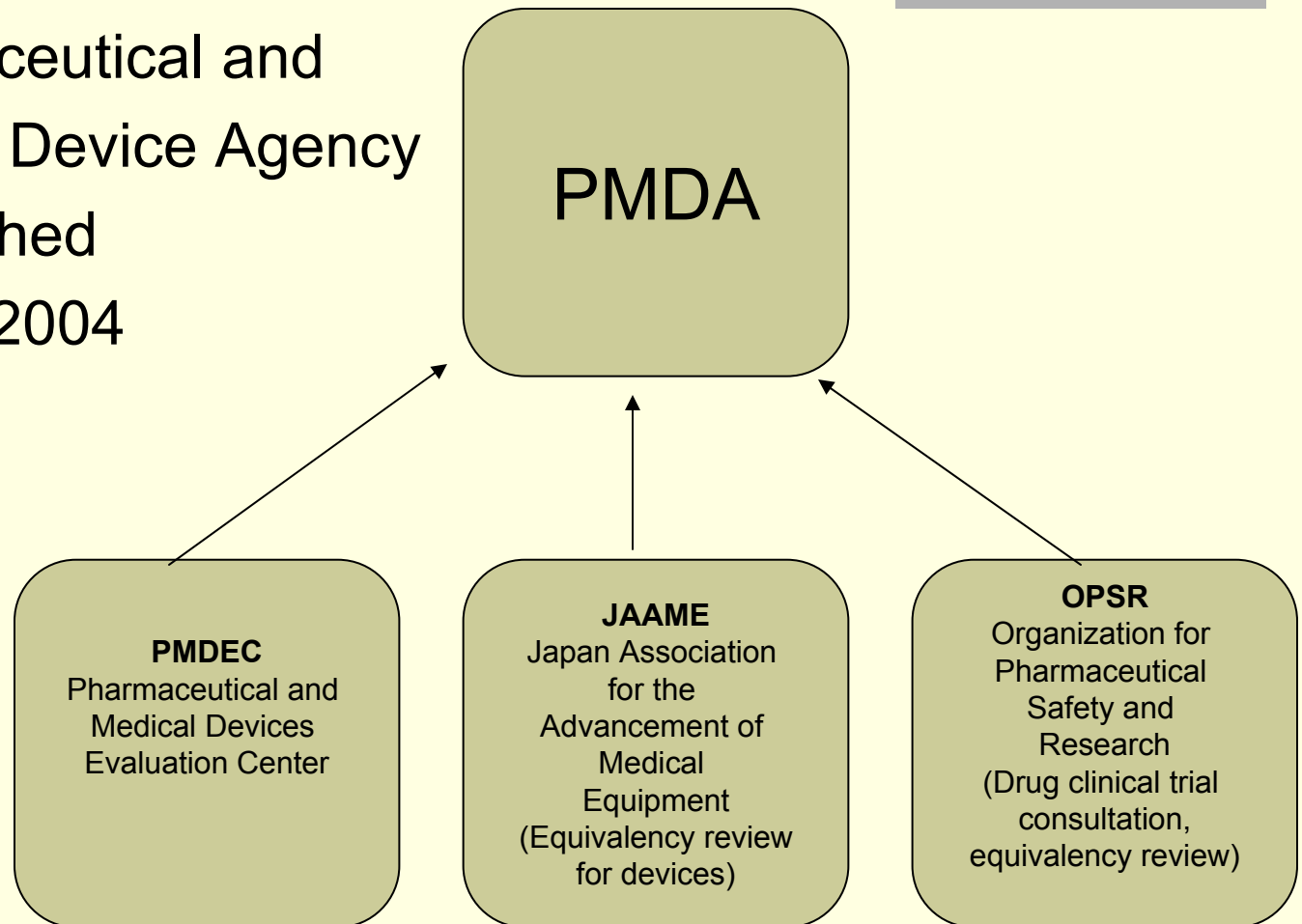
(Ministry of Health,
Labor and Welfare)

MHLW Overview

- Responsible for ensuring good living standards among Japanese people and promoting development of new programs to improve their lives
- Some of the areas regulated by MHLW:
 - Pharmaceutical, medical device and food regulations and safety (including PMDA and PAL)
 - Healthcare services
 - Employment and labor standards
 - Pension and health insurance

Structure of the PMDA

- Pharmaceutical and Medical Device Agency
- Established April 1, 2004



PMDA's Goal

- Get safer and more effective products to the Japanese market in a shorter amount of time

Recently Improved Measures Through the PMDA

- Creation of a system for consultation with the MHLW
 - Reduces time to submission
 - Improves quality of applications
- More medical specialists to review drug and device applications
 - Shorter review time by PMDA
- Products get to the marketplace faster
 - Better for companies
 - Better for patients

PMDA Consultation: Preliminary Consultation

- Offers applicant initial feedback on their situation
- Requires only the applicant be present
- Generally, two days per month are available for making an appointment; consultation will take place about one week later
- Submittal of materials, including an appointment application form and list of questions, is required at the time of scheduling
- Length of consultation: 30 minutes
- Cost: Free of charge

PMDA Consultation: Regular Consultation

- Provides assistance with application without prior review of application documents
 - Topic of discussion example: new vs. partial change application
- Appointments held on Thursdays and Fridays
- Scheduling must be done on Thursday, a week prior to the appointment
- List of questions and relevant materials must be submitted at the time of scheduling
- Length of consultation: 30 minutes
- Cost: about 36,000 yen (about \$350 USD)

PMDA Consultation: Detailed Consultation

- Consultation regarding the application, including prior review of application documents
- A list of questions is required and must be submitted on the Monday three weeks prior to the consultation date
- Applicant, representatives from manufacturer and experts can be present
- Following the consultation, MHLW will prepare the minutes and issue them after receiving approval from applicant
- MHLW will give a recommendation on what they expect to happen during the regulatory process
 - This recommendation will provide insight into what the MHLW is likely to do, but it is non-binding
- Length of consultation: maximum of two hours
- Cost: about 1,700,000 yen (about \$16,000 USD)

The New PAL

(Pharmaceutical Affairs Law)

Goals of the New PAL

- Under the New PAL, the new MAH system will greatly impact foreign medical device manufacturers who are entering the Japanese market or already established in Japan

New International Standards under the New PAL

- Risk-based classification system
- GMP similar to ISO 13845:2003
- Class III devices require STED (Summary Technical Documentation)

Market Authorization Holders

ICC System vs. MAH System

- ICC system:
 - License (kyoka) and approval (shonin) required
 - Manufacturer produced the products *and* released them into the market
- New MAH system:
 - Only production done by manufacturer
 - MAH is an enhanced regulatory control mechanism
 - Gives *final* permission for release of products into marketplace

Purpose of MAH System

- MAH system separates manufacturing and product release
 - Increases quality and safety controls
 - Devices are more closely regulated like drugs

MAH Responsibilities

- Purchase or import products from a manufacturer
- Ensure compliance with GMP, GVP and GQP standards
- Sell products to sales groups
- Temporarily store products in a MAH-licensed establishment

Designating a MAH

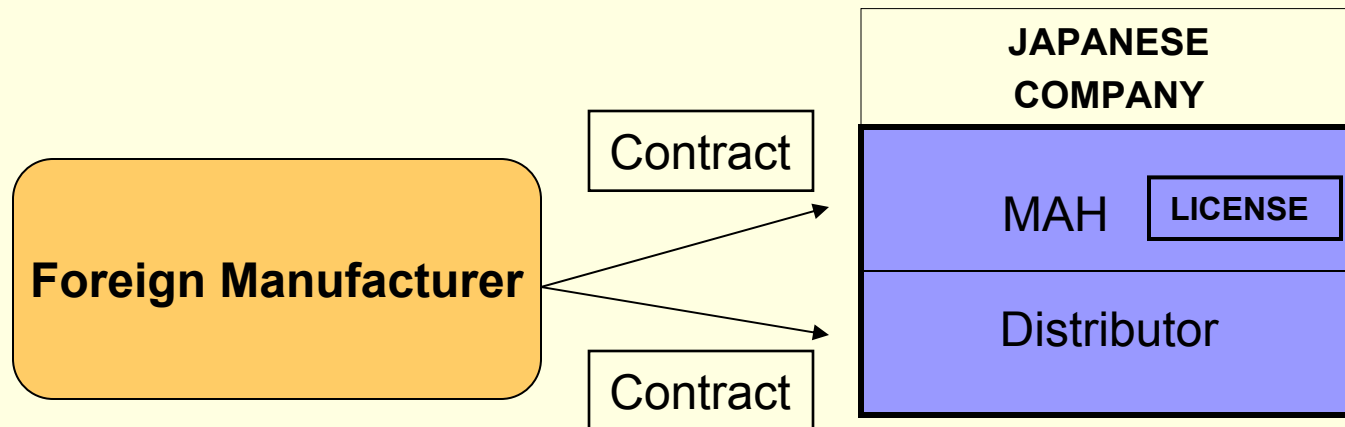
- All companies selling devices in Japan must have a MAH
- MAH must be located in Japan
- A company can designate a distributor/importer, 3rd party, or themselves as their MAH
- If designate themselves →
 - A subsidiary, branch, or representative office in Japan can be their MAH, as long as the MAH meets the MHLW's requirements

MAH vs. Designated MAH (D-MAH)

- If foreign manufacturer does *not* hold product license →
 - Uses MAH (MAH holds license)
 - If foreign manufacturer holds product license themselves →
 - Uses D-MAH
- MAH and D-MAH responsibilities and requirements are the same

Problems with MAH System

- Example:
 - A single company in Japan can provide *both* MAH and distribution services; MAH holds product license for foreign manufacturer
 - If problem with the distributor arises →
 - Difficult and awkward to change distributor since MAH and distributor are same company



Problems with MAH System

- MAH will have access to manufacturer's confidential information, such as
 - Product development
 - Raw materials
 - Manufacturing processes
 - Quality information
- Most manufacturer's will not want to share this information with a 3rd party

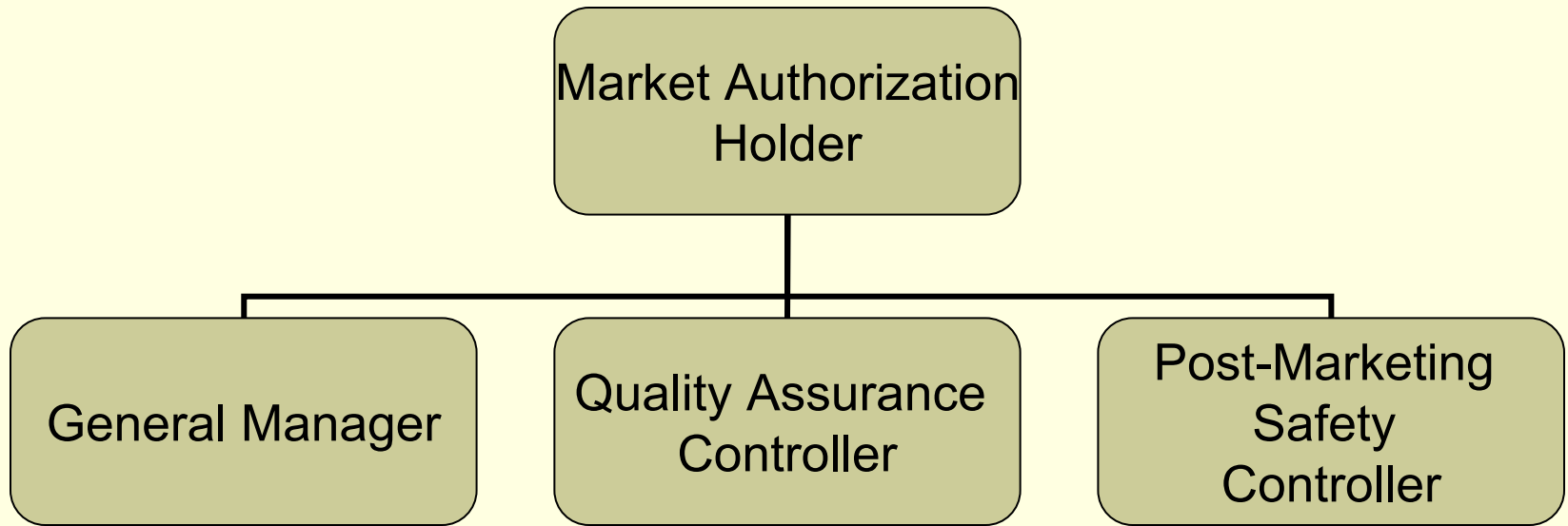
MAH Costs

- Costs vary depending on company's status in Japan - already established vs. entering the market for the first time
 - Example #1:
 - Monthly retainer: \$3K - \$4K
 - PLUS
 - % of sales
 - Example #2:
 - Flat monthly fee of approximately \$6K - \$8K
- Retainer fee covers MAH services previously mentioned, such as GQP, GVP, MAH personnel, product storage, adverse effect reporting, etc.
- Other MAH services, such as product registration, application preparation, translation work, labeling development, etc., require additional fees

MAH Strategies for Foreign Companies

- Foreign companies should develop their MAH strategy based on their current or expected sales in Japan
- Sales less than \$500,000 per year:
 - Would most likely see the independent MAH fees eating into their profit margins
 - If the company does not want to put their confidential product information at risk by using a distributor, they may decide to not enter Japan at all
- Sales around \$500,000 to \$2 million per year:
 - Pay for independent third party to serve as their MAH in order to better protect their confidential information (versus using a distributor) and retain more control of their product marketing
- Sales over \$2 million:
 - May choose to establish their own MAH

MAH Structure



Three Controllers

1. General Manager

- Oversees all MAH duties, including GQP and GVP

2. Quality Assurance Controller

- Responsible for GQP
- Ensure that manufacturer follows proper methods for shipping and receiving
- Notify MHLW of any changes in manufacturing or in-process controls
- Develop release criteria for each product
- Handle communication in the case of a recall

3. Post-Marketing Safety Controller

- Responsible for GVP
- Monitor safety of products released into the market
- Provide reports to health authorities on adverse incidents, recalls, etc.

Good Vigilance Practice SOPs

- Post-marketing surveillance
- Collect and file product safety information
- Evaluate safety information
- Plan and implement counter measures to ensure safety
- Safety assurance training for personnel
- Sub-contracting
- Report to and from QA department
- Self check and audit

Good Quality Practice SOPs

- Release products into the market
- Ensure maintenance of QA documents and reports, including information on any device problems
- QA training for personnel
- Product storage control
- Handling of recalls
- Control of quality at local offices
- Self-check and audit

Controller Requirements by Device

CLASSIFICATION

CONTROLLER(S) NEEDED FOR A MAH

General Devices

One person can serve as all three Controllers

Controlled Devices

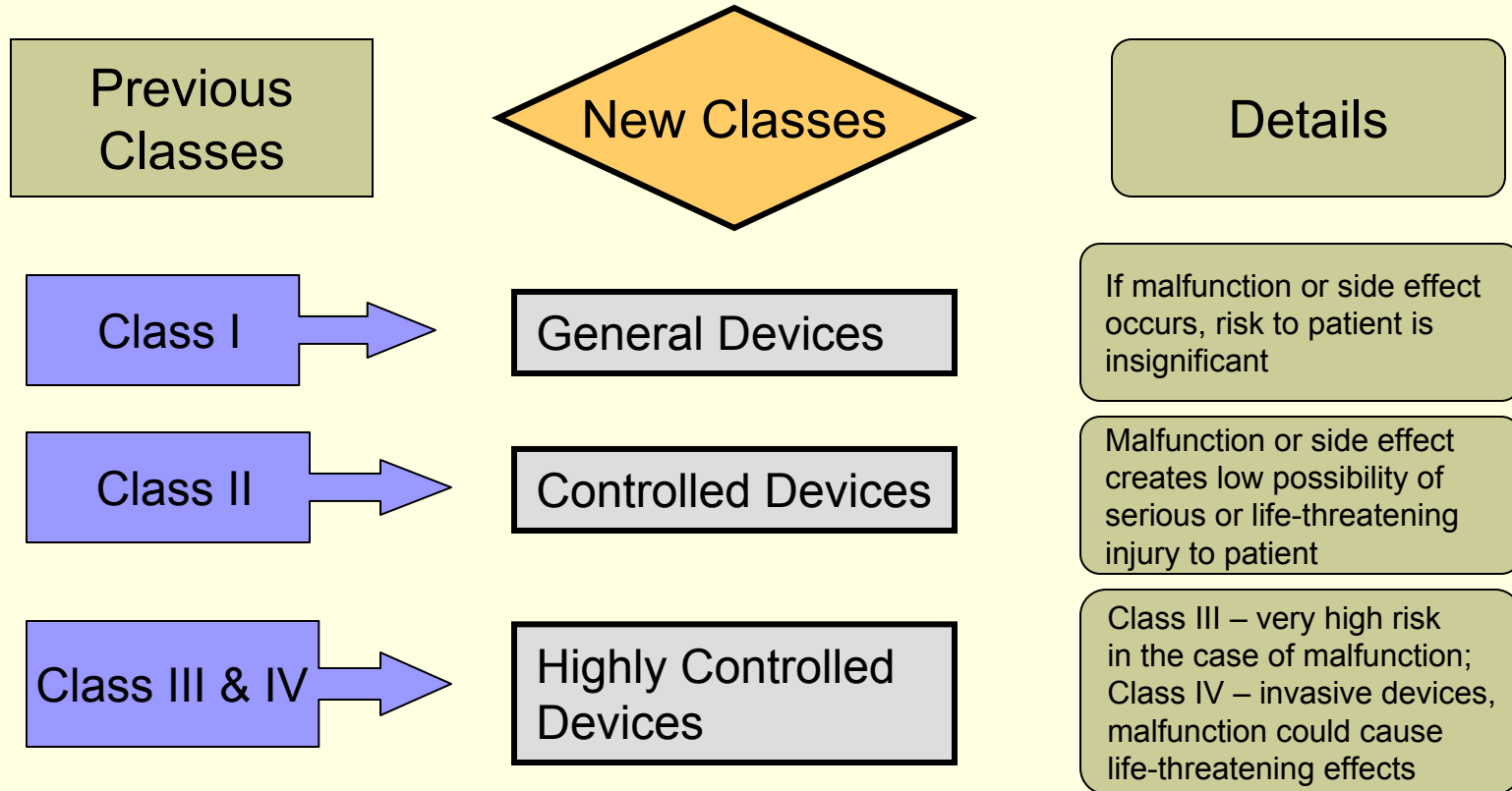
Two Controllers required:
One serves as GVP, the other as the GQP;
the GVP or GQP will also be the GM

Highly Controlled
Devices

Three separate people required, each serving
as one Controller

Product Approval by Classification

New Classification System



Requirements by Classification

CLASSIFICATION

APPROVAL REQUIREMENT

General Devices

No approval needed

Controlled Devices

3rd Party Certification required

Highly Controlled
Devices

Approval from PMDA required

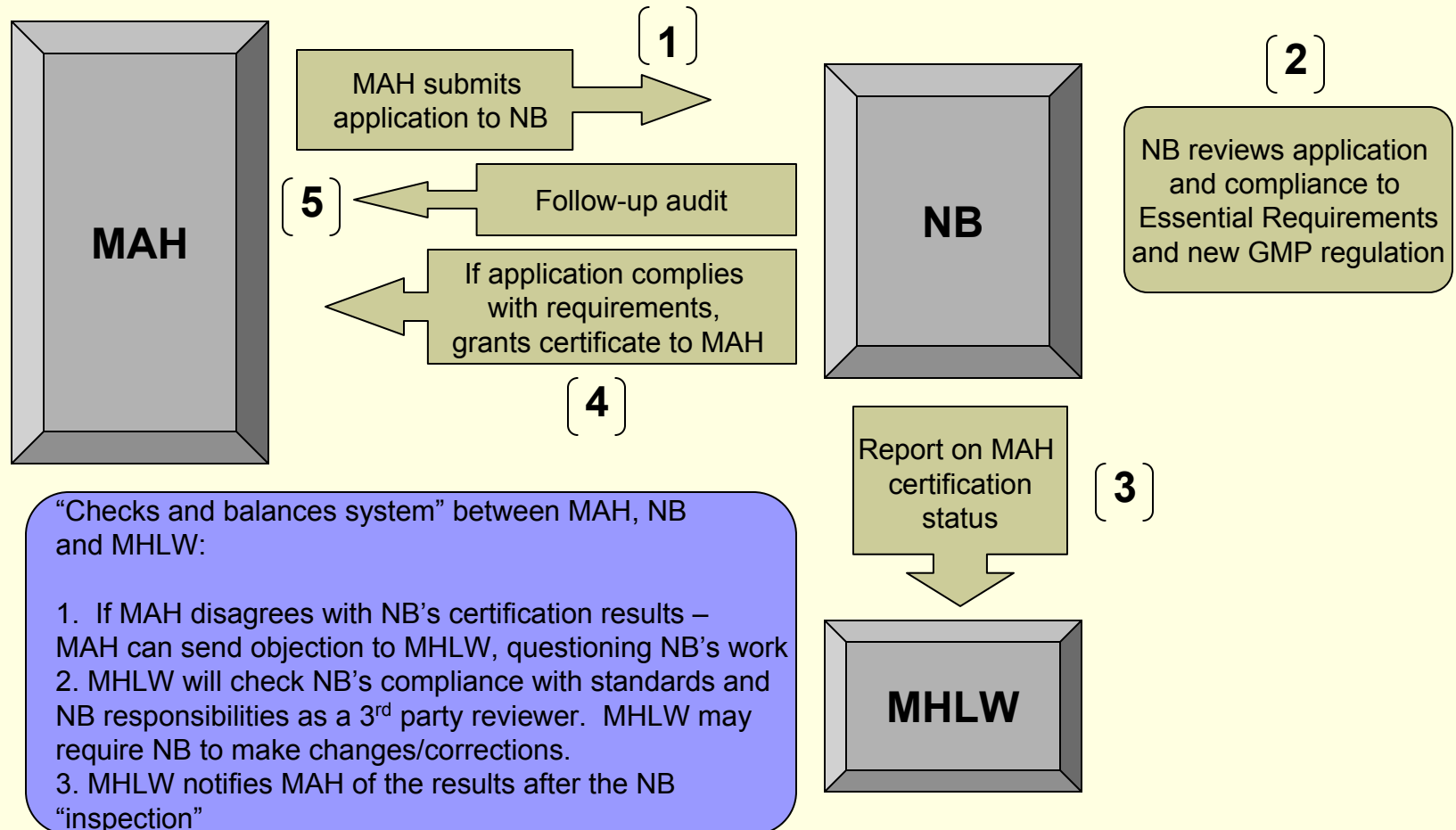
Approval Procedure: General Devices

- No approval or marketing authorization needed

Approval Procedure: Controlled Devices

- 3rd party certification required

Certification through 3rd Party (Notified Body) For Controlled Devices



Accreditation Requirements to Become a Notified Body in Japan

- ISO Guide 62 (Quality system)
- ISO Guide 65 (Product Notification)
- 3rd Party's parent company cannot be a medical device manufacturer
- Executives/board members who are medical device manufacturers must make up less than $\frac{1}{2}$ of the total members

Some Application Requirements for Certification of a Notified Body

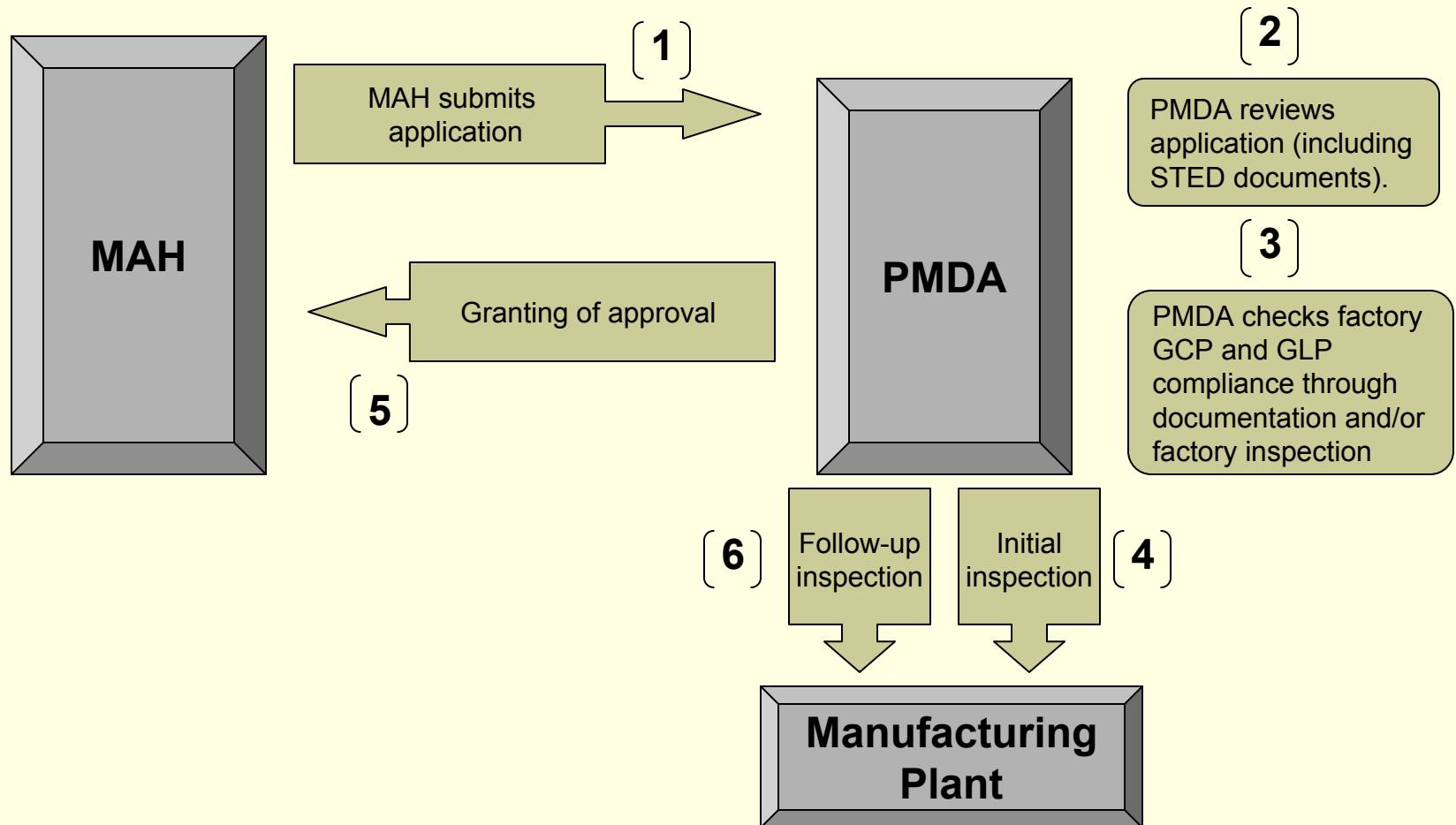
- The following requirements/standards from the Global Harmonization Task Force (GHTF) should be met:
 - Intended performance of device
 - Biocompatibility
 - Proper packaging and labeling
 - Risk management, including:
 - Product risk vs. benefit
 - Product environment (i.e. magnetic fields)
 - Patient safety
 - Adequate product performance throughout intended period of use

Approval Procedure: Highly-controlled Devices

- Need to obtain approval from PMDA

Approval from PMDA

For Highly Controlled Devices



STED Requirements

(Summary Technical Documents)

- Product summary
 - Product development process (including origin and discovery), any adverse effects reports, approval in other countries, etc.
- Product information
 - Purpose of use, specifications, raw materials, structure, efficacy, storage methods, similarity to other products, etc.
- Show compliance to Essential Requirements
(also required for NB Approval of Controlled Devices)
- Manufacturing data
 - Plant and manufacturing process information, quality control, sterility, etc.
- Verification and Validation data
- Risk Analysis data
- Labeling information

STED Details: Size, Structure

- Detailed information on shape and appearance of device and all components of device
- Exact dimensions of device should be provided
- Additional information on structure of device that affects safety/efficacy

STED Details: Raw Materials

- Information on raw materials/component parts of device should be provided
- Include details on any components that may affect the safety or performance of the device
- Animal/human derived – additional requirements and testing standards

STED Details: Manufacturing

- Specific manufacturing conditions should be described for all parts/components
- Processes greatly affecting safety and efficacy should be noted as such
- Animal/human derived – include processes or methods used to eliminate risk of virus

PMDA Product Review Targets

- New Devices → 12 months
- Me-too Devices → 4 months
- Improved Devices → 12 months
- Me-too Partial Changes → 2 months

Product Approval Fees

(Estimated costs for highly-controlled device)

Application review	\$35,000
Data review	\$7,000
GCP and GLP audit	\$11,000
QS audit	\$10,000
TOTAL COST	\$63,000

Previously:

Only application review
fee required

TOTAL COST: \$7,000

**INCREASE OF
900%!**

Product Renewal

- Typically, products have 5-year renewal periods
- Following implementation of New PAL:
 - MHLW will grant companies 1-year grace period to complete renewal
 - Until April 2006
 - Prefectural governments should grant an *additional* 1-year grace period
 - Until April 2007

New GMP Regulations

New GMP

- Similar to ISO 13845:2003
- Includes:
 - New design control requirements
 - Overseas inspection

Quality System

- Some requirements:
 - Designation of “Top Management”
 - Management system, including document control
 - Resource management (education and training opportunities, etc.)
 - Product knowledge, including design and production process and risk management
 - Preventative and corrective action plans

Top Management

- In charge of implementing and maintaining Quality System
- Reviews design and manufacturing process changes
 - Ensures that safety and efficacy are not compromised by the changes
- Should make sure customers are satisfied with use, safety, etc. through review of complaints and any preventative/corrective actions taken

Design and Development Plan

- Need to designate a design and development “manager”
- Step-by-step detailed plan should be created and documented, including a plan for revisions
 - Should include timeframe
 - Groups involved should have set responsibilities, good communication and a strong network

Data for Design Input

- Regulatory requirements
- Safety requirements
- Intended use and performance results
- Data on me-too devices
- Data on risk management
 - Should identify any potential hazards and the measures taken to reduce the risks

Design Verification

- Design input and output are compared
- Design verification includes review of:
 - In vitro and in vivo tests
 - Performance tests
 - Drawings/Plans
 - Packaging and labeling tests
- Should reflect input from manufacturer, sales groups, regulatory groups, etc.

Design Validation

- Conducted to ensure that intended purpose and use of device is met
- Clinical trials are a large part of this process
 - Conducted at final stage of design
 - Performed under simulated or actual conditions

Quality System Inspection

- Before issuing final approval, MHLW will conduct inspection of manufacturing facility
 - Compliance to new GMP standards to be checked
- May be a top-down inspection
 - Start with management of facility, then manufacturing process, design system, etc.

Post-Marketing Safety

- Collect, file and evaluate product safety information
 - Must file adverse effect reports to PMDA
- Plan and implement corrective/preventative measures
- Safety data should always be available in the case of an inquiry by the PMDA



Reimbursement

Changes in Reimbursement

- Implemented in 2002
- Applicants can choose from 4 main categories of reimbursement:
 - A
 - B
 - C
 - F
- Separate application form for each category
 - MHLW reviews application and announces evaluation result in the form of a yes/no decision
 - Applicants can challenge a medical device's assignment to a category

Definition of Category A

- A1: Medical procedure utilizing medical device is considered to match a procedure for which fees are reimbursed
 - In this case, device is not separately reimbursable
 - Products include devices used in procedures, such as a catheter or suture
- A2: Medical procedure utilizing medical device is considered to match a classification of procedures that allows a specific procedural fee reimbursement for device
 - Procedure that allows for additional component fee to cover optional device under main procedure's fee
 - Products included are specific to a procedure

Definition of Category B

- Medical device is considered to match functional classification of device that has a specified reimbursement level

Categories A & B: Reimbursement

- Procedural fee for A1 and A2 or reimbursement price of B devices
- Classification of device declared at approval stage of application
 - Reimbursement bound to approved classification
- Determined according to existing lists of procedural fees and medical device prices
- A1 does not allow for reimbursement of medical devices
 - Cost for devices included in procedural fee
 - Usage of devices in A1 category covered in hospital's overhead
- Reimbursement prices for devices in same classification are equal, even if there is a difference in former price or manufacturing cost

Categories A & B: Reimbursement Timeframe

- A1 products are reimbursable about 3 weeks after the pricing application is submitted
- A2 and B products are eligible for reimbursement around the beginning of each month

Definition of Category C

- C1: Usually for improvements of already-existing devices
 - Device is entitled to a new functional classification; corresponding fee already established
- C2: Medical procedure using device is entitled to a new functional category and procedural fee

Category C: Reimbursement

- C1 and C2 allow for creation of new procedural fees or new reimbursement prices
- Used if applicant needs to obtain new price level for a device due to manufacturing cost
- Success rate of C1 or C2 applications depends on how applicant highlights features and advantages of device vis-à-vis existing devices in the market
- Once a reimbursement rate is established, it is very difficult to increase reimbursement in Japan unless one can statistically prove that the new device can benefit the Japanese government

Category C : Reimbursement Timeframe

- C1 products listed every six months
 - Prior to 2002, listing occurred every 2 years
- C2 products are listed every 2 years

Definition of Category F

- The medical device (or medical procedure utilizing the device) is not eligible for reimbursement

New PAL Summary

- Foreign companies must designate/establish MAH/D-MAH
 - Manufacturing facility must meet new GMP requirements and be prepared for audit
 - Additional requirements for product application, such as STED documents
- Foreign companies should have made these changes by April 2005

What kind of office can you
set up in Japan?

Representative/Liaison Office

- Simplest form of business structure
 - Usually one person with assistant
 - Established in preparation for future expansion into branch or subsidiary
 - All activities must support and represent parent company
- Functions
 - Advertising
 - Public relations
 - Market research
 - Monitor activities of Japanese distributors/agents handling parent company's products
 - Cannot sell or conduct any “real business”
 - cannot generate any profits

Branch Office

- Requires simple registration process
 - Registration fee
 - Filing the company's representative "seal"
 - Registering tax and related expenses items
 - Submitting proxy notifications
- Must appoint an official representative responsible for local operations
 - Does not have to be a Japanese citizen, but must be a legal resident of Japan
- Branch offices can earn income and remit to parent company
 - Can also be established to conduct activities that do not generate income
- Subject only to income tax on Japan source net income only
 - Deduction can be claimed for reasonable head office expenses
 - Profits can be remitted to home office; not subject to withholding tax
- Good option if losses are expected – may be included in U.S. federal tax return

Subsidiary Corporation

Kabushiki Kaisha (KK)

- A KK is similar to U.S. public corporation, though not listed on the stock market
 - Often wholly owned
- Advantages:
 - Easier to arrange local financing, lease office space, attract local employees
 - Prestige
 - Indicates long-term commitment
 - Limited liability
 - Freely transferable shares
 - Well-defined procedures of establishment and management
- Requirements
 - Minimum capital of approx. \$100K
 - 25% of shares must be issued
 - Three directors; at least one must reside in Japan

Some Important Cultural Issues

Western Approach	Asian Approach
Do a deal	Build relationships
Maximize short-term profits	Establish long-term foundations
Be frank	Don't deliver bad news
Make changes quickly	Move when ready

A Different Way of Thinking

- Use and View of Time
 - Americans – minute/hour
 - Japanese – event/season
 - Events move forward when *group* is ready
- Relationships
 - Company to company
 - Person to person (how business relationships develop)
 - Family relationship
 - Most successful Japanese companies keep records of client information (birthdays, anniversaries, etc.) and sent cards
- Japanese Logic
 - Often based on emotion rather than reason
- “Group” and “Individual”
 - Group consensus – no single person should be targeted
 - Emphasis on company spirit
- When Things Go Wrong
 - Apology is very important

Social Interactions

- Japanese society has a carefully-defined hierarchy; this structure extends into the corporate world
- Japanese also identify themselves as members of a group (i.e. family group, work group)
 - Groups are defined based on the situation, example:
 - Foreigner and Japanese counterpart of same company meet to do business →
 - If business goes well, Japanese counterpart may consider foreign as a member of his group
 - If problems or disagreements arise, Japanese may consider foreigner an outsider
- *Face*:
 - Person's *face* represents their company, even during non-business hours
 - One should be careful never to criticize or offend – this could cause loss of face and could ruin a business relationship

Holding a Meeting

- Planning
 - Time is money
 - Appointments/meetings should be scheduled in advance
- Introductions
 - Rank Determines Order of Introductions
 - Senior leaders introduced first (handshake with foreigners, bow between Japanese)
 - Business Cards (*meishi*)
 - Should be given to each member of the other delegation
 - Present and receive with both hands, taking a moment to read each card
 - Treat card with care – do not write on card or toss in briefcase
- Corporate Materials
 - Summary of company information; short bio of President/Chairman
 - Press clippings/third party endorsements
 - All items should be professionally translated into Japanese
 - Packets/kits should be distributed to each member of the meeting

Holding a Meeting

(Continued)

- The Meeting
 - Seating Arrangements
 - Attitude and Direct Communication
 - Language
 - Interpreters
 - Negotiating
 - About Your Negotiator

Little Things That Mean A Lot

- Bowing
 - Traditional greeting, though handshake is more common
- Shoes
 - Should be removed in some restaurants and most homes
- Gifts
 - Honored guests usually presented with a gift
 - Businesses should have high quality, but not too expensive gift for other company
 - Gift should be wrapped and presented with both hands

Pacific Bridge Medical Contact Information

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