Japan Medical Device Regulatory Updates and Recent Revisions

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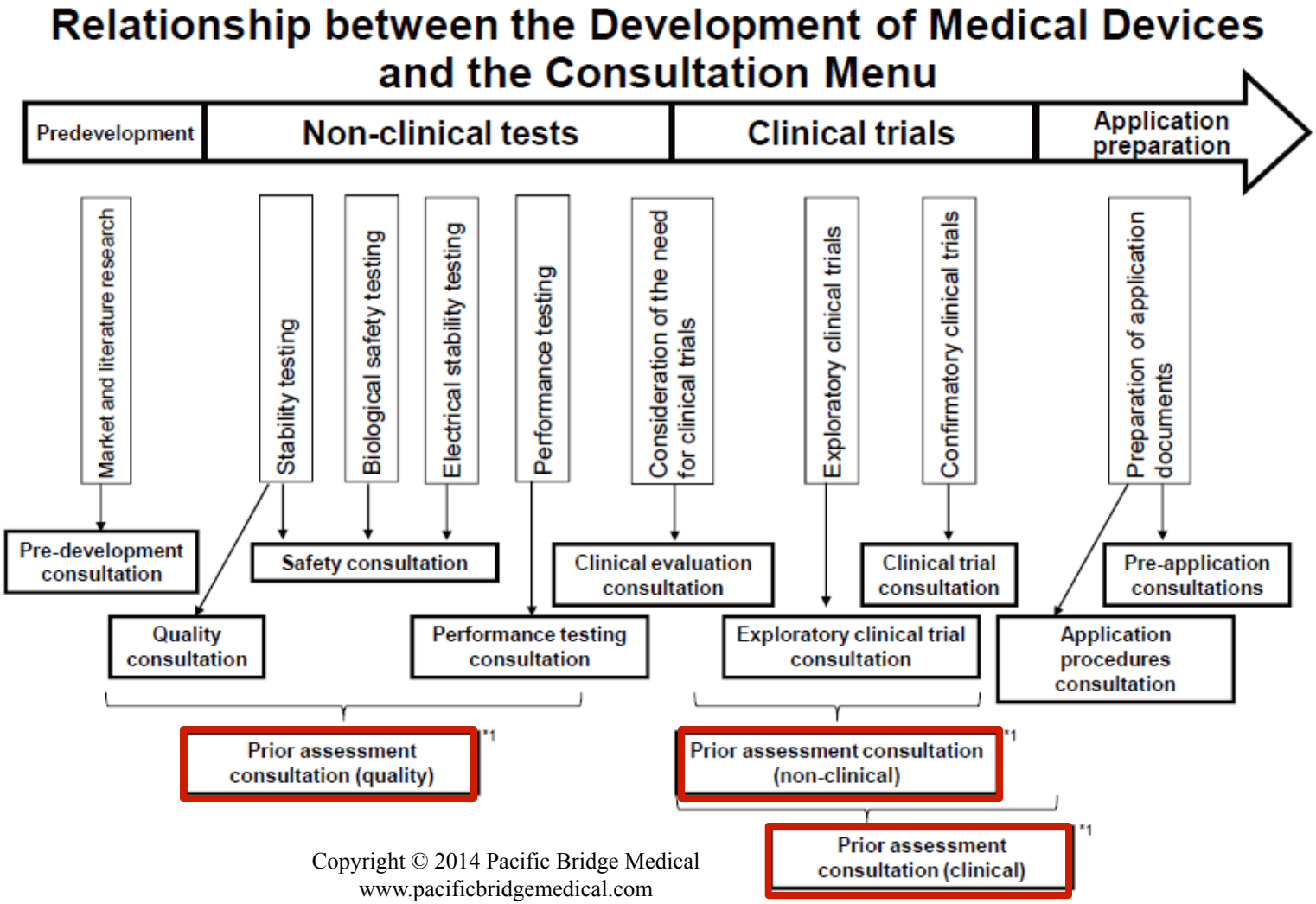
Japan Geography

Pre-consultation Meeting

Overview	The PMDA pre-meeting is a) to obtain explanation from PMDA about the Japanese Pharmaceutical Affairs Law (PAL) b) to discuss which PMDA consultation category is appropriate and what information/ document you have to prepare for the PMDA meeting. This consultation is also to have a follow-up discussion for topics that is not substantive issues such as minor changes after the PMDA clinical trial consultation, etc.
Document to be prepared for the meeting	Document related to the question
Length of meeting	a) 10 minutes (Face-to-face or on a phone) b) 30 minutes (Face-to-face or on a phone)
Fee	None.

PMDA Consultation Meetings for Medical Devices



Clinical Evaluation Consultation

Overview	Consultation for the necessity of new clinical trial data for product registration. The PMDA will evaluate other clinical data, usage survey based on published articles or non-clinical test reports, etc., and offer advice if additional clinical data is required for the product registration.
Document to be prepared for the meeting	Overview of product (includes intended use, structure and principles, raw materials, product specifications, etc.), protocol and data of clinical trial if conducted before (target disease/ patient, patient selection/exclusion criteria, end point, results, etc), non-clinical testing data(methods, samples, results), literature survey, etc.
Deadline to submit required document	3 weeks prior to the consultation meeting
Length of meeting	2 hours (Face-to-face)
Fee	¥1,026,600 ($9,872)

Clinical Trial Consultation

Overview	Consultation on the study design, target number of cases, etc. of a pivotal clinical trial based on safety tests, quality tests, exploratory clinical trials, usage survey in foreign countries, information of similar products, etc.
Document to be prepared for the meeting	Current treatment methods of the target disease, issues of the current treatment methods and advantage of the investigational devices, Indication for use in foreign countries and Japanese translated version, chart of the course of development, full data package(safety testing data, performance testing data, clinical data, etc. If you plan to use clinical data obtained outside of Japan for a product registration, please describe the clinical data and states of the clinical data in registration document), the latest version of the Investigator's brochure(IB), protocol plan and draft of informed consent, a list of clinical data, a list of safety tests, published articles, record of the PMDA consultation(if conducted before)
Deadline to submit required document	3 weeks prior to the consultation meeting
Length of meeting	2 hours (Face-to-face)
Fee	¥2,413,000 ($23,203)

Device Classification

Device Classification in Japan

- The Japanese Medical Device Nomenclature (**JMDN**) is a combination of the classification rules of the GMDN and of the GHTF (GHTF/SG1-N15:2006 *Principle of Medical Devices Classification*) which uses the word "risk" to classify 4 classes (Class A-D).

Medical Device Classification

Category	Classification/Definition	Registration Category	Review Body
General	Class I: The risk to patients in the event of malfunction is regarded as almost negligible.	Notification	n/a
Controlled	Class II: The risk to patients in the event of malfunction is regarded as relatively low.	Certification or Approval	NB or PMDA
Specially controlled	Class III: The risk to patients in the event of malfunction is regarded as relatively high.	Approval	PMDA
	Class IV: The device is highly invasive with potential fatal risk to patients.	Approval	PMDA

Todokede, Ninsho, or Shonin?

Category	Description
Todokede / Notification	Class I: The MAH only needs to file a notification (todokede) to the PMDA with no assessment by the PMDA
Ninsho / Certification	Some of Class II: The class II devices specified as designated controlled devices (with certification standards) are subject to Ninsho. The MAH needs to file a Ninsho application with a NB to obtain their certification.
Shonin / Approval	Class II (not designated controlled devices), III, & IV: The MAH has to file a Shonin application with the PMDA and obtain their approval.

Application Categories for Medical Device Registration – 1/3

Application Category	Overview
New medical devices (clinical trial data required)	Medical devices that are clearly different from those with approval or certification in Japan in terms of structure, principle, method of use, efficacy, and/or performance. GCP clinical trial data must be provided to prove clinical safety and efficacy.

Application Categories for Medical Device Registration – 2/3

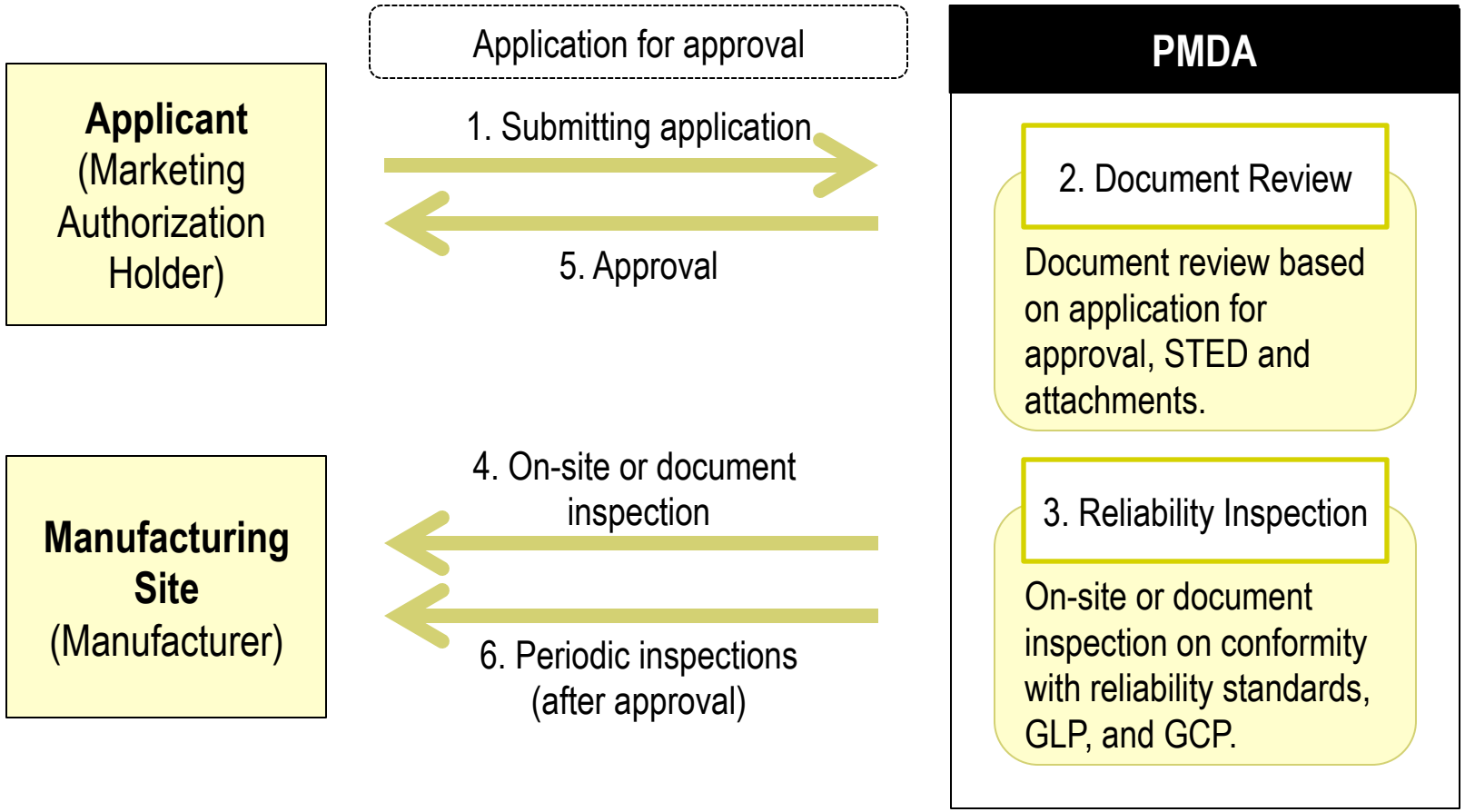
Application Category	Overview
Improved medical devices (clinical trial data required)	This category is for medical devices that 1) do not have an applicable approval standard or do not meet the requirements of the approval standard; 2) cannot be proven to be "me-too" devices (refer to the "me-too" medical device section below)
Improved medical devices (clinical trial data NOT required and not compliant with approval standards)	This category is for medical devices that 1) do not have an applicable approval standard or do not meet the requirements of the approval standard; 2) cannot be proven to be "me-too" devices

Application Categories for Medical Device Registration – 3/3

Application Category	Overview
"Me-too" medical devices (clinical trial data NOT required and NOT compliant with approval standards)	This category is for medical devices regarded as the "me-too" type that 1) do not have an applicable approval standard or do not meet the requirements of the approval standard; 2) are not regarded as new medical devices or improved medical devices; and, 3) can be proven safe and effective with non-clinical data.
"Me-too" medical devices (clinical trial data NOT required and compliant with approval standards)	This category is for medical devices regarded as the "me-too" type that 1) have an applicable approval standard and meet the requirements of the approval standard; and, 2) can be proven compliance to the approval standard.

Product Registration

Review Process with PMDA



Third Party Certification Will be Expanded

- Currently Class II products can be Ninsho (third party) or Shonin (PMDA), depending on risk
- Obviously, certification easier with third party certification
- Future more certifications by third parties for Class II medical devices with medium risk
- Future some Class III products will undergo certification by third parties too
- However, PMDA will increase supervision of third parties, and more QMS data required to be reported to the PMDA

Medical Device Application Form

- Medical Device Category
- Name (General Nomenclature/Trade Name)
- Intended Use and Efficacy or Effects
- Shape, Structure, and Principle
- Raw Materials or Components
- Product Specifications
- Operation or Usage Method
- Manufacturing Method
- Storage Method and Shelf Life
- Manufacturing Site of the Product to be Marketed
- Manufacturing Site of Raw Materials
- Remarks – Medical device classification, MAH license number of the applicant, etc.

Items Described in Each Application Attachment – 1/2

Attachments	Items to be Described
A. Materials regarding background of origin or discovery, and status of use overseas, etc.	Materials regarding background of origin or development
B. Materials regarding setting of specifications	Materials regarding specifications and setting of specifications
C. Material regarding stability and durability	Materials regarding stability and durability
D. Materials regarding conformity with standards stipulated in Article 41, Paragraph 3 of the PAL	Materials regarding declarations of conformity to Essential Requirements

Items Described in Each Application Attachment – 2/2

Attachment	Items to be Described
E. Materials regarding performance	Materials regarding tests supporting performance and safety
F. Materials regarding risk analysis	Materials regarding systems for implementing risk analysis
G. Materials regarding manufacturing methods	Materials regarding manufacturing processes and manufacturing facilities
H. Materials regarding clinical trial results	Materials regarding test results of clinical trials

Data to be Attached to Application – 1/3
New Medical Devices

Application Category	A			B	C	D		E			F		G			H	
	Development			Specification	Stability	Conformity with standards		Performance			Risk analysis		Manufacturing			Clinical	
	1	2	3	1	1	1	2	1	2	3	1	2	1	2	3	1	2
Class IV, III or II	○	○	○	○	△	○	○	○	△	△	○	○	○	△	○	○	○

○: Attachment required
△: Determined by individual medical devices
×: Attachment not required

Data to be Attached to Application – 2/3 Improved Medical Devices

Application Category	A			B	C	D		E			F		G			H	
	Development			Specification	Stability	Conformity with standards		Performance			Risk analysis		Manufacturing			Clinical	
	1	2	3	1	1	1	2	1	2	3	1	2	1	2	3	1	2
Class IV, III or II (with clinical data)	○	○	○	○	△	○	○	○	△	△	○	○	○	△	○	○	×
Class IV, III or II (no approval standard, no clinical data)	○	○	○	○	△	○	○	○	△	△	○	○	○	△	○	○	×

Data to be Attached to Application – 3/3
Me-Too Medical Devices

Application Category	A			B	C	D		E			F		G			H	
	Development			Specification	Stability	Conformity with standards		Performance			Risk analysis		Manufacturing			Clinical	
	1	2	3	1	1	1	2	1	2	3	1	2	1	2	3	1	2
Class IV, III or II (no approval standard, no clinical data)	○	○	○	○	△	○	○	○	△	△	○	○	○	△	○	×	×
Class IV, III or II (with approval standard, no clinical data)	×	△	○	○	△	○	○	○	△	△	○	○	○	△	○	×	×

Summary Technical Document (STED) – 1/2

1. General overview of product
   - Overview of product requiring color photos for confirming the outer appearance of the product
2. Essential requirements and conformity to the essential requirements
   - List of reference standards
3. Device description
   - General information
   - Raw materials
   - Product specifications describing why the established product specifications are necessary and sufficient for securing the effectiveness, safety and quality of the product.

STED – 2/2

4. Labeling
5. Risk Analysis
6. Manufacturing Information
7. List of supporting data and attachments (e.g. certificate of conformity, test reports, etc.)

Things to Note

- Make sure to determine and know the following:
  - JMDN Code and Class I, II, III, or IV
  - Applicable or recognized international or Japanese standards
- The PMDA reviewers do like as much detail as they can get, as demonstrated in the previous slides.
- Presentation is very important; make everything as easy and clear to understand with graphics, flow charts, tables, etc.

Foreign Manufacturer Accreditation (FMA)

FMA Process

- **All manufacturing facilities** involved in the production of a medical device, **including sub-contractors**, must be accredited by the MHLW.
- Before applying for accreditation, a Japanese marketing authorization holder (MAH) for an "applicant" or a foreign manufacturer needs to submit "Business Number Registration Form", reporting information on the applicant's business and manufacturing establishment, in order to obtain a "Business Number."

Current System: Foreign Manufacturer Accreditation

- The Minister of Health, Labour, and Welfare (MHLW) has the authority to grant a foreign manufacturer a FMA. (Article 13-3 of PAL).

Category	Description
Cell/tissue-based medical device	All or part of the manufacturing process of the medical devices designated by the MHLW (e.g. cell/tissue therapy drugs, and specified biological products)
Sterile medical device	All or part of the manufacturing process of sterile medical devices (excluding packaging, labeling, storage)
General medical device	All or part of manufacturing process of medical devices other than those indicated in the preceding two categories (excluding packaging, labeling, storage)
Packaging, labeling, storage	For only the process of packaging, labeling, or storage among the manufacturing processes of medical device indicated in the preceding two items

Current System: What documents will be reviewed for the Foreign Manufacturer Accreditation?

- ☐ **Self-declaration of Health Stability** Form
- ☐ **Personal History of Responsible Person** Form
- ☐ **Product and Process List** Form
- ☐ **Facility Building Outline** Form with following information
  - Diagram showing layout of all site buildings (An aerial photo [e.g. Google Earth or Map] is acceptable. Specify the relevant buildings.)
  - Floor plan of the site
- ☐ **Executive Organizational Chart**
- ☐ Marketing License, Manufacturing License, Marketing Approval, or Marketing Certificate of the medical devices
  - **ISO 14385 Certificate**
  - **Printout of FDA Establishment Registration**
  - **Certificate of Foreign Government**
  - **Certificate of Free Sales**

FMA Revision

- Old system need to submit documents on previous pages
- New system – no manufacturing facility information required. Only submit personnel information, such as organization flow charts
- Only if FMA audit on-site, then information on previous pages needed – but this is rare

Quality Management System (QMS) Audit

QMS: Facilities to be Audited/ Inspected

Ordinance 169

1. **Manufacturing Facility**
2. **Contract Sterilization Facility**
3. **Contract Testing Facility**
4. **Contract Design/Development Facility**
5. **Distribution Center**

On-site Inspection or Document Review?

Risk	Product Risk	Manufacturing or Process Risk	Other Risk
Low  High	• Class II • Class III • Class IV • New medical devices • Cell/Tissue-based medical devices	• Testing • Design & development • Packaging, labeling or storage • Outsourced sterilizing • Critical processes such as assembly	• GHTF member countries (Yes/No) • History of past inspections, etc. (Good/Bad)

QMS Requirements

- Documents for product specifications and QMS
- Manufacturer needs to keep copy of all documents equivalent to lifetime of medical device
- Maintain infrastructure needed for conformity

QMS Revisions

- QMS done according to product group, instead of individual products
- Regulators have not yet devised product groups – key factors usage of products, manufacturing process and risk of device
- Product families need to be manufactured by same establishments

Can Overseas Clinical Data be Used for Medical Device Approval?

Can Overseas Clinical Data be Used for Medical Device Approval?

- Official guideline of using clinical data which obtained outside of Japan for a product registration is

  - **PFSB/OMDE Notification No.0331006 (March 31, 2006)**
    "Handling of clinical study data on medical devices which was carried out in foreign countries"
  - **PFSB/OMDE Notification (June 23, 2006)**
    "Re: Q&A for the Handling of Clinical Trial Results on Medical Devices Obtained in Foreign Countries"

Source: http://www.pmda.go.jp/operations/shonin/info/iryokiki/iryokiki-list.html
http://www.pmda.go.jp/english/service/regulation.html

Can Overseas Clinical Data be Used for Medical Device Approval?

1. Acceptable countries or regions

   In case GCP principles for medical devices which are equivalent to or better than J-GCP are established under device regulation laws in the country or region where the clinical study was conducted, material on the clinical study data conducted in accordance with that GCP principles or of equivalent clinical studies can be attached to the application form for approval.

Source: http://www.pmda.go.jp/operations/shonin/info/iryokiki/iryokiki-list.html
http://www.pmda.go.jp/english/service/regulation.html

Can Overseas Clinical Data be Used for Medical Device Approval?

	FY2007	FY2008	FY2009	FY2010	FY2011	FY2012
Foreign clinical data only	20	26	32	29	38	23
Both foreign and Japanese clinical data	4	2	6	2	5	3
Japanese clinical data only	24	14	14	19	14	23

Source: PMDA Annual Report FY2012

Can Overseas Clinical Data be Used for Medical Device Approval?

Japan	USA	EU
• J-GCP	• US-GCP 21CFRs	• MMD ISO 14155:2011

Submitted to PMDA/MHLW as an attachment to a product approval application

Source: PMDA presentation at RAPS 2012

Can Overseas Clinical Data be Used for Medical Device Approval?

- ISO 14155 :2011 (issued on February 1, 2011)

  Clinical investigation of medical devices for human subjects

  -- Good clinical practice

  ISO 14155:2011 addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.

  ISO 14155:2011 specifies general requirements intended to protect the rights, safety and well-being of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

Source: http://www.iso.org/

Can Overseas Clinical Data be Used for Medical Device Approval?

	ISO 14155:2011	J-GCP
Principal investigator	Qualified person responsible for conducting the clinical trial	Physician or dental physician
Sponsor's audit	Useful	Mandatory for submitting pre-market approval application
Risk evaluation	Mandatory for initiating the clinical investigation	Useful prior to initiating the clinical investigation, but essential for submitting pre-market approval application.

Source: PMDA presentation at RAPS 2012

Can Overseas Clinical Data be Used for Medical Device Approval?

	ISO 14155:2011	J-GCP
Role of Head of clinical investigation site	No provisions	Several responsibilities of the Head
Reporting deadline of adverse events	By the national regulations	Differ between “expected” and “unexpected” adverse events
Clinical investigation team	Not specifically defined	Define clinical investigation staff but not mandatory of compiling their CV

Source: PMDA presentation at RAPS 2012

PMDA Inspection for Clinical Data

Application Category: Brand-New & Improved Medical Devises with Clinical Data

	FY2008	FY2009	FY2010	FY2011
Document-based conformity inspection	51	50	64	63
GCP on-site inspection	0	1	3	1

Source: PMDA presentation at RAPS 2012

J-GCP Clinical Trials for Medical Devices in Japan

J-GCP Clinical Trials for Medical Devices in Japan

- Article 14, Paragraph 3 of the Pharmaceutical Affairs Law

> A person intending to obtain the approval specified in Paragraph 1 shall attach data related to the results of clinical trials or any other pertinent data to the application as specified by the Minister of Health, Labour and Welfare (MHLW) Ministerial Ordinance. In such cases, when the drug or medical device in the application is specified by MHLW Ministerial ordinance, these data shall be those collected and prepared in accordance with the standards specified by the Minister.

J-GCP Clinical Trials for Medical Devices in Japan

- The J-GCP Ordinance
  - MHLW Ministerial Ordinance No. 36 (Mar 23, 2005)
  - MHLW Ministerial Ordinance No. 163 (revised on Nov 28, 2008)
  - MHLW Ministerial Ordinance No. 68 (revised on Mar 31, 2009)
  - MHLW Ministerial Ordinance No. 161 (revised on Dec 28, 2012)
  - MHLW Ministerial Ordinance No. 11 (revised on Feb 8, 2013)

- J-GCP PFSB/OMDE Notification
  - PFSB/OMDE Notification No.0208-1 (Feb 8, 2013) -- the latest notification

J-GCP Clinical Trials for Medical Devices in Japan

- Chapter I. General Provisions
- Chapter II. Standards for Preparing for Clinical Trials
  - Section 1. Standards for Preparing for Clinical Trials by Persons Who Intend to Sponsor Clinical Trials
  - Section 2. Standards for Preparing for Clinical Trials by Persons Who Intend to be a Sponsor-investigator

Source: http://www.pmda.go.jp/operations/shonin/info/iryokiki/iryokiki-list.html
http://www.pmda.go.jp/english/service/regulation.html

J-GCP Clinical Trials for Medical Devices in Japan

- Chapter III. Standards for Clinical Trial Management
  - Section 1. Standards for Clinical Trial Management by Sponsor
  - Section 2. Standards for Clinical Trial Management by Sponsor-investigator
- Chapter IV. Standards for Conducting Clinical Trials
- Chapter V. Standards for Documents Submitted in Reexamination, etc.
- Chapter VI. Standards for Sponsoring Clinical Trials, etc.
- Supplementary Provisions

Source: http://www.pmda.go.jp/operations/shonin/info/iryokiki/iryokiki-list.html
http://www.pmda.go.jp/english/service/regulation.html

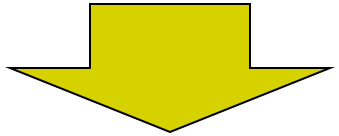
J-GCP Clinical Trials for Medical Devices in Japan

This is an example of a sponsor clinical trial process for an investigational new medical device.

Planning and Preparation	1. Prepare written operating procedures 2. Plan the trial details and prepare documents ❑ SOPs ❑ Protocol ❑ Investigator's brochure (IB) ❑ Case report form (CRF) ❑ Informed Consent ❑ List of prospective investigators and sub-investigators. ❑ Documents on the burden of expenses for the clinical trial ❑ Document explaining compensation to the subject in the event of trial-related injuries ❑ Service agreement, etc.

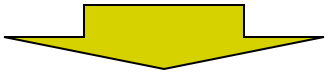
J-GCP Clinical Trials for Medical Devices in Japan

Planning and Preparation (continued)	3. Conduct pre-selection/screening of medical institute ❑ Confirm the medical institutions have sufficient systems and staff to conduct a clinical trial. (proper facilities, IRB and SOPs, skilled surgeons, etc.) 4. Submit a notification for the clinical trial to PMDA/MHLW 5. Obtain IRB/IEC approval ❑ Submit the necessary documents to the head of medical institution ❑ Obtain the IRB's approval ❑ Obtain the medical institution's approval 6. Contract ❑ Sign the clinical trial contract with the medical institution



J-GCP Clinical Trials for Medical Devices in Japan

Conducting a clinical trial	7. Register to a clinical research database (voluntary) 8. Supply/handle investigational devices 9. Conduct a clinical trial ❑ Establish an efficacy and safety assessment committee ❑ Keep collecting/evaluating information of the investigational devices (e.g. AEs) and report to the heads of the medical institutions. ❑ Monitoring ❑ Conduct audits, etc.



Completion	10. Prepare a clinical study report 11. Report the completion of the clinical trial to PMDA/MHLW 12. Keep records during a required period

J-GCP Clinical Trials for Medical Devices in Japan

- Summary of the revision
  - The guidance of the J-GCP was revised on Feb 8, 2013 followed by the ISO 14155:2011 and GHTF/SG5/ N5:2012.
  - The key changes are the definition and reporting procedures of adverse events related to the clinical trials.

Source: 薬食発0208第4号通知

Regulation Updates: PAL

- The Pharmaceutical Affairs Law (PAL) revisions were passed by the Japanese Diet in November 20, 2013 and will become effective within one year
- Key changes:
  - Medical device regulations will be revised based on device characteristics
  - Medical device and drug safety measures strengthened
  - Tissue and cellular therapeutic product regulations introduced
  - Post-market surveillance: re-examination system → outcome examination system

New Labeling Regulations

- Under the revised PAL, the packet insert language for a Class IV must be filed with the MHLW in advance as well as published online
  - A new medical device application must include a draft of the package insert
  - This applies to both new devices and to changes on the insert of a currently marketed device

Medical Software to be Regulated in Future

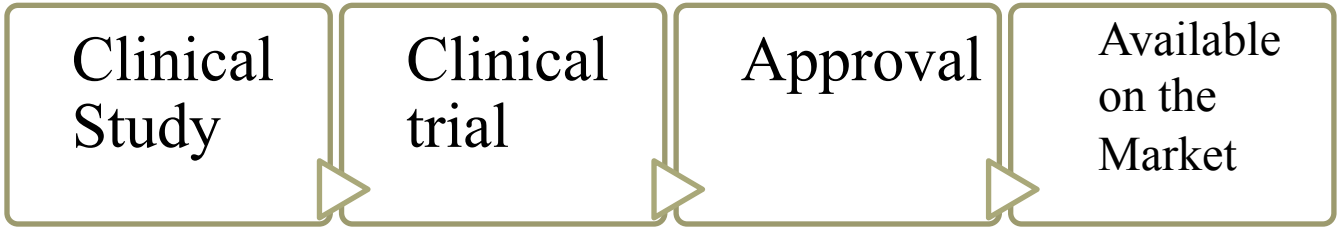
- Currently only a combination of software with hardware is regulated in Japan
- Software not in a medical device is *not* regulated
- Under the new PAL, software will be regulated independently

New Regulations for Cellular and Gene Therapy

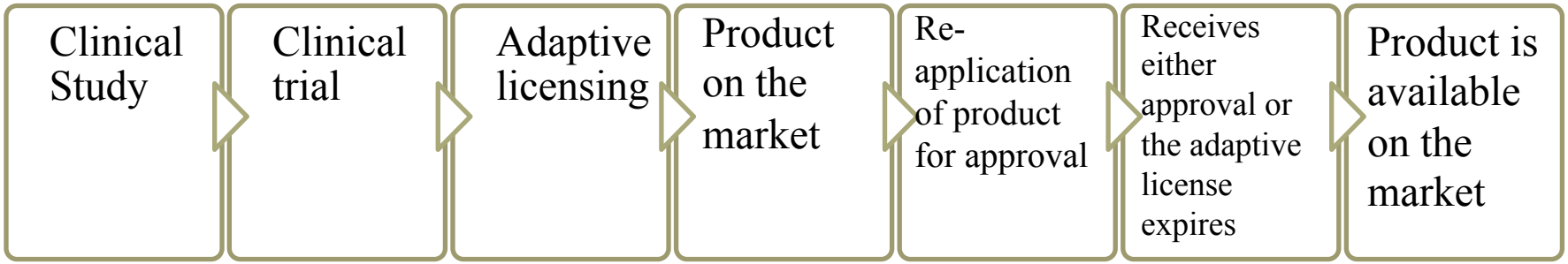
- Currently, products registered as either device or drug
- The Japanese Diet passed the Act regarding Ensuring of Safety of Regenerative Medicine on November 20, 2013
  - This law sets definitions and standards for medical institutions and processing facilities, ensuring safety and setting standards, expediting regenerative medicine usage
- The revised PAL also introduces MAH and tissue and cellular therapeutic product regulations
  - Cellular and tissue therapeutic products will be categorized differently
- New system – classified as new category with new regulations for approval and clinical studies

New Regulations for Cellular and Gene Therapy ctd.

- The new PAL calls for a new approval system for cellular and tissue therapy products
- Current system of approval



- New system of approval



Change of Raw Materials

- Old system: change raw materials, may need to do new registration
- Notification in March 2013
- NOT for Biology derived raw materials
- If you can show the safety and function of the raw materials is equivalent to the previous product – only need minor change notification
- If you can show raw material change in the foreign country has lots of experience with usage and is listed as acceptable on the PMDA website – minor change notification
- Otherwise, need to do a partial change approval application

Future Trends

- Outcomes to be emphasized in the future:
  - More rigor with Post Marketing Surveillance
  - More crucial devices to be fast tracked
  - PMDA hoping to speed up general review process

Device Reimbursement

Product (STM) Reimbursement Categories

Category	Description
A1	**(Inclusive)** Included within the technical fee. No separate reimbursement is made for the device itself. Product examples: gloves, gauze, sutures
A2	**(Designated inclusive)** Technical fee granted for use of the device or class of devices. No separate reimbursement is made for the device itself. Product examples: MRIs, CTs, and most types of capital equipment
B	**(Individual evaluation)** "Me-too" products that are similar to other products on the market. As a result, these products fit into existing technical fee and STM reimbursement categories. Product example: CoCr hip stem
C1	**(New function)** New products based on existing products/therapies.
C2	**(New function and New technology)** New products that result in a new therapy or procedure. No predicate product or treatment exists.
F	Products that does not match the reimbursement system in place or that are not suitable for insurance coverage

Reimbursement Price Revision

- Reimbursement prices are adjusted/cut every two years (2014 next revision) based on one of two mechanisms:
  - **Reasonable Zone (R-zone): general revision method**
  - **Foreign Average Pricing (FAP): extraordinary revision method**

R-Zone Reduction Example

Basic Formula

New STM = weighted average price per survey x (1+consumption tax) + R-zone

Current STM Reimbursement Price of "Product – XYZ"	¥2,500
Weighted average selling price of "XYZ" per survey	¥2,000
Add consumption tax (5%)	+¥100
Selling Price Total	¥2,100
Add 2012 R-zone (4%)	+¥84
New STM Reimbursement Price for "XYZ"	¥2,184

Foreign Average Price (FAP)

Basic formula

New STM = Original STM × (FAP × 1.5 / Weighted average price per survey)

- The STM reimbursement reduction is up to 25% of the original STM.
- Reference countries: USA, UK, France, Germany, and Australia added in 2012.

Thank you for your consideration!

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