独立行政法人
医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

Overview of Our Review Practices

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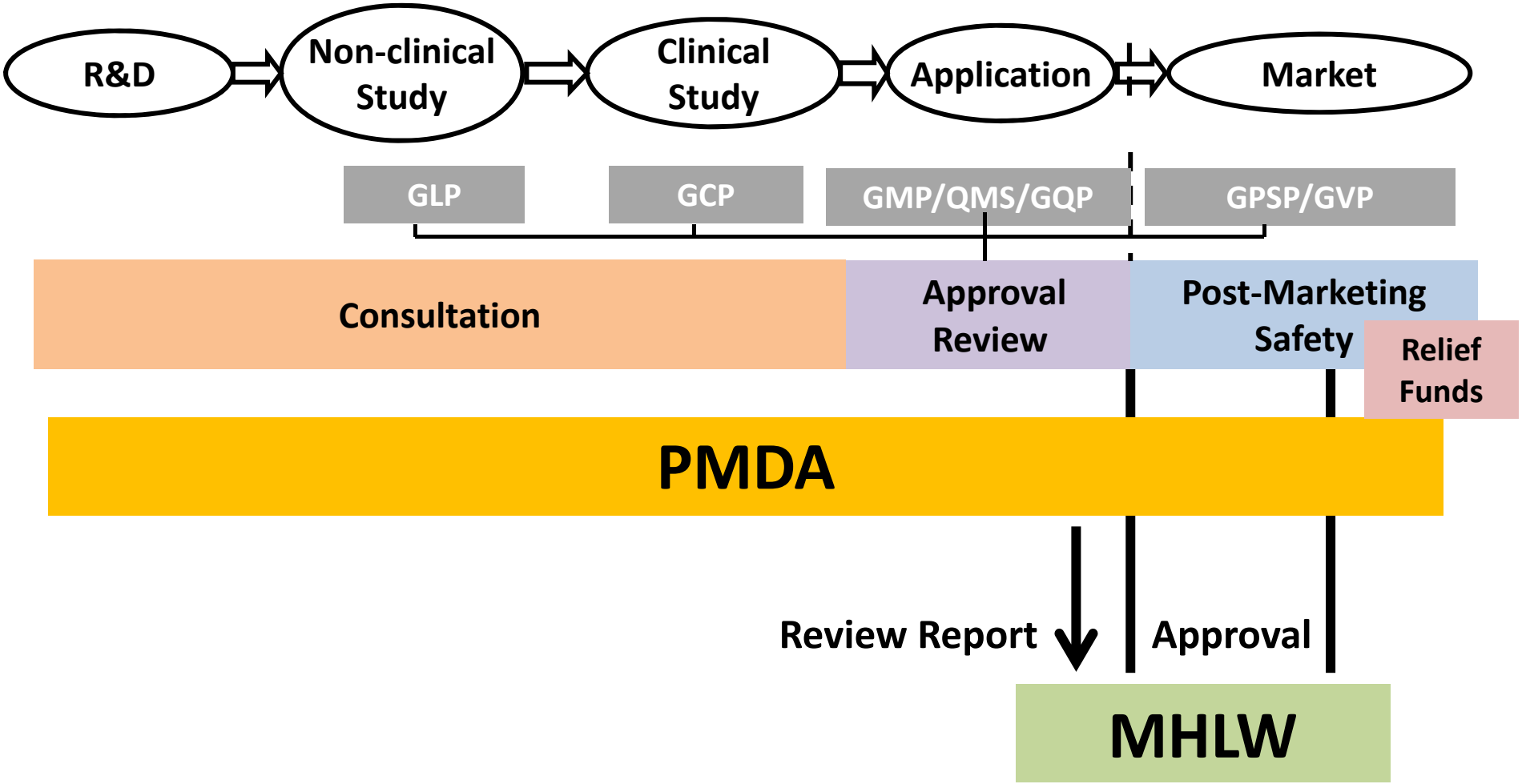
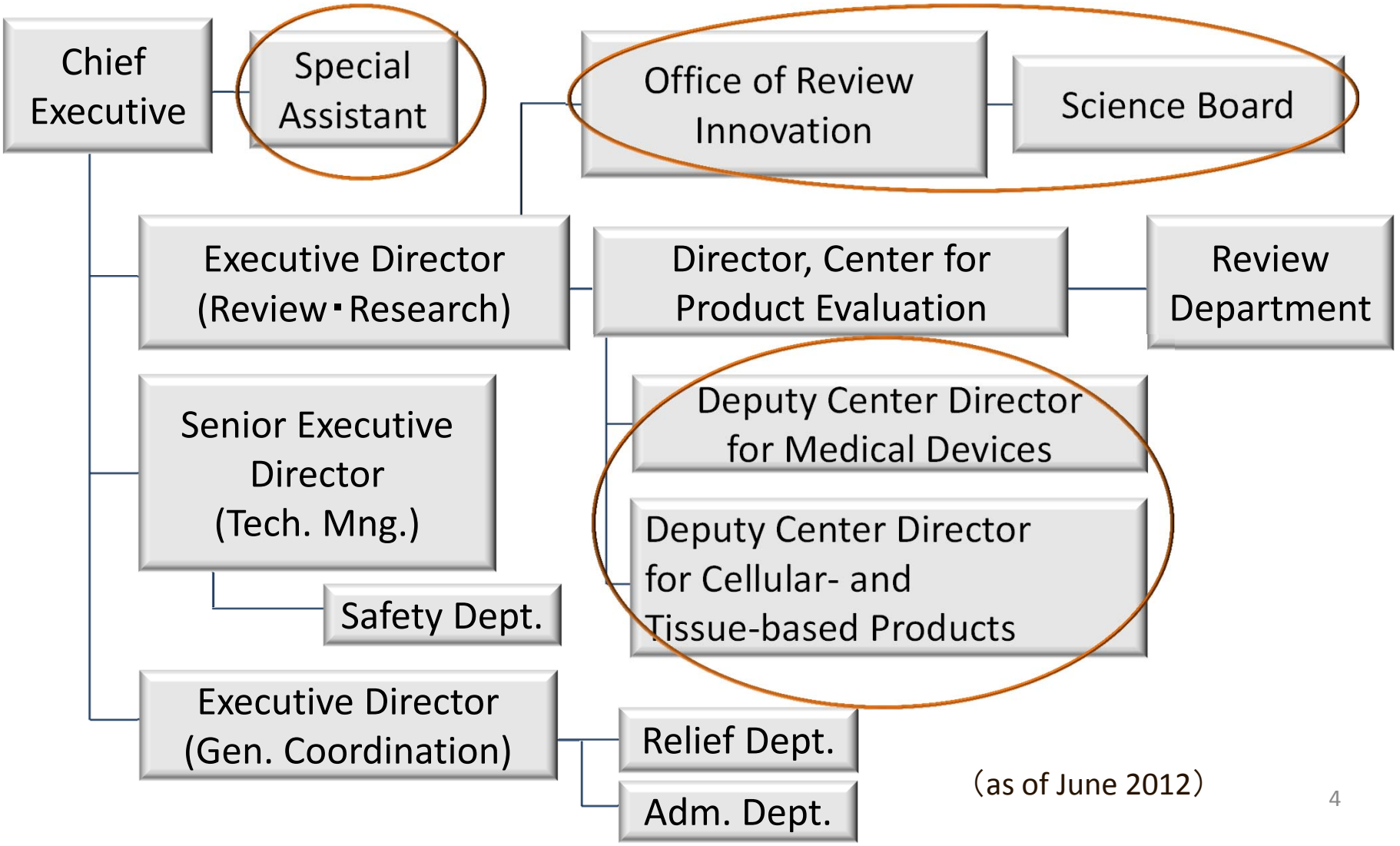
Outline of My Presentation

- ✓ Functions and Roles of PMDA
- ✓ Overview of PMDA review process
  - overview of orthopedics review
  - case introduction
  - changing procedures
- ✓ Action program

Functions and Roles of PMDA



New Organization To Strengthen MD Review System



（as of June 2012）

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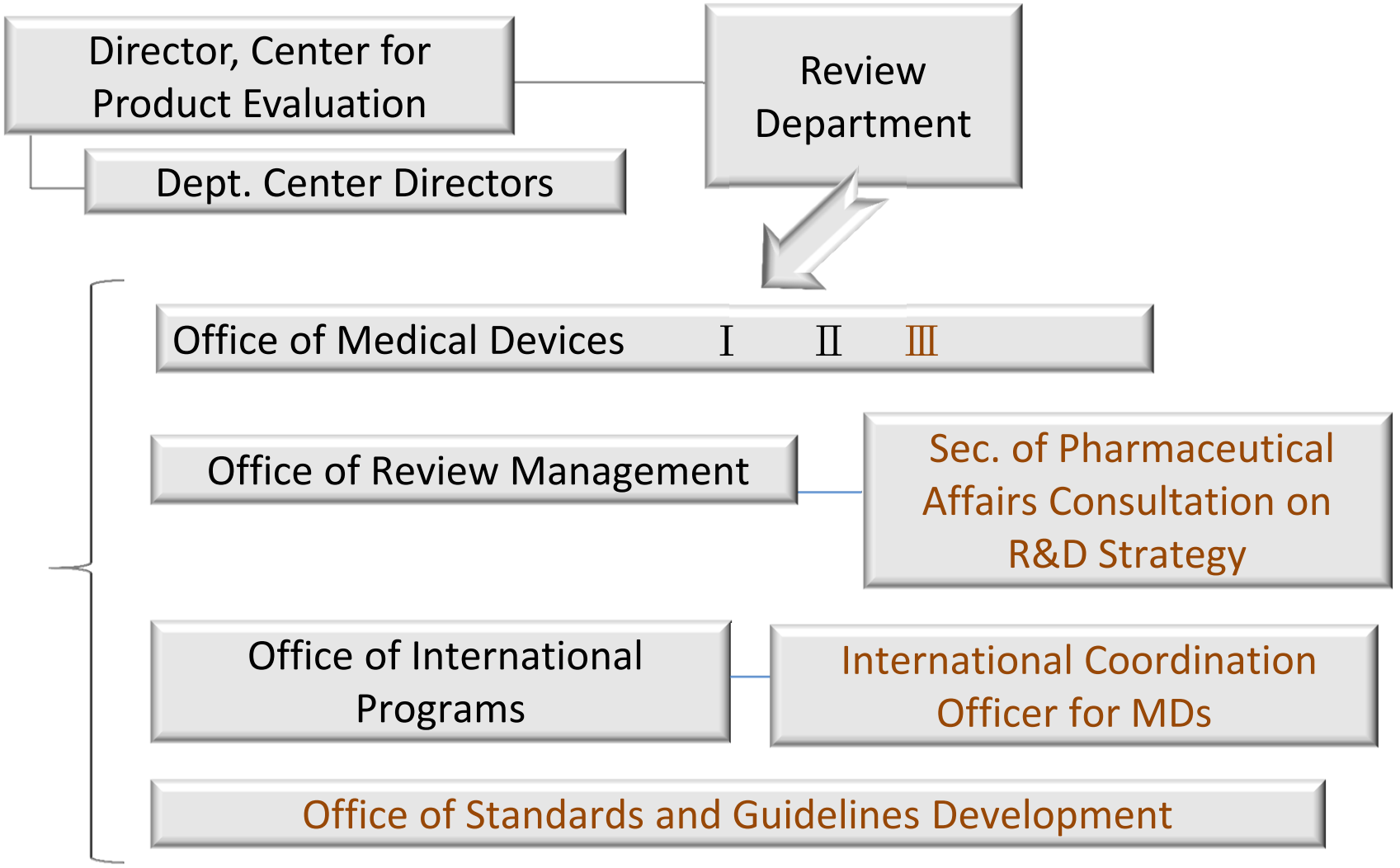
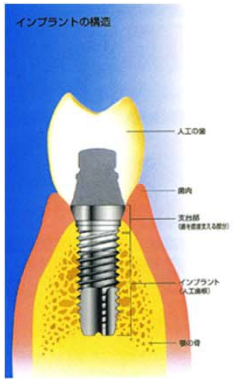
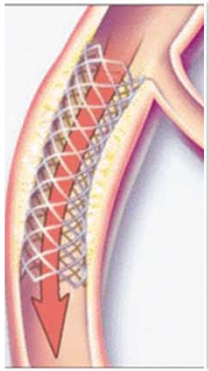
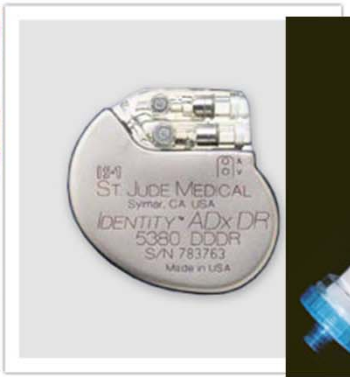
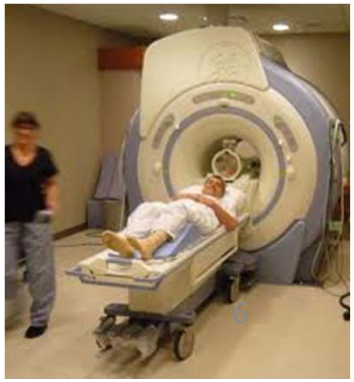


Review Teams of MDs

Team 1	Field of ophthalmology, otorhinolaryngology
Team 2	Field of dentistry
Team 3	Field of neurosurgery, cardiology, vascular surgery, respiratory
Team 4	Field of neurosurgery, cardiology, vascular surgery, respiratory (electronic devices)
Team 5	Field of gastroenterology, urology, gynecology
Team 6	Field of orthopedics, plastic surgery, dermatology
Team 7	In vitro diagnostic medical devices
Team 8	Others

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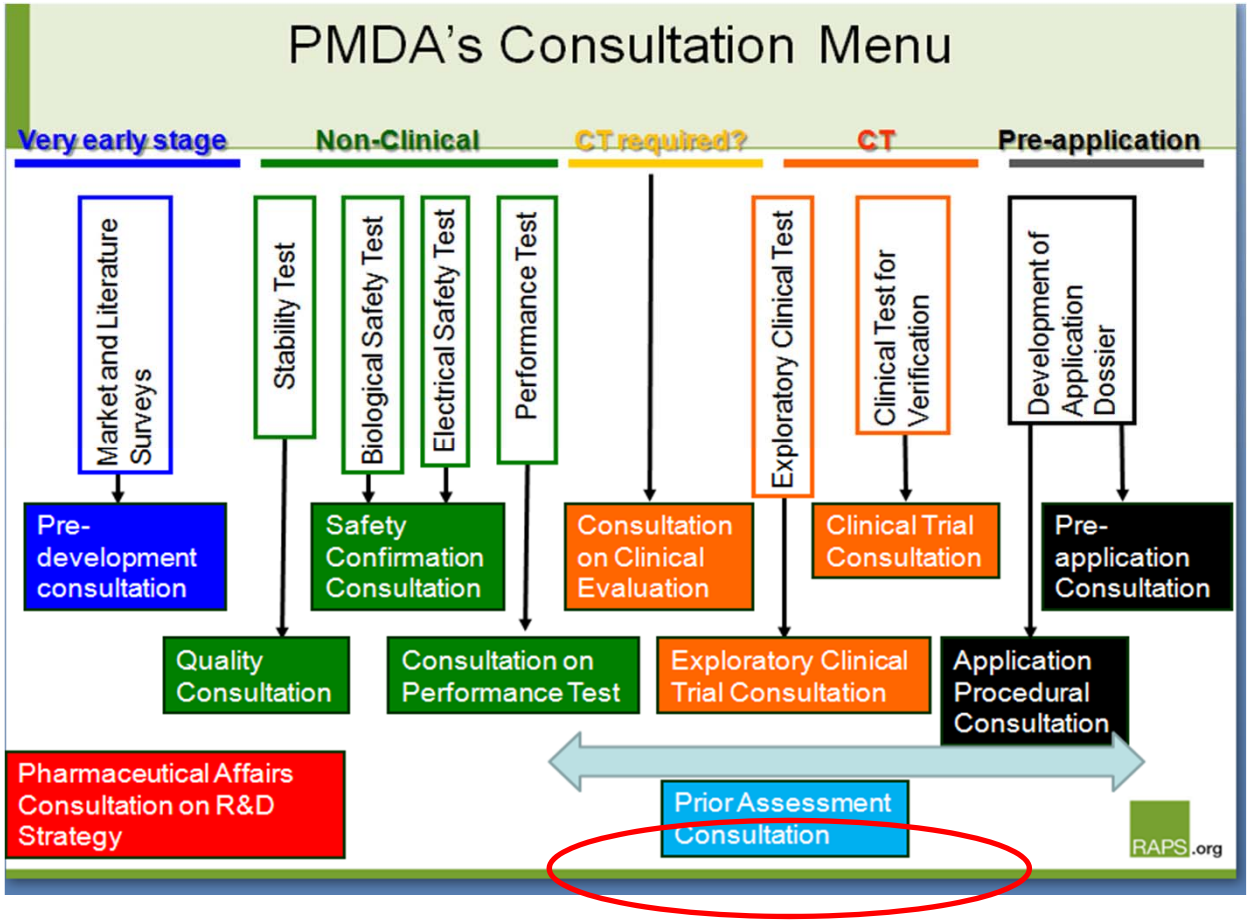
Overview of Pre-Market Regulation for MDs

GHTF Classification		PAL classification		
		Category	Pre-market regulation	Nomenclature
Class A	extremely low risk X-Ray film	General MDs (Class I)	Self declaration	1,195
Class B	low risk MRI, digestive catheters	Controlled MDs (class II)	Third party Certification	1,786 (1364 for 3rd Party)
Class C	medium risk artificial bones, dialyzer	Specially Controlled MDs (class III & IV)	Minister's Approval (PMDA's review)	755
Class D	high risk pacemaker, artificial heart valves			337

(MHLW Ministerial Notification No.298, July 20, 2004)

Prior Assessment Consultation

PMDA evaluates the data set prior to an application



Application Dossier

- ✓ Brand-new MDs
  - Application Form
  - Summary of the technical documents (STED)
  - Attachment
    - Evaluation reports
    - Declaration of conformity
    - etc.
- ✓ Improved MDs, Generic MDs
  - Application Form
  - Attachment (STED with data set)

Application Form

✓ Identities of the product

"approved product information"

- Category
- Designation
- Purpose of use, indication
- Shape, structure and principles
- Raw materials or component parts
- Specification of the device
- Method of operation or usage
- Manufacturing method
- Storage and expiry date
- Manufacturers of items for production and distribution
- Manufacturer of raw materials
- Remarks

STED

1. Outline of the device
2. Basic requirements, and compatibility with the basic requirements
3. Information on the device
4. Summaries of design verification and documents confirming validity
5. Labeling
6. Risk analysis
7. Information on manufacturing

General Review Points

the purpose of development

Clinical positioning

- Alternative? Unmet need?
- Similar products or innovative?

Non-clinical test

Appropriate evaluation based on its concept

<u>Novel materials</u>
- Efficacy
- Safety

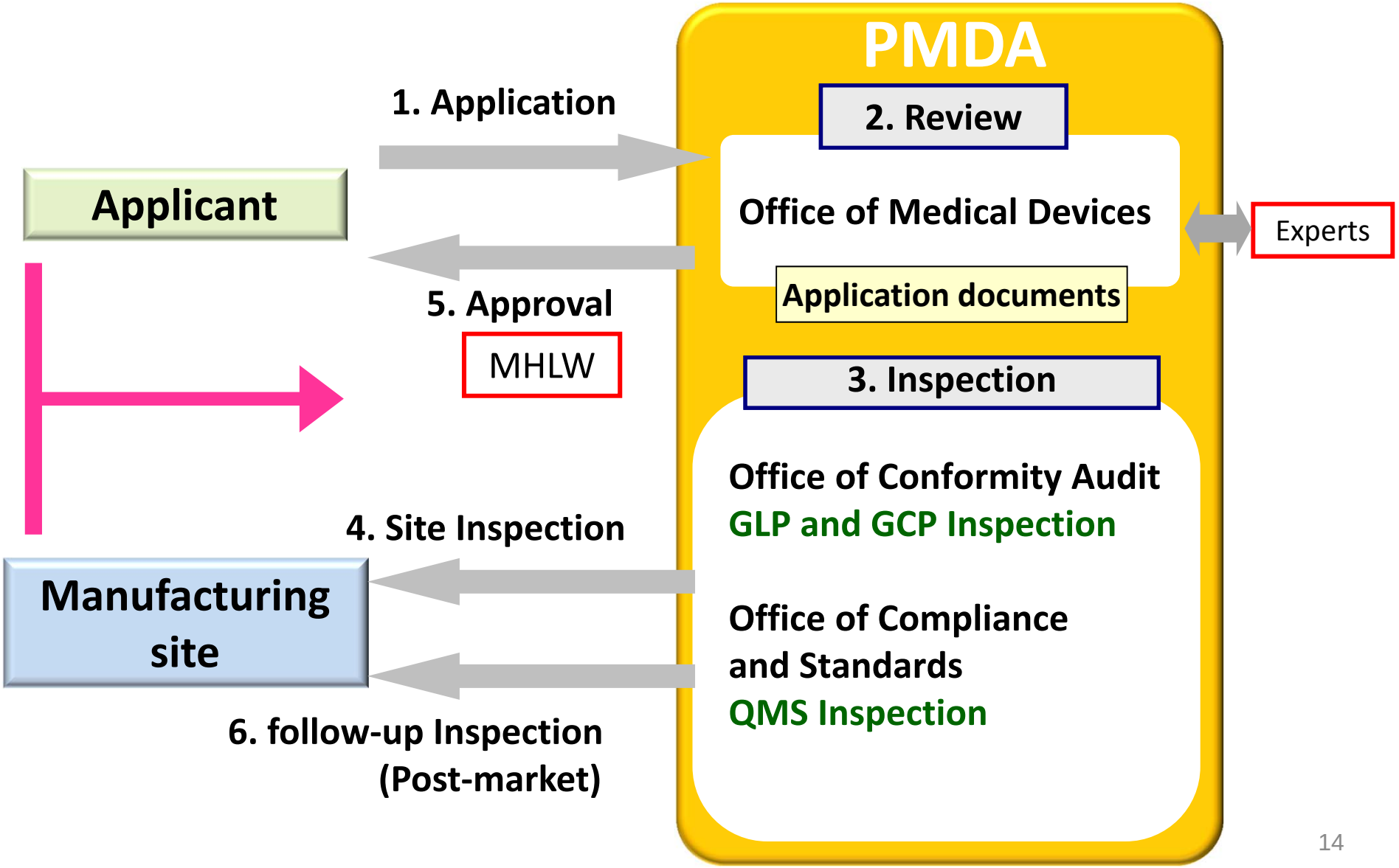
<u>Device performance</u>
- Efficacy
- Safety

Clinical trial

- Purpose
- Study population
- Control
- endpoint
- Safety
- duration

Appropriate study design & evaluation based on its clinical positioning

Overview of review process



SOPs and Templates

✓We have developed several standard operating procedures(SOPs) on review process

✓SOPs provide annotated report templates indicate how they should be completed, as well as blank templates

Review SOP Examples

- ✓About the whole process of review
- ✓About consultation on clinical evaluation
- ✓About review of brand-new devices, improved devices and generic devices
- ✓About management of original application dossiers
- ✓About review progress meeting
- ✓Etc.

Review Points of Orthopedics MDs

- ✓Substantial equivalence of shape and construction to the predicted devices
- ✓Specification of devices used together
- ✓Evaluation of the efficacy and safety of the whole system

Review of Hip Joints

There is a review guideline for hip joints:

- ✓ Specification of the indication for use
- ✓ A range of materials those have been used
- ✓ Requirements of the products
  - physical and chemical properties,
  - biological safety,
  - mechanical performance,
- ✓ stability
- ✓ validation of sterilization, etc

<人工股関節の一例>

Review of Hip Joints

mechanical performance

e.g. Strength

-ISO7206-4 for stems

-ISO7206-8 for necks

cement or non-cement,

surface coatings, etc

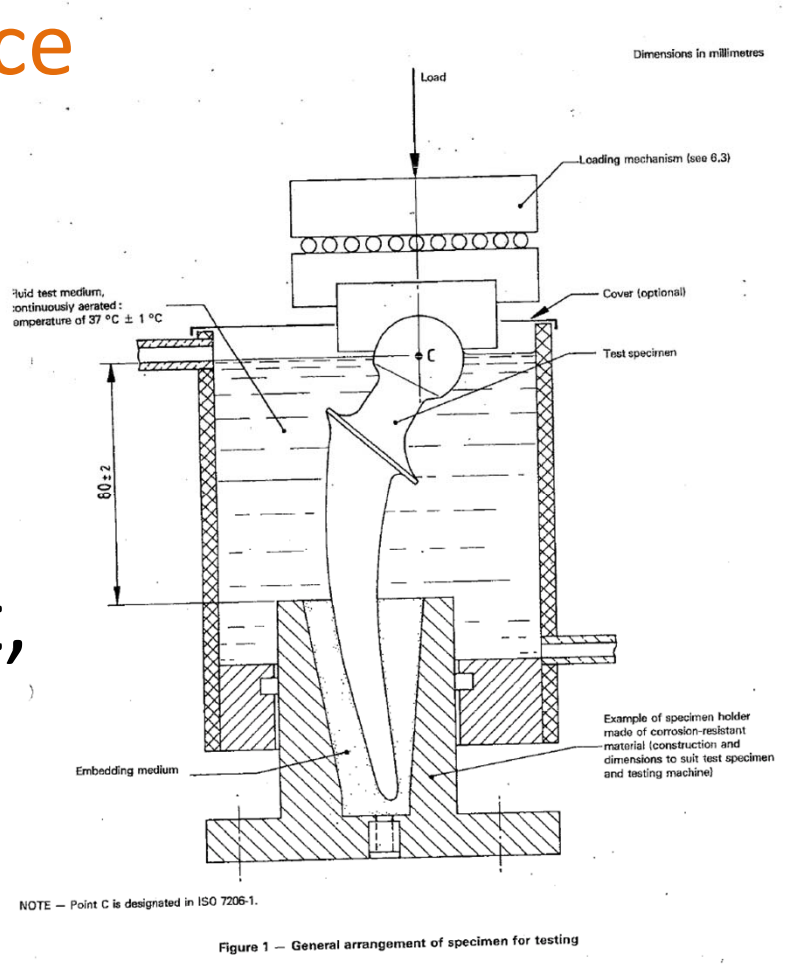


Figure 1 — General arrangement of specimen for testing

ISO7206-4

Review of Bone Graft Materials

- ✓ Specification of the materials and evaluation of their biological safety
- ✓ Specification Final composition
- ✓ Pore size, pore percentage, morphology
- ✓ Compression strength, bending strength
- ✓ In vivo study (animal experimentation) to show decomposition characteristics and bone growth

Examples of Our Questions

- ✓ About substantial equivalence to predicted devices
- ✓ About design concepts
- ✓ About sales performance and safety hazards in other countries and areas
- ✓ About biological safety
- ✓ About mechanical performance

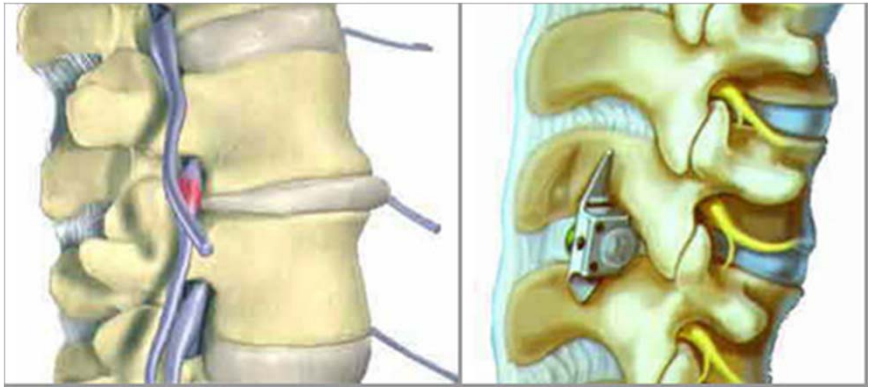
Case introduction-The X STOP ®

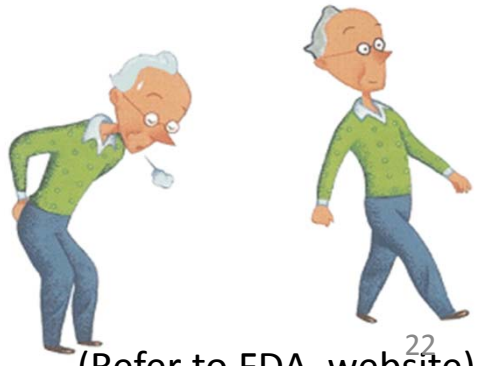
The X STOP ® Interspinous Process Decompression System

✓relieve symptoms of lumbar spinal stenosis, a narrowing of the passages for the spinal cord and nerves
✓a titanium implant that fits between the spinous processes of the lower (lumbar) spine
✓made from titanium alloy and consists of two components: a spacer assembly and a wing assembly.

Indications for use:

patients aged 50 or older suffering from pain or cramping in the legs secondary to a confirmed diagnosis of lumbar spinal stenosis.





(Refer to FDA website)

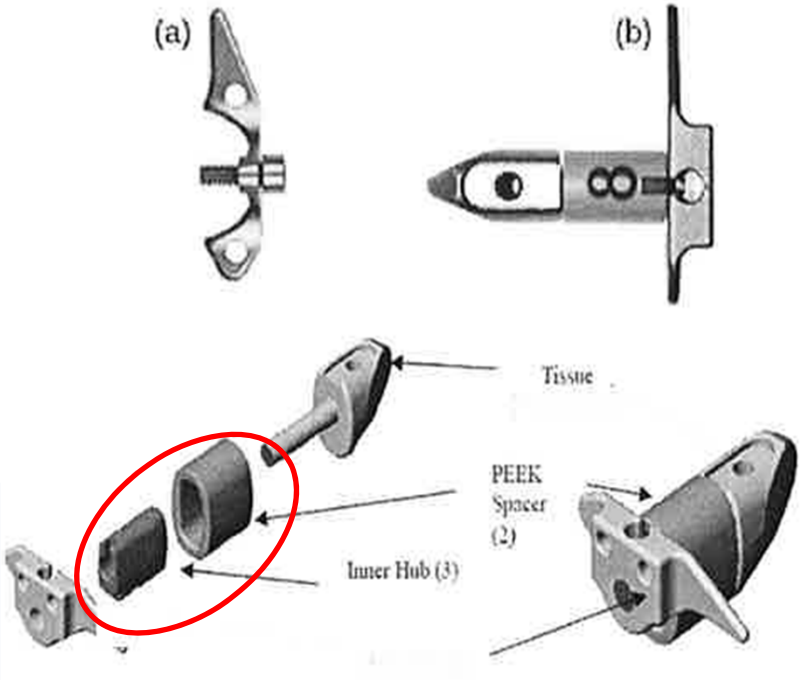
Case introduction -The X STOP ®

Nonclinical evaluation

✓ the change of the construction of the spacer

Before
a single layer with titanium alloy

After
Two layers with a titanium alloy inner hub and a PEEK outer shell.



(Refer to PMDA website)

Case introduction -The X STOP ®

clinical evaluation

✓ the validity of using the clinical data of the products before changing

✓the benefit and risk of X-STOP among the current treatment options for lumbar spinal stenosis

✓Conduct a post-approval study to determine whether patient selection criteria are adequate and whether the clinical study results are generalizable to Japanese patient population

(Refer to PMDA website)

Clinical Study Data Carried Out in Foreign Countries

- ✓ Clinical data acceptable
  - – Corresponding country or region has its official legal regulation for performing clinical investigation of medical devices, and
    - ① Such regulation is considered to be equivalent to or exceed the Japanese GCP regulation, and the data were obtained according to such regulation, or
    - ② The data of investigation considered to be equivalent to the above.

Changing Procedures

- MHLW/PMDA has the responsibility for "**approved product information**"
- PMDA has the responsibility to review changes of devices related to the quality, efficacy and safety

If approved products change,
procedure is required

Changing Procedures

There are three procedures for changing

- ✓Partial changes are not required
- ✓Minor change notification
- ✓Partial change approval application

"Procedures Associated with Partial Change for Medical Devices"

MHLW Notification by Director, OMDE, Yakushokuki-hatsu No.1023001 dated October 23, 2008 (Japanese)

Changing Procedures

Partial changes are not required

Changes that are not related to the efficacy and the safety, and the equality is maintained

e.g.

- ✓Change of indicator from light bulb to LED
- ✓Change of length/shape of pumping/suction tube exceed the scope of the access site

Changing Procedures

Minor change notification

Changes except for following:

- ✓Change of manufacturing method related to essence, characteristics, performance and safety
- ✓Deletion/change of properties and specifications
- ✓Change related to quality, efficacy and safety

e.g.

Changes of shape and size within the approved range without change of purpose, affected area, method of operation and specification.

Changing Procedures

Partial change approval application

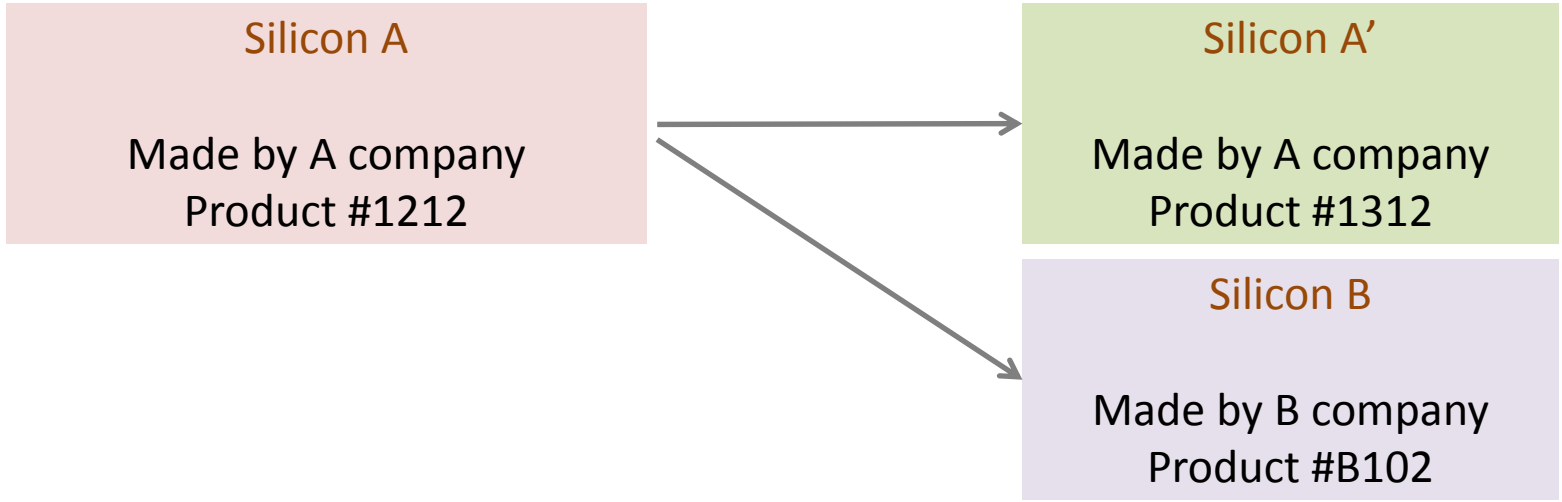
Changes except for minor change notification/no action required

e.g.

- ✓The intended use
- ✓Materials of implantable devices
- ✓Principle composition adding

A Common Case

Change of materials -Silicon

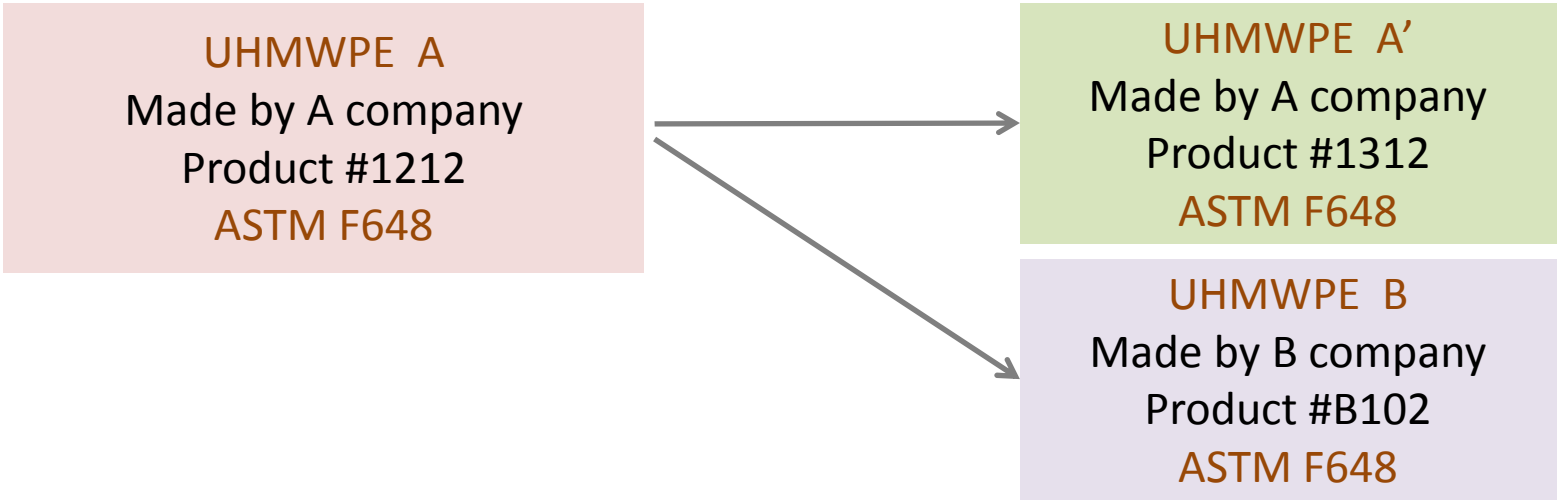


If the applicant could not show substantial equivalence between Silicon A to Silicon A' or Silicon B, a partial change approval application is necessary although they seem familiar commonly.

A Common Case

Change of Materials

- ultra high molecular weight-polyethylene(UHMWPE)



a partial change approval application is not necessary
because all of them conform the same industry standard ASTM F648 which guarantees their substantial equivalence .

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Action Program for Acceleration of MDs Reviews

(issued in Dec. 2008)

accelerate the Medical Device review processes and reduce total review time* to approval,

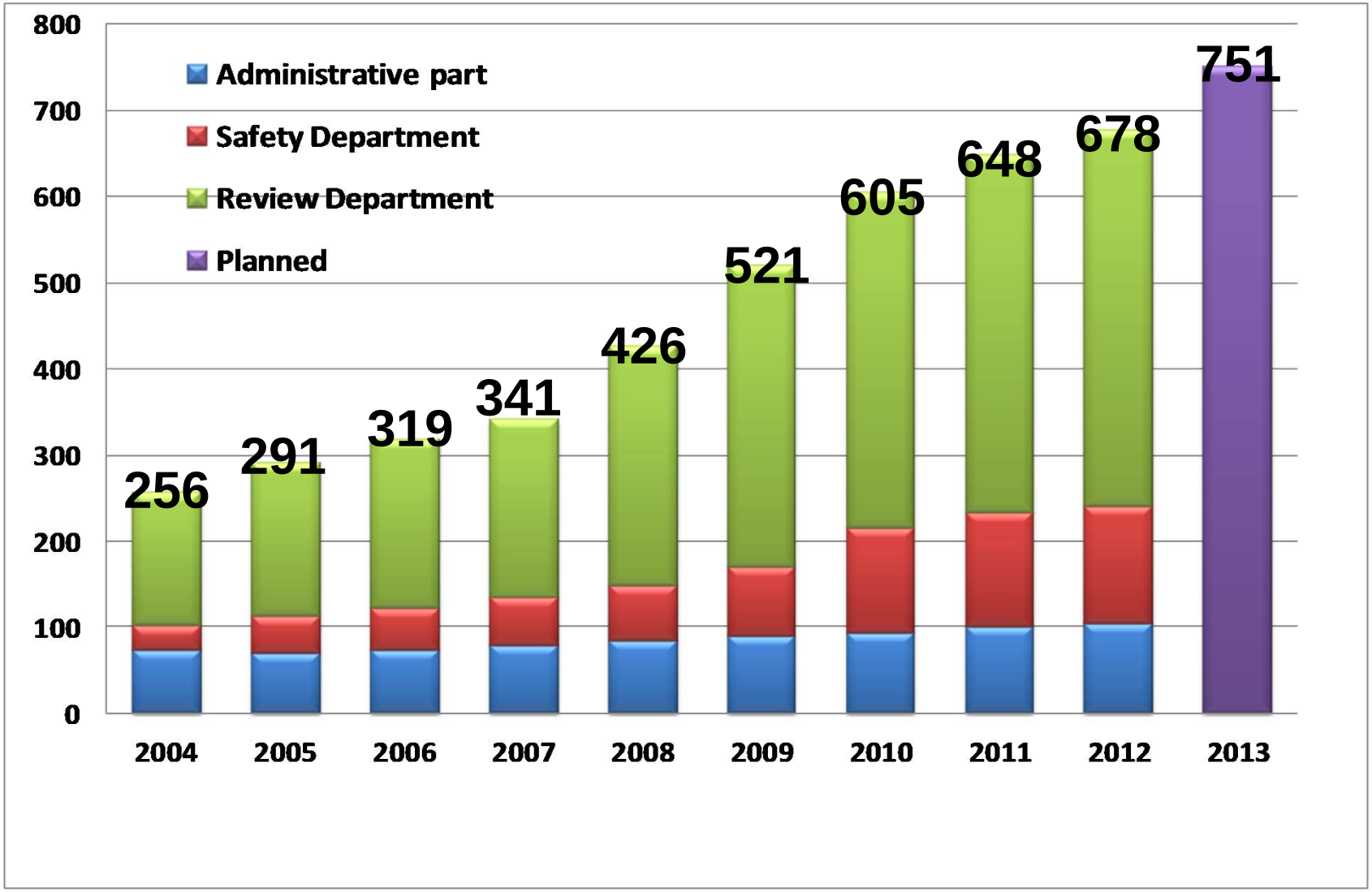
- on the premise of ensuring quality, efficacy, and safety of medical devices
- paying due consideration to minimize burdens to applicants
- under combined efforts by both the regulatory side and the applicants side
- by taking scientific and reasonable measures

(* Total elapsed time from submission to approval)

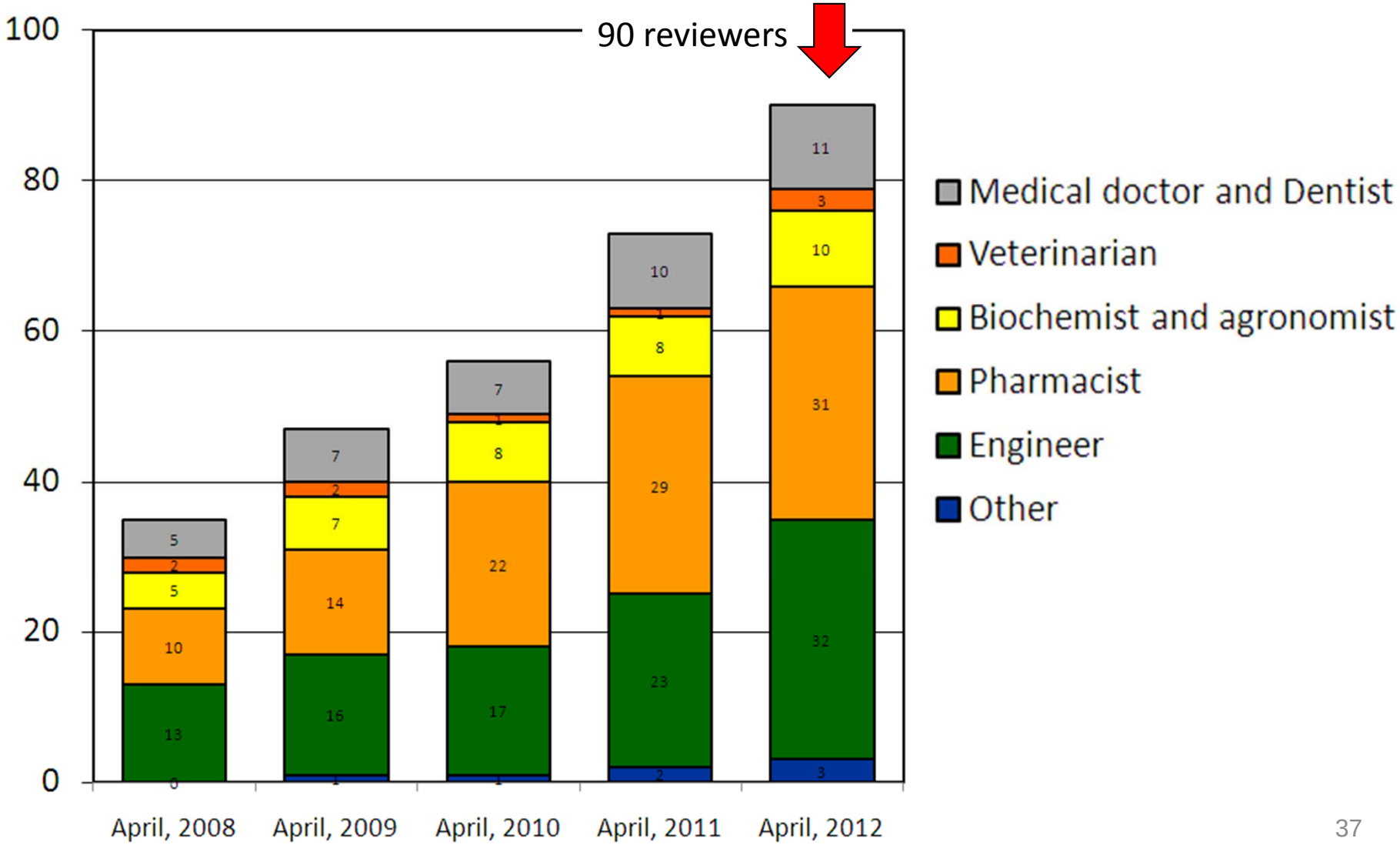
Performance Goal & Annual Milestone of Action Program

	2009	2010	2011	2012	2013
Improve quality by increasing the number of staff and enhancing training	Increase reviewers from 35 to 104 by 2013 Design Training Program				
Introduce 3-Track system	Prepare the operation		3-track Review System		
Clarify review criteria	Formulate Approval standards/Good Review Guideline				
Set review time goals	Brand-New MD : Standard 14 mos. Priority 10 mos. Improved MD : w/ clinical data 10 mos. w/o clinical data 6 mos. Generic(Me-too) MD 4 mos.				
Full transition to Third-party Certificate of Class Ⅱ MDs	Transit by FY2011				

PMDA Staff Size



Background of MDs Reviewers



Performance Goal of the Time Period

With combined efforts by both regulatory & applicants, total review time should be reduced to the below goal:

Performance Goal: total review time (median, unit: months)			~ FY2008	FY2009	FY2010	FY2011	FY2012	FY2013
Brand-new MD (Shin)	Standard items	total time	~ 21	21	21	20	17	14
		for agency	~ 8	8	8	8	7	7
		for applicant	~ 14	14	14	12	10	7
	Priority items	total time	~ 16	16	16	15	13	10
		for agency	~ 9	8	8	7	7	6
		for applicant	~ 9	9	9	8	6	4
Improved MD (Kairyo)	clinical data required	total time	~ 16	16	16	14	12	10
		for agency	~ 9	8	8	7	7	6
		for applicant	~ 7	7	7	6	5	4
	w/o clinical data	total time	~ 11	11	11	10	9	6
		for agency	~ 6	6	6	6	5	4
		for applicant	~ 5	5	5	5	4	2
Substantially equivalent MD (Kohatsu) (w/ specific criteria)		total time	~ 8	8	6	5	4	4
		for agency	~ 5	5	4	4	3	3
		for applicant	~ 3	3	2	1	1	1

Performance Goal and Results of FY2011

review time (median, unit: months)			FY2011		
			Performance Goal	Results	# of Approval
Brand-new MD (Shin)	Standard items	total time	20	9.7	27
		for agency	8	5.1	
		for applicant	12	3.4	
	Priority items	total time	15	4.3	6
		for agency	7	2.9	
		for applicant	8	1.3	
Improved MD (Kairyo)	clinical data required	total time	14	13.9	55
		for agency	7	7.0	
		for applicant	6	7.2	
	w/o clinical data	total time	10	13.3	218
		for agency	6	5.6	
		for applicant	5	6.5	
Substantially equivalent MD (Kohatsu) (w/ specific criteria)		total time	5	5.0	907
		for agency	4	2.5	
		for applicant	1	2.3	

Thank you!!

Pharmaceuticals and Medical Devices Agency

http://www.pmda.go.jp/english/