Review process essentials and the experience of reviewing innovated medical devices developed in Japan

YOKOYAMA Yoshimasa, PhD.

Reviewer

Office of Medical Devices Ⅱ

Pharmaceuticals and Medical Devices Agency

9th Sep. 2021

Take home message

The medical device regulation should be an EFFICIENT AND EFFECTIVE ACTION.

- The medical device review needs effective methods to evaluate the efficacy and safety of medical devices , in order to promote the approval of good medical devices as early as possible for patients.

- The pharmaceutical authorities should have clear vision to review medical devices.

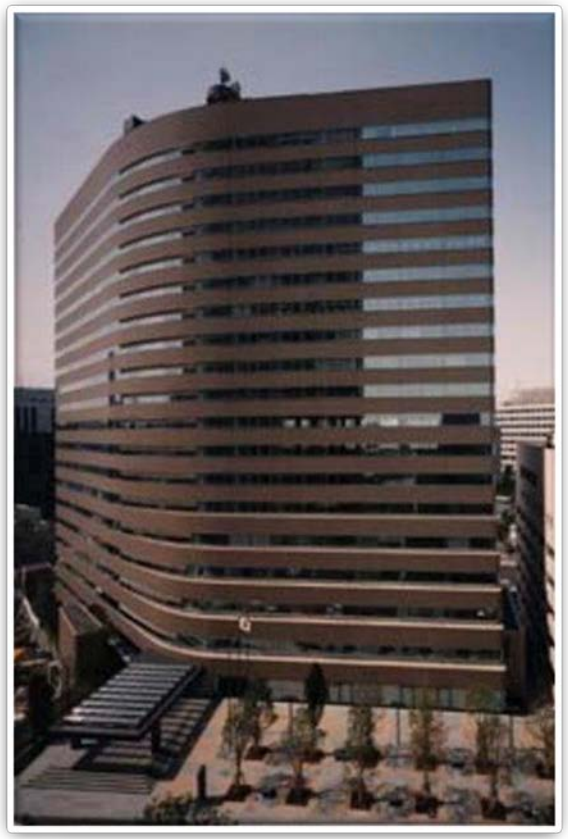
Agenda

1. Outline of PMDA’s work for medical device regulation
2. Concept and process of reviewing the application for marketing approval
   - Review Standpoints-① -Essential Principle-
   - Review Standpoints-② -Evaluation of effectiveness and safety-
3. Examples of recent approved medical devices

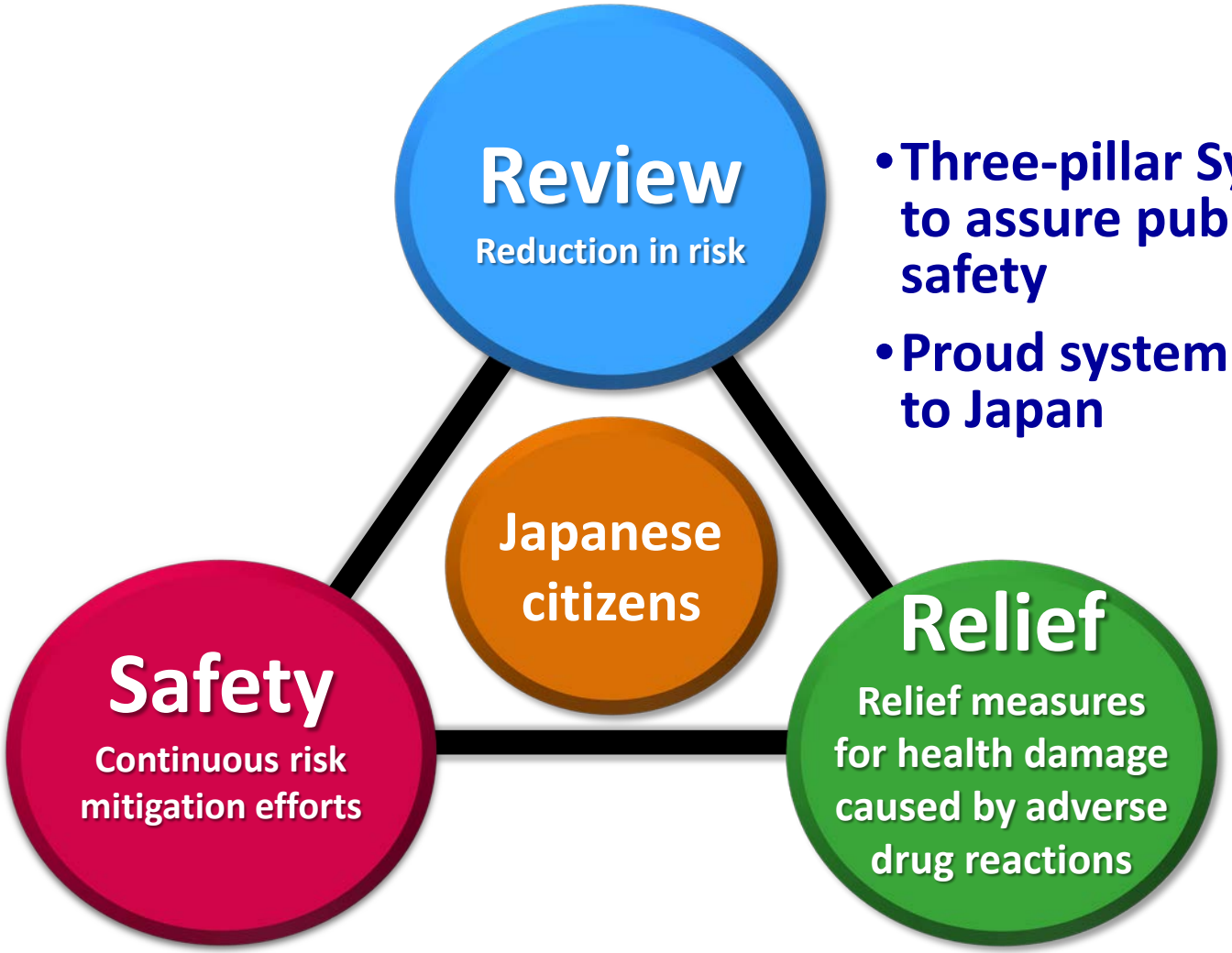
   - Highlight of medical device review -

   - TITAN BRIDGE
   - NeuCure BNCT System & NeuCure Dose Engine
   - Sure App SC Digital therapeutic and CO Checker for Nicotine Dependence

1. Outline of PMDA's work for medical device regulation

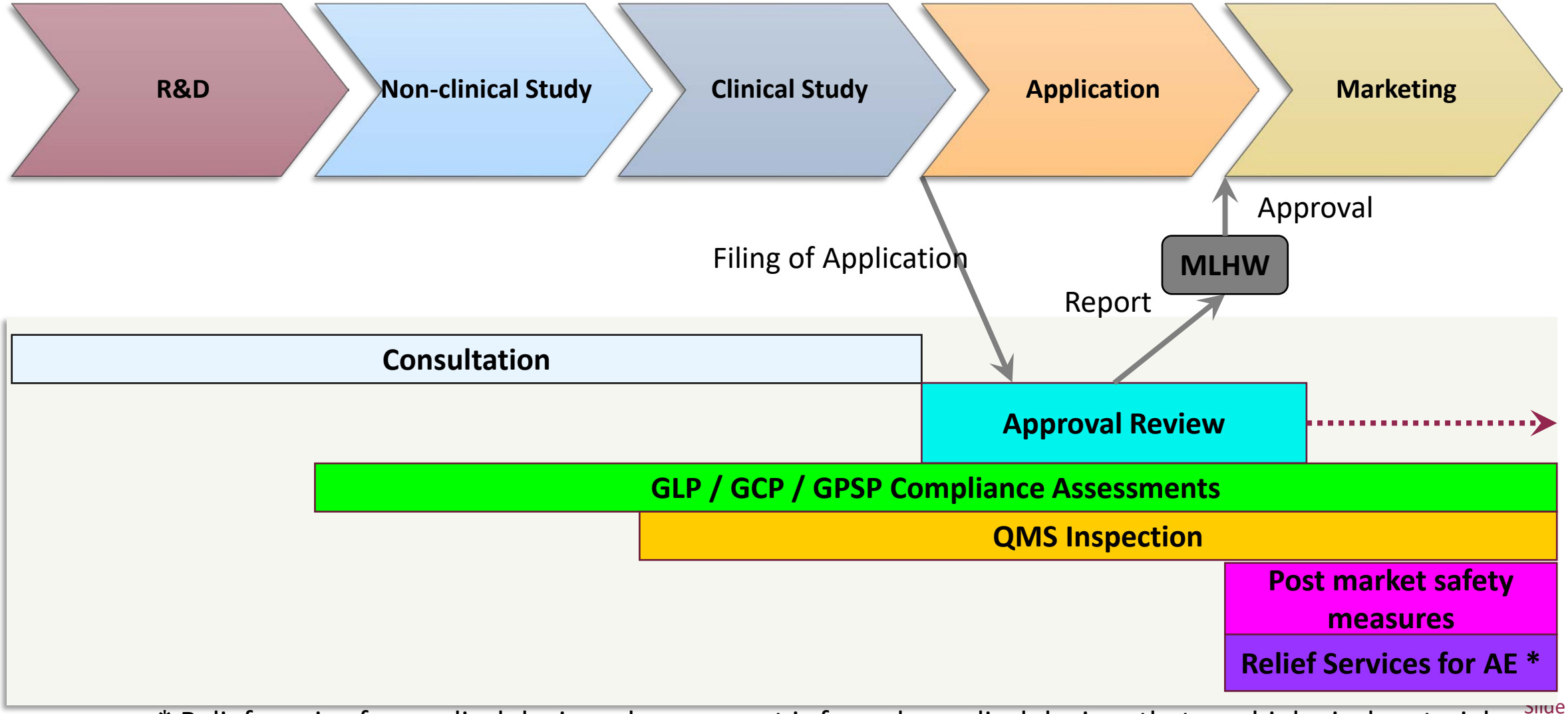


PMDA's role :
Three major services - Safety Triangle



- Three-pillar System to assure public safety
- Proud system unique to Japan

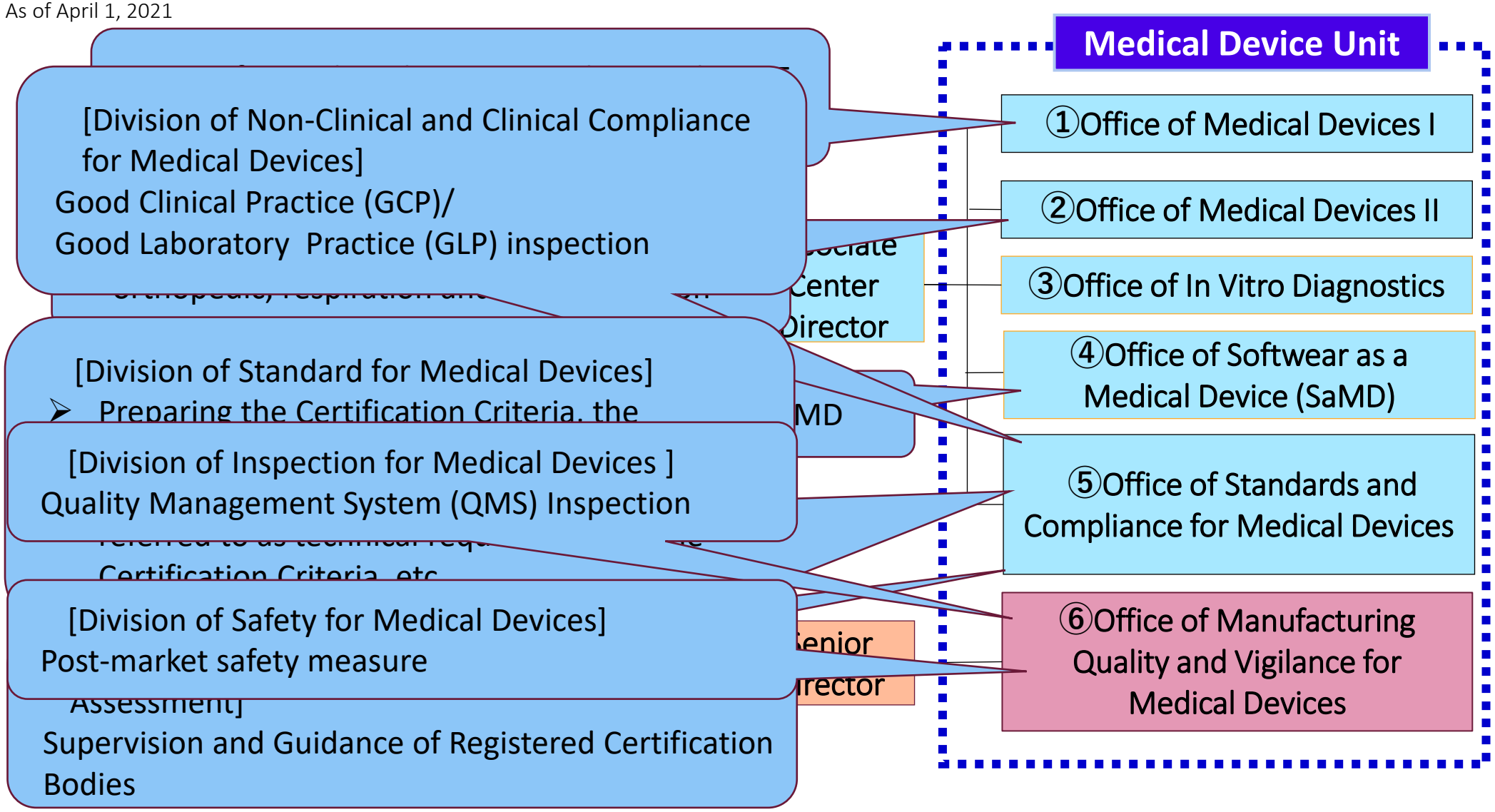
Services related to marketing approval of medical devices



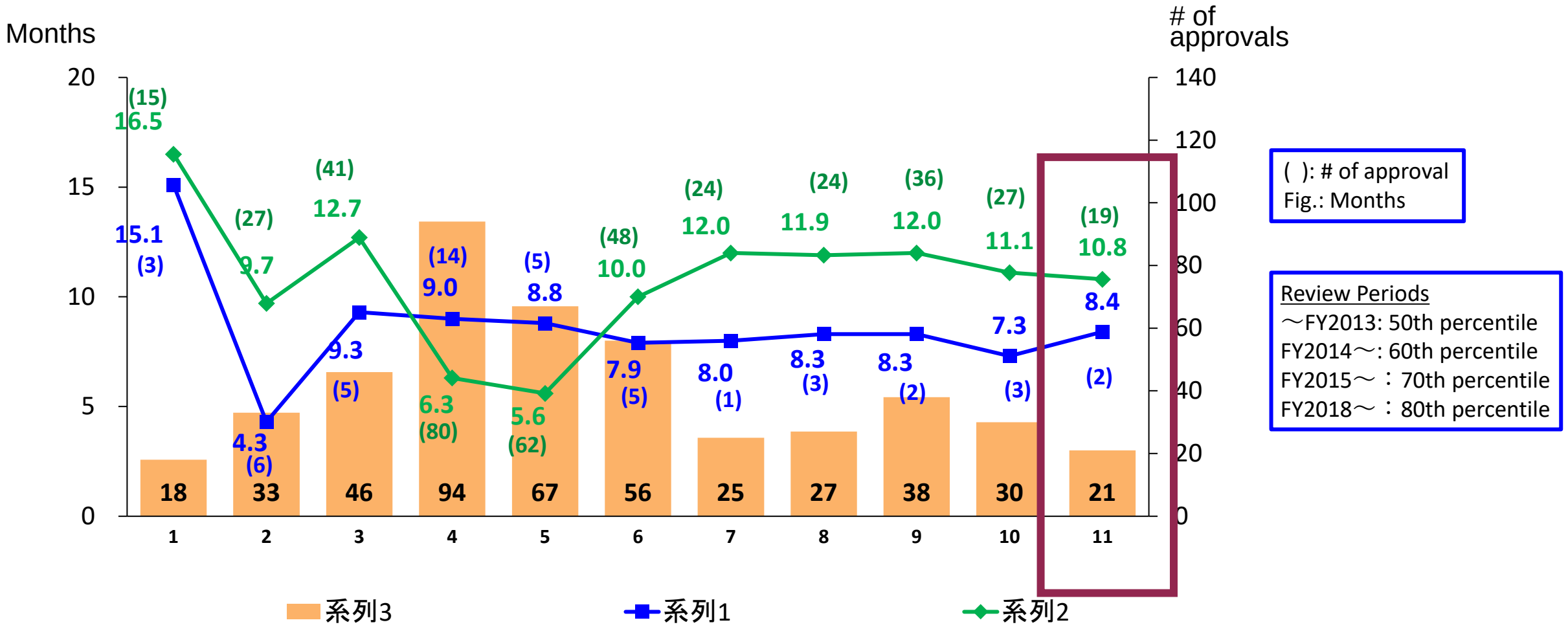
* Relief service for medical device adverse event is for only medical devices that use biological materials.

Organization Chart of “Medical Device Unit”

As of April 1, 2021

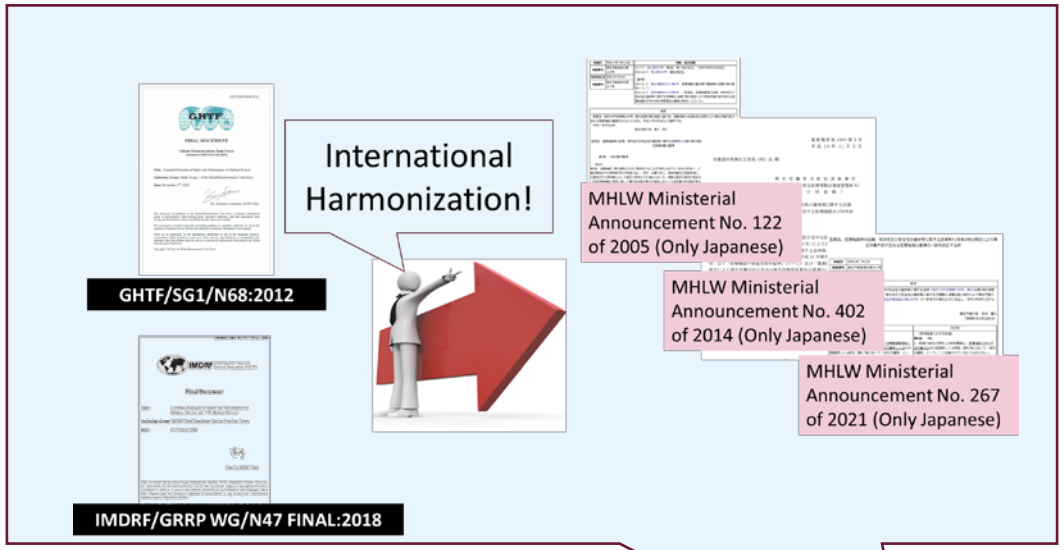


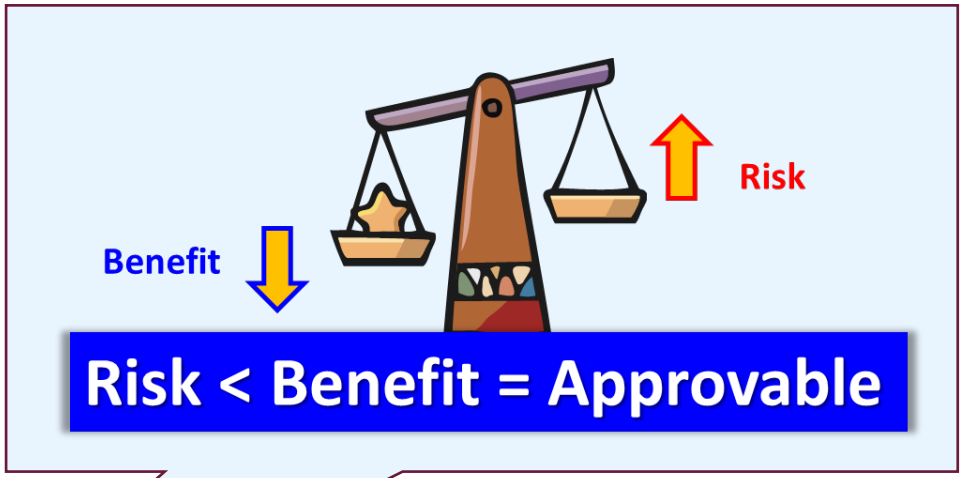
Number of approvals and review periods of medical devices

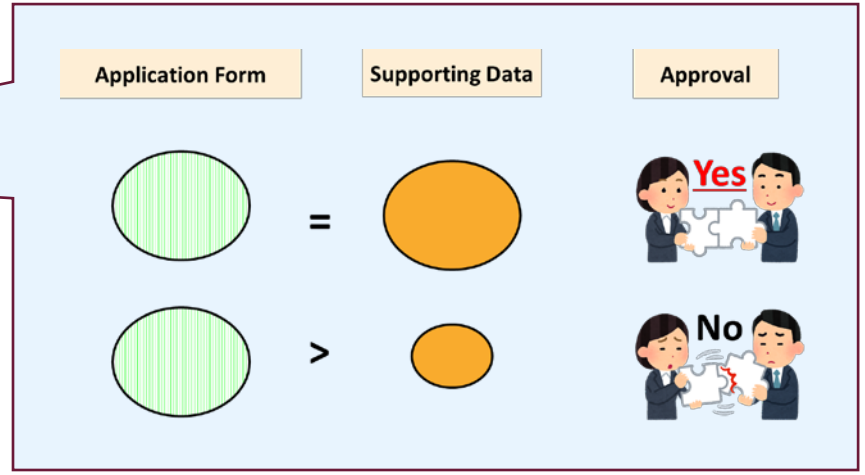


FY			'10	'11	'12	'13	'14	'15	'16	'17	'18	'19	'20
Target median value (Month)	New Medical Devices	Priority	16	15	13	10	10	10	10	10	10	10	10
		Standard	21	20	17	14	14	14	14	14	14	14	14

2. Concept and process of reviewing the application for marketing approval







Risk Classification of non-IVD Medical Devices

As of July, 2021

GHTF Classification		Classification in Japan			
Class	Risk level	Class	# of JMDN**	Category	Pre-market regulation
A	**Low** Surgical retractors/ tongues depressors	Ⅰ	1,214	General MDs	Self declaration***
B	**Low to Moderate** Hypodermic needles/ suction equipment	Ⅱ	2,003	Controlled MDs + Designated Controlled MDs	Third party Certification (Review by RCB*) (**Designated** Controlled MDs and **Designated** Specially Controlled MDs)
C	**Moderate to High** Lung ventilator/ bone fixation plate	Ⅲ	812	Specially Controlled MDs + Designated Specially Controlled MDs	**Ministerial Approval (Review by PMDA) (Controlled MDs and Specially Controlled MDs)**
D	**High** Heart valves / implantable defibrillator	Ⅳ	372		

*RCB: Registered Certification Bodies

**JMDN: Japanese Medical Device Nomenclature

***MD software classified as Class I is **NOT** subjected to restrictions on the PMD-Act

Japanese Medical Device Nomenclature (JMDN)

◆JMDN was developed based on 2003 version of Global Medical Device Nomenclature (GMDN) and implemented in 2005 in Japan.

◆Each medical device is identifiable by JMDN.

Generic Name

Definition

JMDN code

Risk-based Classification

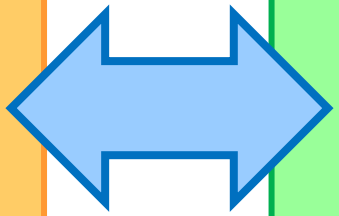
Japanese Medical Device Nomenclature (JMDN)	Definition	de	Classifica
Single-use interspinous placement	A device to be placed between the spinous processes to relieve lower lim pain and leg pain. With the placement, it holds the lumbar spine in the flexed position and prevents it from being in the extended position whenever possible.	4702 003	Ⅲ
Control unit for central venous placement temperature management system	A control unit that controls temperature and circulation of the perfusate circulating in the circulatory catheter of a temperature management system with percutaneously placed central venous catheters. It also monitors the body temperature and gives a warning, etc.	44709003	Ⅲ
Catheter for central circulatory angiography	A flexible tube designed for injection of a contrast agent into vessels in the central cardiovascular system for vascular imaging in the target section of the body.	10688104	Ⅳ
Catheter for balloon dilatation angioplasty	A flexible tube for dilation of a narrowed vessel or dilation after stent placement in the vessel (an artery, vein, or shunt), except for coronary blood vessels or intracranial cerebral vessels, by controlled inflation and deflation of a balloon. The device usually consists of a double-lumen catheter with a balloon at the distal end. Some catheters have channels for pressure measurement or delivery of an angiographic agent, or have a balloon with blades, wire, or the like.	17184014	Ⅳ
Catheter for coronary balloon dilatation angioplasty	A flexible tube used for dilation of a narrowed coronary artery vessel by controlled inflation of a dilating balloon. The device usually consists of a double-lumen catheter with a balloon at the distal end. Some catheters have channels for pressure measurement or delivery of an contrust agent. Some catheters have a balloon with blades, wire etc.	17184024	Ⅳ

Application dossier

Application Form

Identification of application items

- Type
- Name
- Purpose of use or effect
- Form, structure and principles
- Raw materials
- Specifications for performance and safety
- Method of operation
- Storage method and expiration period



Supporting Data

Justifying data

Efficacy
Safety
Quality

Categories of MD Used in application for marketing approval

Background of Development

Clinical impact

Appropriate evaluation is …

Clinical Evaluation & Non-clinical test

- Clinical trial
- Clinical study
- Commonly used test
- Simple Mechanical test
- Published standards for safety

Brand New

Improved with clinical data

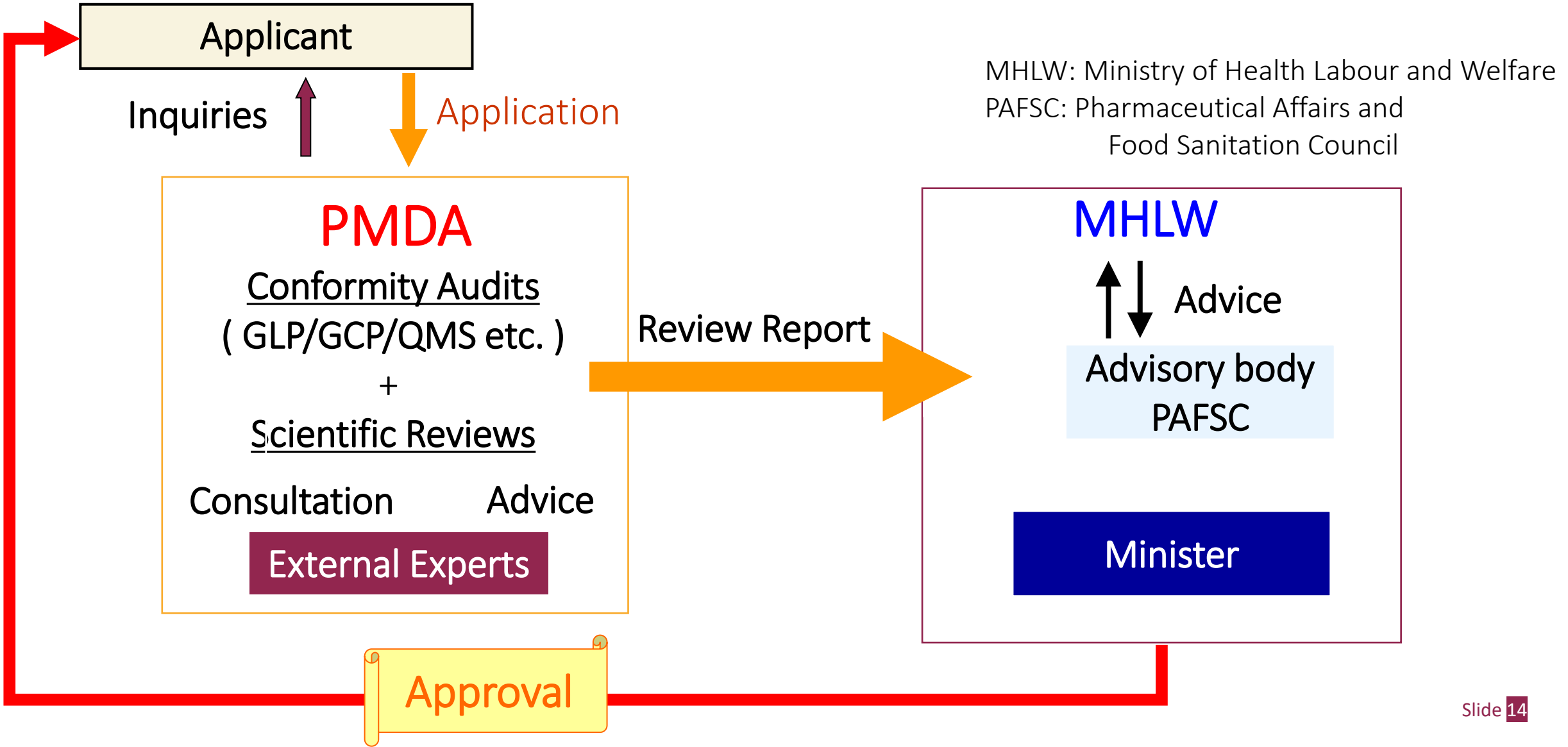
Non-clinical test

- Commonly used test
- Simple Mechanical test
- Published standards for safety

Improved w/o clinical data

Generic

Outline of review process - brand-new medical devices-



MHLW: Ministry of Health Labour and Welfare
PAFSC: Pharmaceutical Affairs and Food Sanitation Council

Review concept for medical device in Japan

＜Reason of Rejection of Approval＞ PMD Act, Article 23-2-5

(a) The given device is judged that it does not have its own efficacy, effectiveness and/or performance as to be concerned in the application.
(b) The given device is judged of no value for medical use because its adverse effect(s) far exceed its efficacy, effectiveness and/or performance.

Risk < Benefit = Approvable

Review Standpoints-① -Essential Principle-

IMDRF/GRRP WG/N47 FINAL:2018

IMDRF International Medical Device Regulators Forum

Final Document

Title: Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices

Authoring Group: IMDRF Good Regulatory Review Practices Group

Date: 31 October 2018

Yuan Lin, IMDRF Chair

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IMDRF/GRRP WG/N47
FINAL:2018

Fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance' to ensure this outcome.

Safe and perform as intended, ***should have risks that are acceptable when weighed against the benefits to the patient***..."

Review Standpoints-① -Essential Principle-


GHTF/SG1/N68 2012

FINAL DOCUMENT

Global Harmonization Task Force

Title: Essential Principles of Safety and Performance of Medical Devices

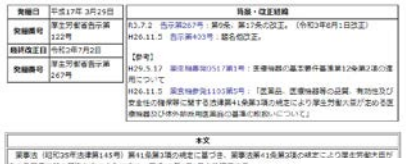
Authoring Group: Study Group 1 of the Global Harmonization Task Force

Date: November 2nd, 2012

Dr. Kazunari Asamura, GHTF Chair

GHTF/SG1/N68:2012

International Harmonization!


発出日 平成17年 3月29日
発出番号 厚生労働省告示第122号
最終改正日 令和2年7月2日
発出番号 厚生労働省告示第267号

MHLW Ministerial Announcement No. 122 of 2005 (Only Japanese)


薬食機参発 1105 第 5 号
平 成 26 年 11 月 5 日
各都道府県衛生主管部（局）長 殿
厚 生 労 働 省 大 臣 官 房 参 事 官
医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律第41条第3項の規定により厚生労働大臣が定める医療機器の基準の一部を改正する件

MHLW Ministerial Announcement No. 402 of 2014 (Only Japanese)

発出日 令和3年 7月2日
発出番号 厚生労働省告示第267号

MHLW Ministerial Announcement No. 267 of 2021 (Only Japanese)


IMDRF/GRRP WG/N47 FINAL:2018

IMDRF International Medical Device Regulators Forum

Final Document

Title: Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices

Authoring Group: IMDRF Good Regulatory Review Practices Group

Date: 31 October 2018

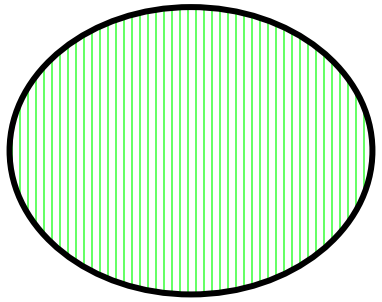
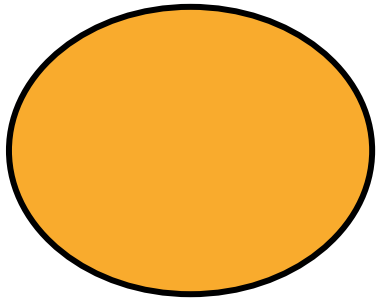
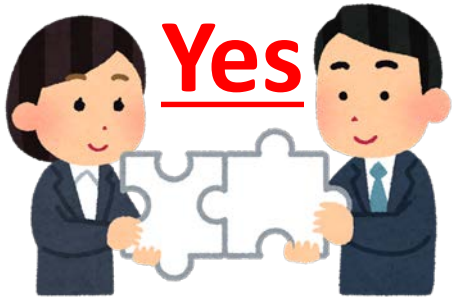
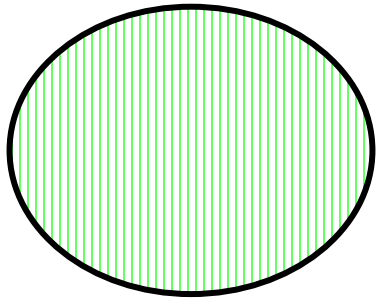
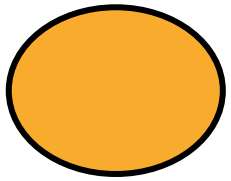
Yuan Liu, IMDRF Chair

IMDRF/GRRP WG/N47 FINAL:2018

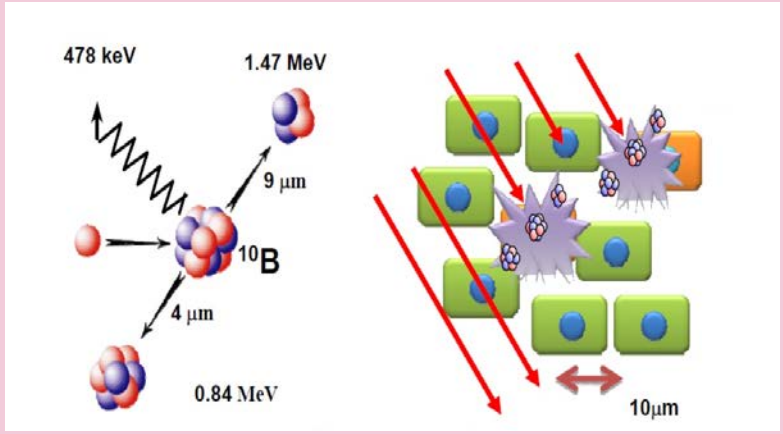
Action to implement “Essential principle” in MD regulation in Japan and improve the regulation

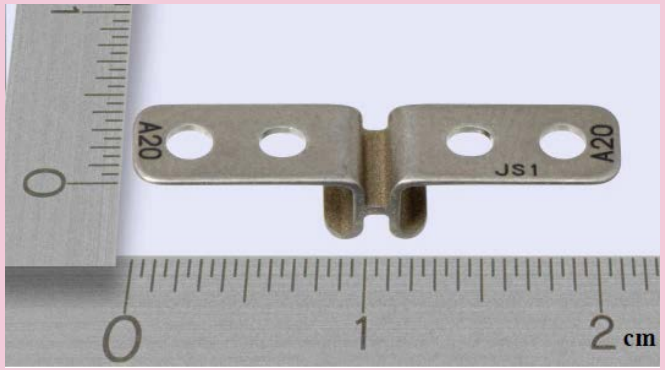
Review Standpoints-②

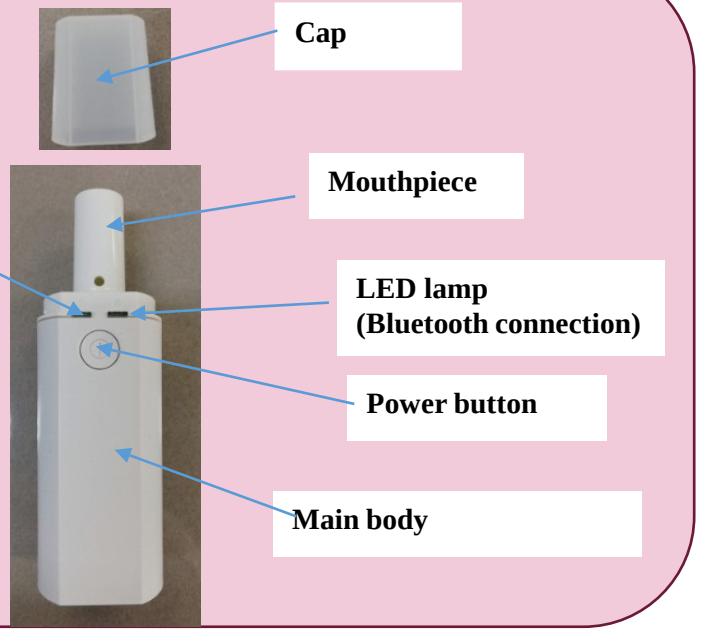
-Evaluation of effectiveness and safety-

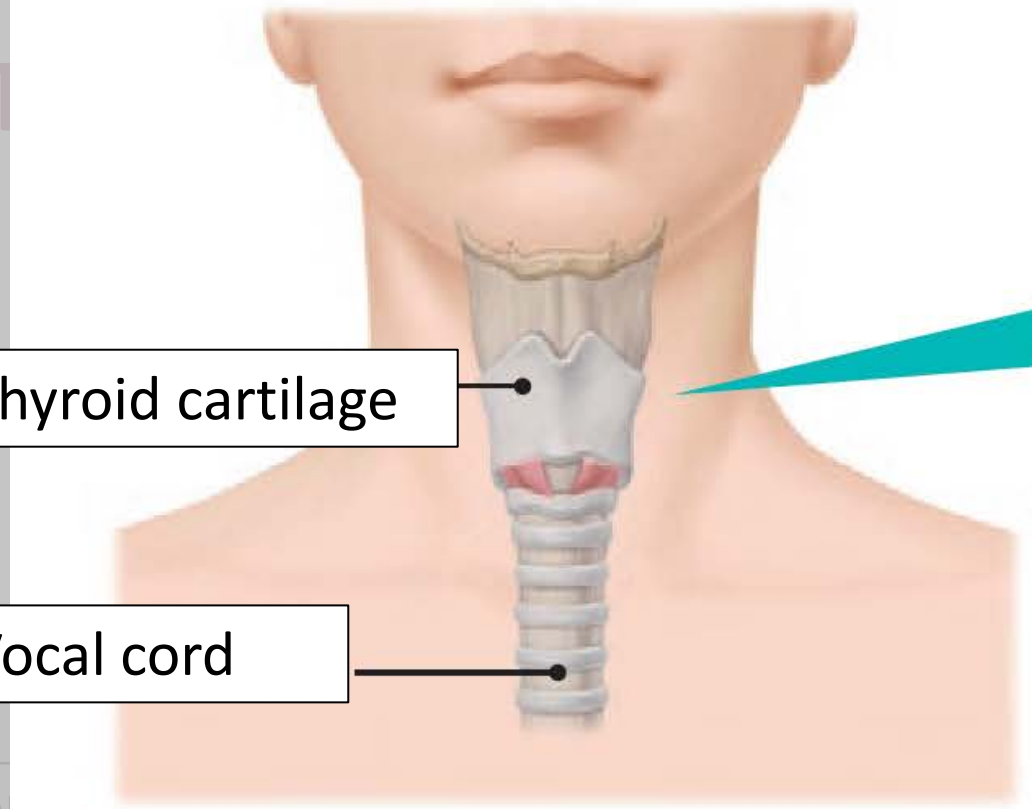
Application Form		Supporting Data	Approval
	=		
	>		

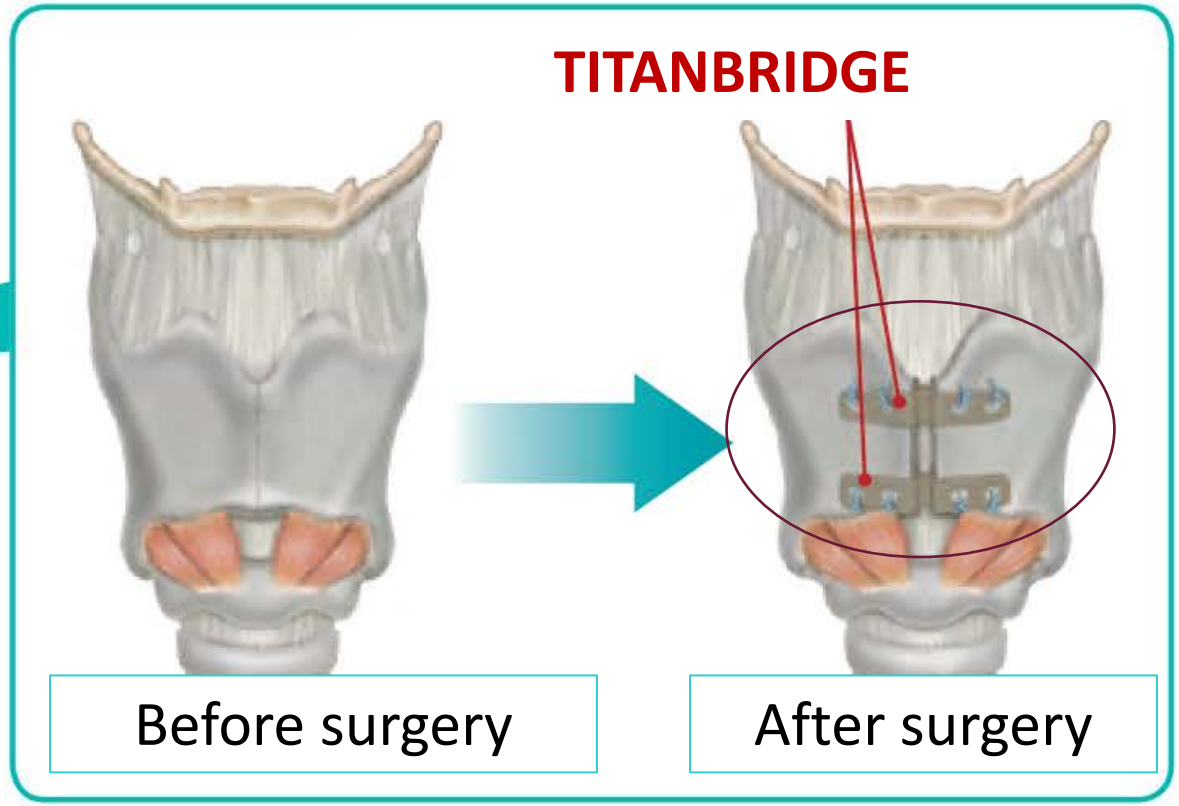
3. Examples of recent approved medical devices –Highlight of medical device review-



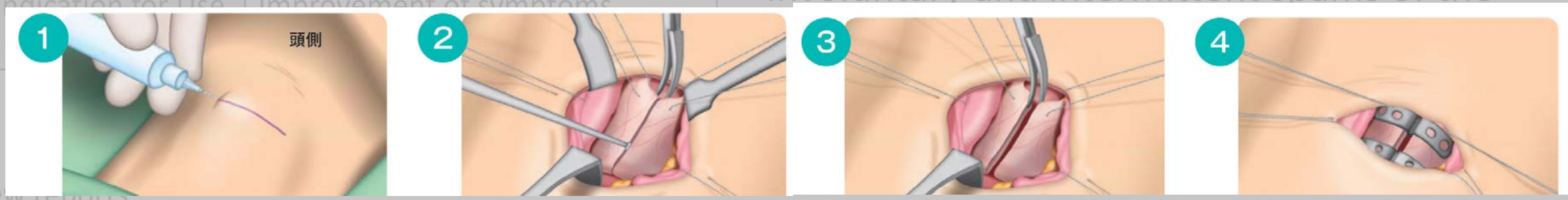






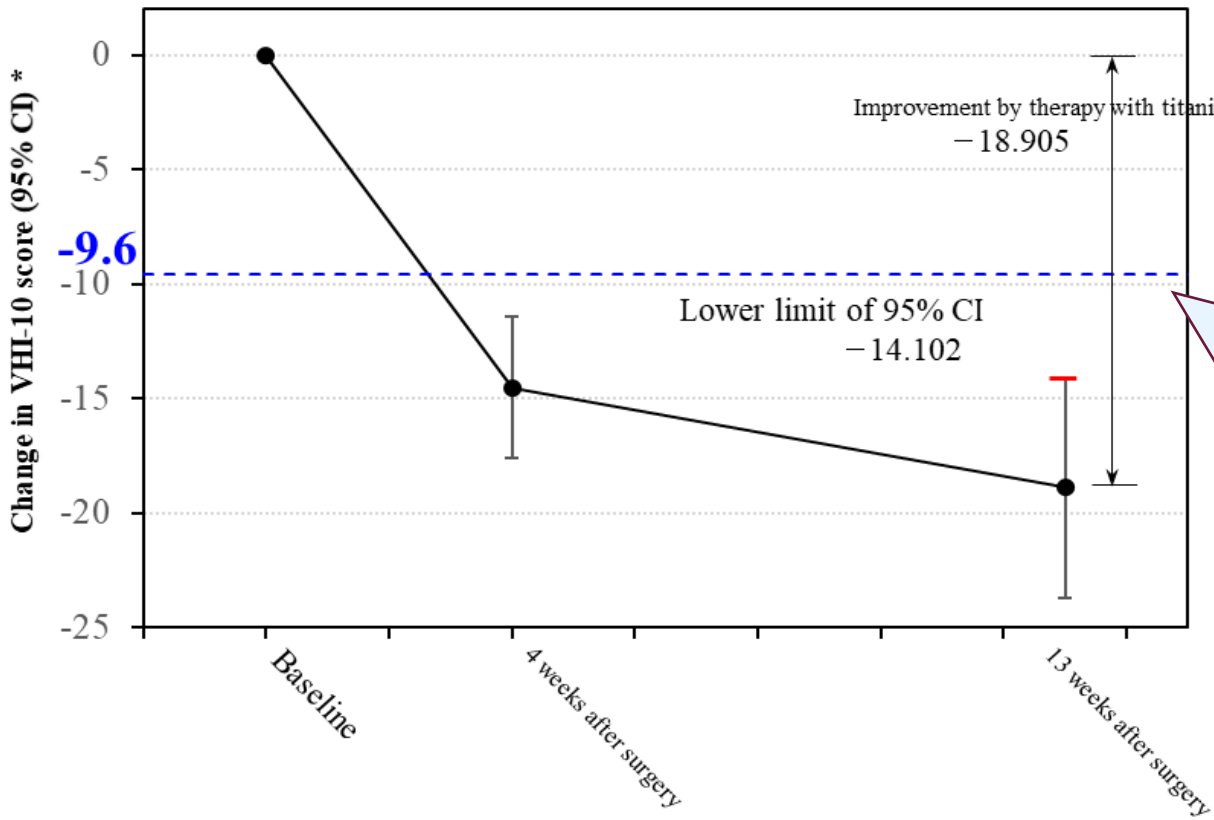


Prevent tight closure of glottis



Review reports
https://www.pmda.go.jp/files/000225027.pdf

Clinical Trial for TITANBRIDGE

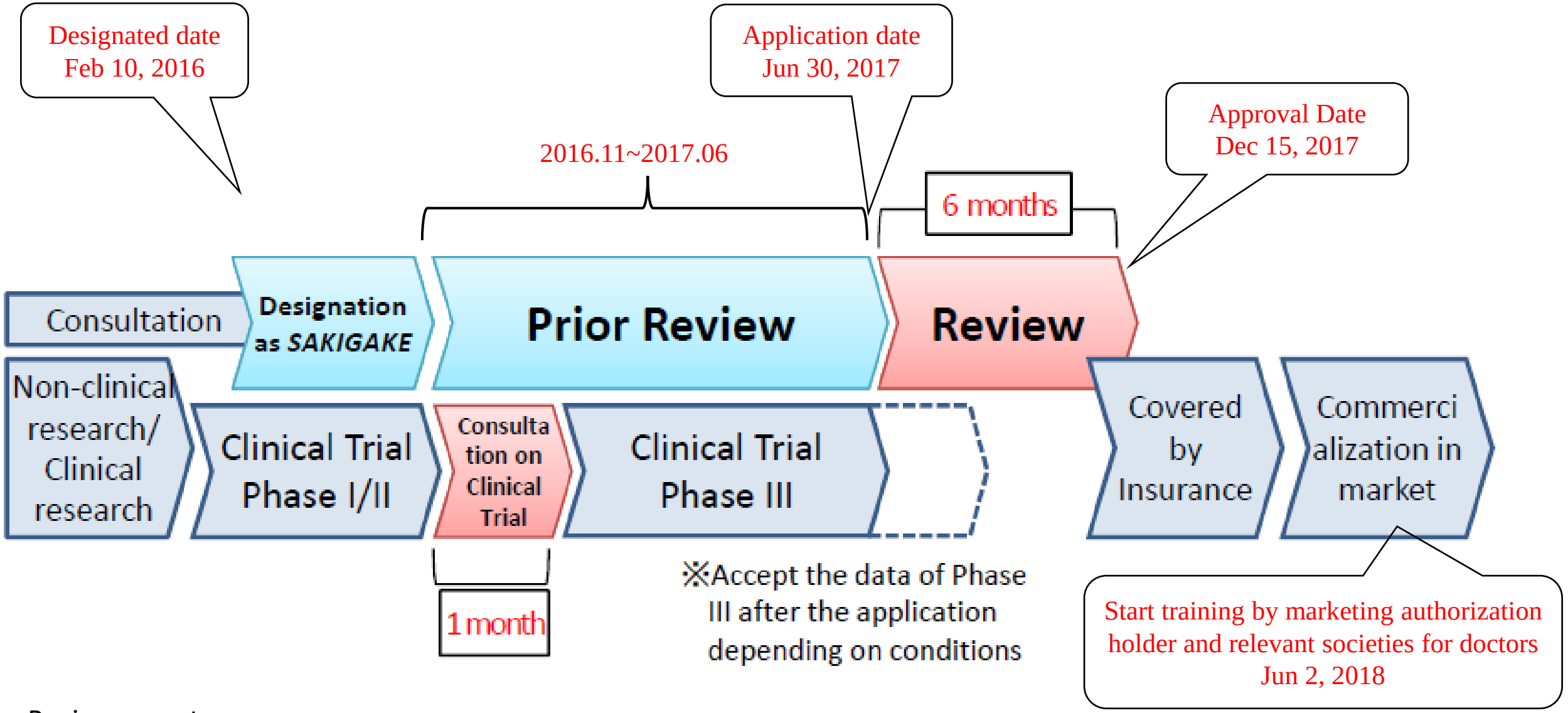


Change from baseline in VHI-10 score at 13 weeks after surgery (FAS)
(Review Report pp.27)

the outcome of botulinum toxin type A injection in a clinical study reported in the literature (the difference before and after treatment, –9.6)

VHI-10 : Voice Handicap Index-10. The VHI-10 is accepted internationally as a means to assess patients' perception of the severity of their voice disorder and recommended by the Japan Society of Logopedics and Phoniatrics.

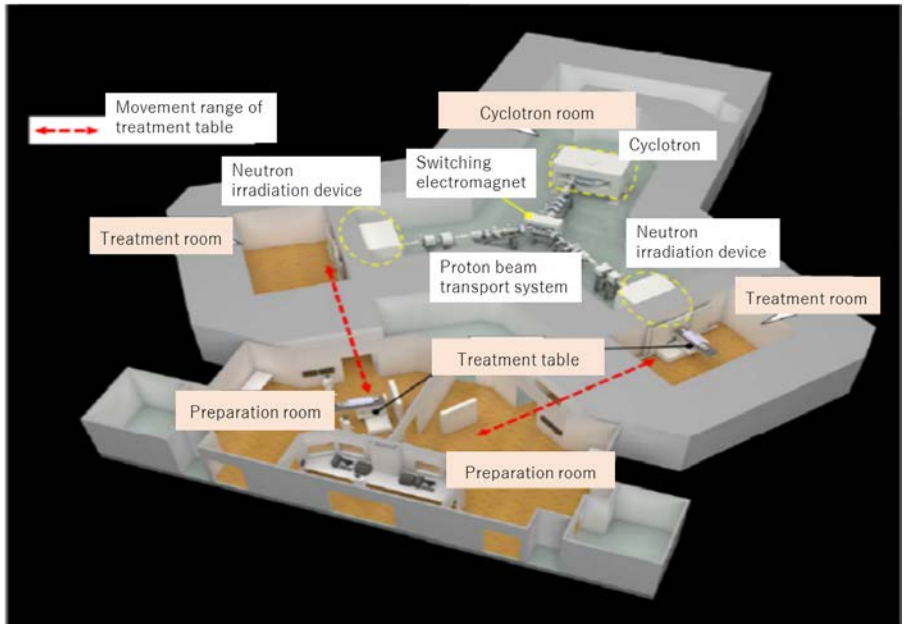
Review under SAKIGAKE Designation System for TITANBRIDGE



Review reports
https://www.pmda.go.jp/files/000225027.pdf

NeuCure BNCT System & NeuCure BNCT Dose Engine

MAH	Sumitomo Heavy Industries, Ltd
Approval Date	February 19, 2020
Indication for Use	**NeuCure BNCT System** is a neutron irradiation device intended to be used for boron neutron capture therapy to treat unresectable, locally advanced or locally recurrent head and neck cancer, and used in combination with the following drug: ・Non-proprietary Name: Borofalan (^{10}B) Brand Name: Steboronine 9000 mg/300 mL for Infusion **NeuCure BNCT Dose Engine** is a program that calculates dose distribution achieved in boron neutron capture therapy based on contour information and irradiation conditions, to assist physicians in developing treatment plans with boron neutron capture therapy for patients with unresectable, locally advanced or locally recurrent head and neck cancer. NeuCure BNCT Dose Engine is used in combination with the following drug: (Same Drug of NeuCure BNCT)

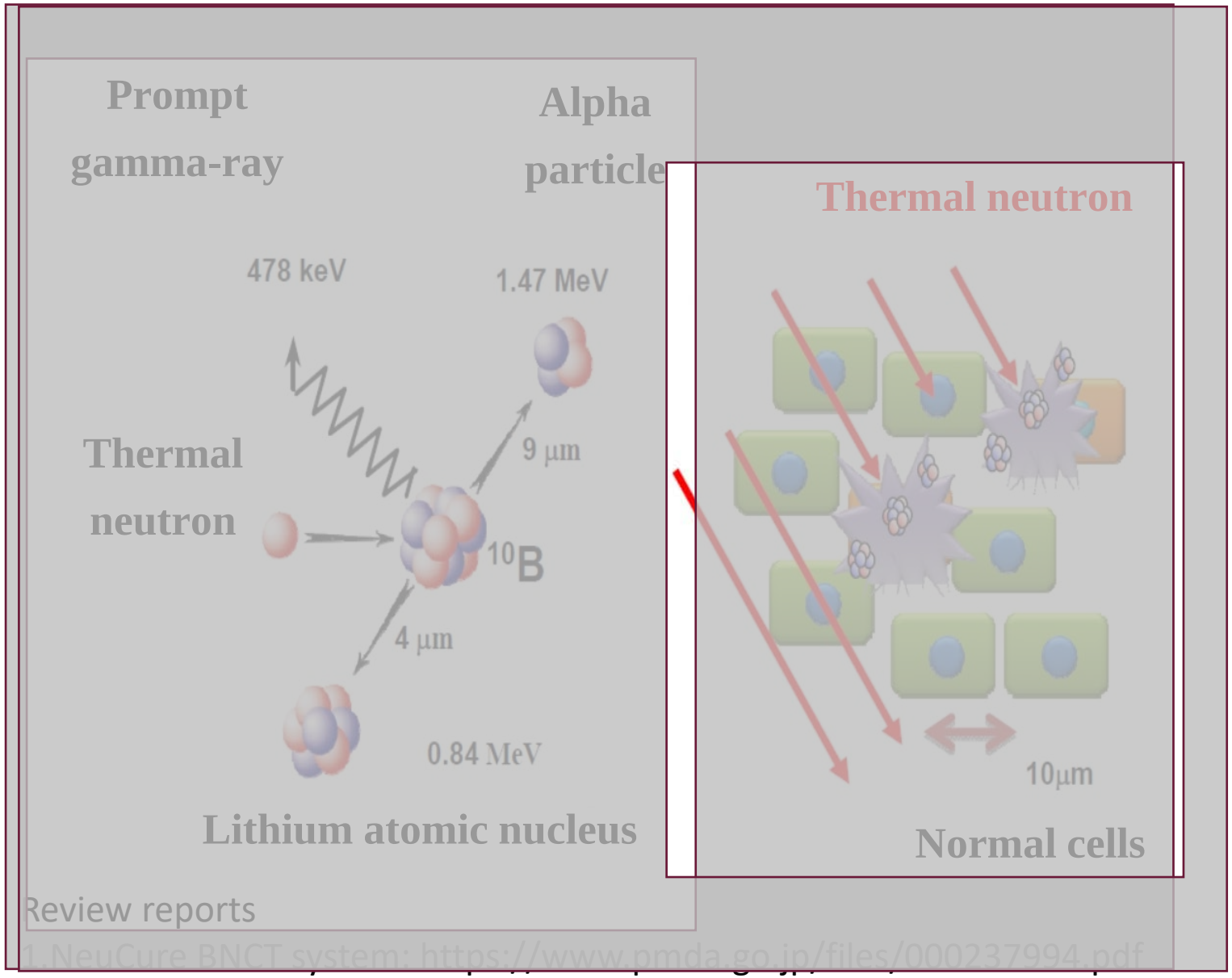


NeuCure BNCT System

It was also reviewed under SAKIGAKE Designation System.

Review reports
1. NeuCure BNCT system: https://www.pmda.go.jp/files/000237994.pdf
2. NeuCure BNCT Dose Engine: https://www.pmda.go.jp/files/000237993.pdf

Boron Neutron Capture Therapy (BNCT) (Review report 1. pp.10)



- A patient treated with a highly tumor-accumulating boron drug is irradiated with neutrons, yielding heavy charged particles (ionizing radiation).

- These heavy charged particles directly ionize molecules constituting tumor cells that have incorporated boron.

- Ionization of the molecules causes DNA damage, inducing cell death.

Review reports

1.NeuCure BNCT system: https://www.pmda.go.jp/files/000237994.pdf

2.NeuCure BNCT Dose Engine: https://www.pmda.go.jp/files/000237993.pdf

NeuCure BNCT System -Facility having 2 treatment rooms-

Appearance of neutron irradiation device (Review report 1. pp. 13)

atment rooms (Review report 1. pp.11)

Review reports
1. NeuCure BNCT s
2. NeuCure BNCT Dose Engine: https://www.pmda.go.jp/files/000237993.pdf

NeuCure Dose Engine with RayStation

System configuration of NeuCure Dose Engine with RayStation (Review report 1. pp.14)

*RaySearch Japan K.K., approval number 22900BZI00014000

Review reports
1. NeuCure BNCT system: https://www.pmda.go.jp/files/000237994.pdf
2. NeuCure BNCT Dose Engine: https://www.pmda.go.jp/files/000237993.pdf

Outline of Evaluation data -NeuCure BNCT System & NeuCure BNCT Dose Engine-

Performance and safety specifications (Review report 1. pp.61-62)

	Contents	
	Performance	Safety
NeuCure BNCT System	・the repeatability and stability of calibration of the dose monitoring system ・the linearity of the dose monitoring system, depth-dose curve, peak dose ・positioning reproducibility of the treatment bed, measurement precision of the charge monitors of charged particle beam ・irradiation field size, and time of continuous proton beam irradiation	・electrical safety ・electromagnetic compatibility ・mechanical safety ・radiation safety
NeuCure BNCT Dose Engine	・the dose distribution calculation functions (data acquisition, BNCT dose calculation, and data output) ・the dose calculation algorithm	the use by unauthorized personnel, establish data limits, protect data from tampering, and ensure accurate data transfer

Review reports

1. NeuCure BNCT system: https://www.pmda.go.jp/files/000237994.pdf
2. NeuCure BNCT Dose Engine: https://www.pmda.go.jp/files/000237993.pdf

Outline of Evaluation data -NeuCure BNCT System & NeuCure BNCT Dose Engine-

Best overall response and response rate (blinded independent central review based on “Response Evaluation Criteria in Solid Tumor (RECIST)* ver.1.1”)(Phase Ⅱ Clinical Trial) (Review report 1. pp.68 and 70)

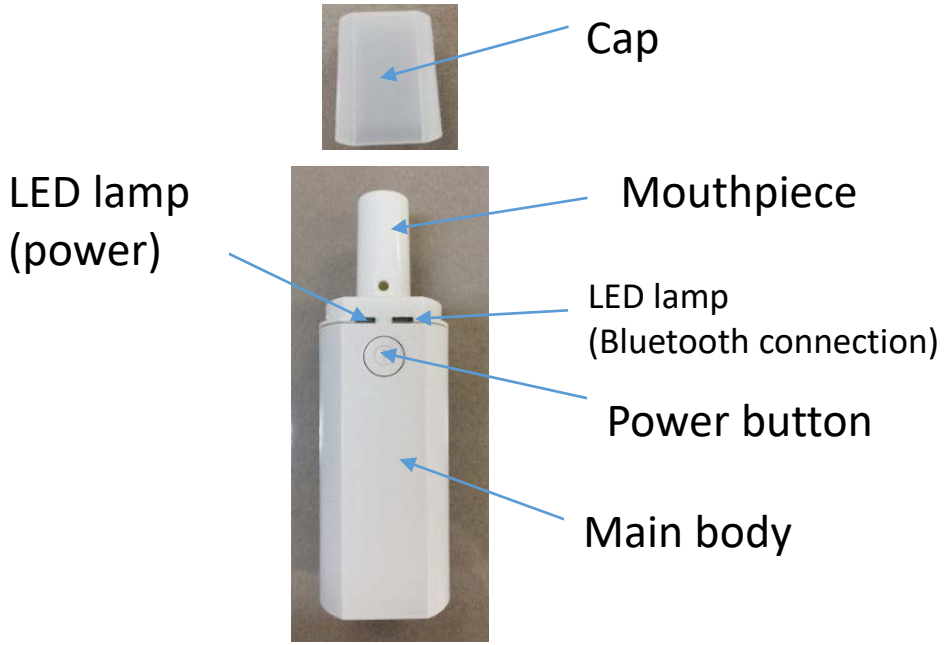
Best overall response	n (%)		
	N = 21	(a) Patients with squamous cell carcinoma (N = 8)	(b) Patients with non-squamous cell carcinoma (N = 13)
Complete response (CR)	5 (23.8)	4 (50.0)	1 (7.7)
Partial response (PR)	10 (47.6)	2 (25.0)	8 (61.5)
Stable disease (SD)	5 (23.8)	1 (12.5)	4 (30.8)
Progressive disease (PD)	0	0	0
Not evaluable (NE)	1 (4.8)	1 (12.5)	0
Response (CR + PR) (response rate [90% CI*] %)	15 (71.4 [51.3, 86.8])	6 (75.0 [40.0, 95.4])	9 (69.2 [42.7, 88.7])

The lower limit of 90% confidence interval (CI) of the response rate (51.3%) exceeded the prespecified threshold response rate (20.0%). No clear difference was observed in the response rate between these tissue types.

PMDA considered

- A certain level of efficacy of BNCT has been demonstrated in patients with unresectable, locally advanced or locally recurrent head and neck cancer.
- Localized control of the lesions is considered to have a certain level of clinical significance.

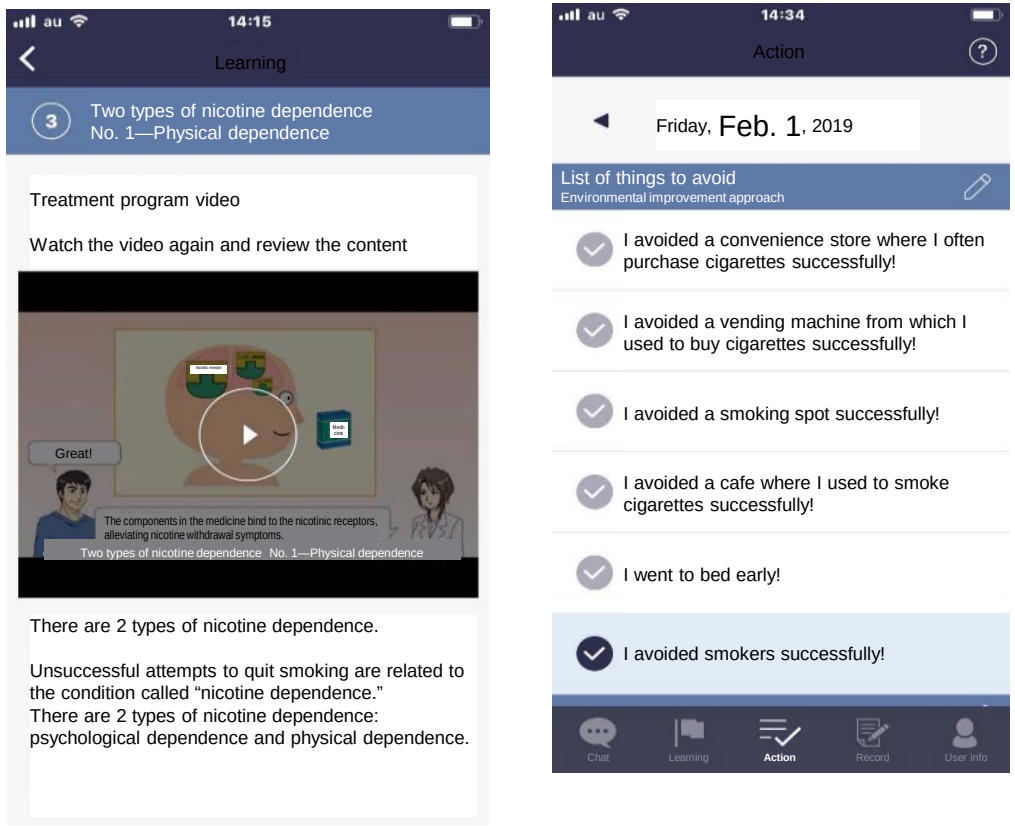
CureApp SC Digital Therapeutic and CO Checker for Nicotine Dependence (CASC system)



Appearance of “Exhaled carbon monoxide meter (CO checker)”

MAH	CureApp, Inc.
Approval Date	May 28, 2020
Indication for Use	Assistance in smoking cessation treatment of patients with nicotine dependence

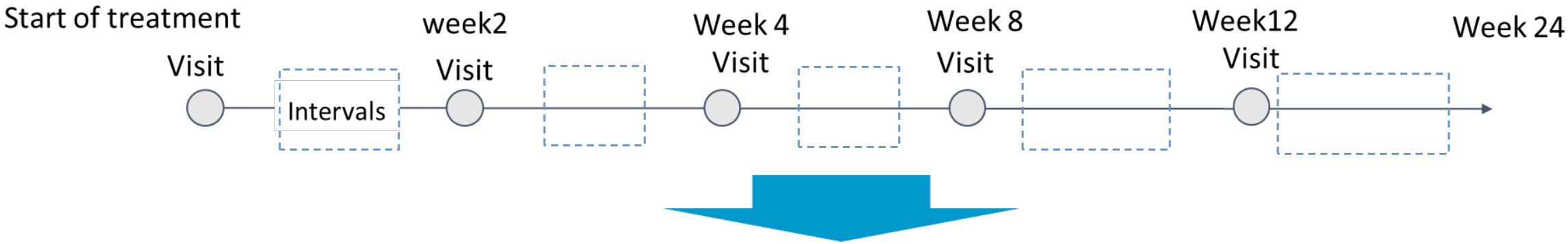
Review reports
https://www.pmda.go.jp/files/000238855.pdf



A sample display of the application for patient

Standard smoking cessation treatment program and treatment intervention by the CASC system (Review report pp.11)

<Standard smoking cessation treatment program>



<Treatment program combined with the CASC System>

Review reports
https://www.pmda.go.jp/files/000238855.pdf

Outline of Evaluation data - CASC system -

Performance and safety specifications (Review report pp.11)

	Contents	
	Performance	Safety
CO checker	・measurement range and measurement accuracy	・electrical safety ・electromagnetic compatibility ・mechanical safety ・biological safety ・software life cycle process
Application (patients app and doctor app)	・smoking cessation diary ・treatment program ・action management ・chat ・patient self-management display, support ・patient user information management ・patient data display ・diary linked with the doctor app ・treatment program linked with the physician ・treatment assistance for the physician	・software life cycle process

Outline of Evaluation data - CASC system

Results of Primary endpoint (Review report pp.19)

	CASC group	control group	Odds ratio for CAR in the CASC group to the control group
CAR during 16 weeks from Weeks 9 to 24	63.9% （182/285 subjects）	50.5% （145/287subjects）	1.73 (the logistic regression analysis) （95% CI：1.239～2.424） （p=0.001)

Among subjects who declared being abstinent, none had measured CO levels of >10 ppm at any time point.

CAR in the CASC group was significantly higher than that in the control group (p = 0.001)

Incidence of adverse events (% of subjects who developed adverse events) (Review report pp.20)

	CASC group	control group
Mild	54.7%（156/285）	47.4% (136/287)
Moderate	14.0% （40/285）	17.1% (49/285)
Severe	0.7% （2/285）	2.1% （6/285）
Serious	2.8% （8/285）	3.5%（10/285）

A causal relationship to the CASC system or the control device was ruled out for all events.

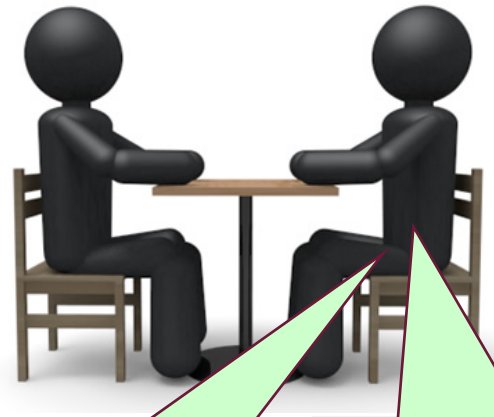
Appropriate usage of CASC System (Review report pp.26-28)

The CASC checks the exhaled CO levels of the patient measured with the CO checker!

Discussion with applicant

Is it appropriate to include patients who are exclusively used to heated tobacco products that do not raise exhaled CO level?

PMDA



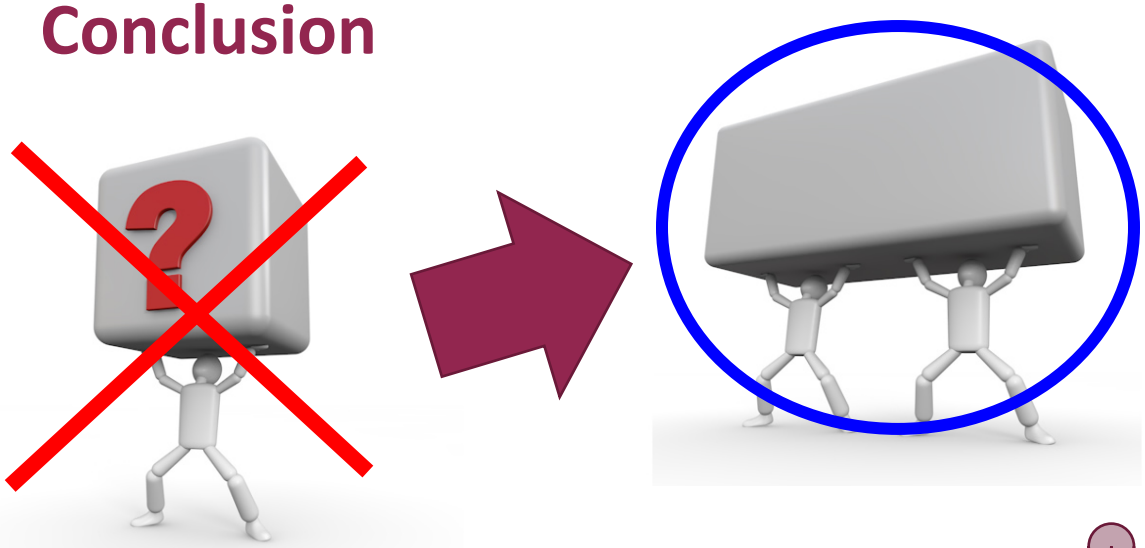
Applicant

Users of heated tobacco products that do not raise the level of exhaled CO will be exclude from the intended treatment population for the CASC system.

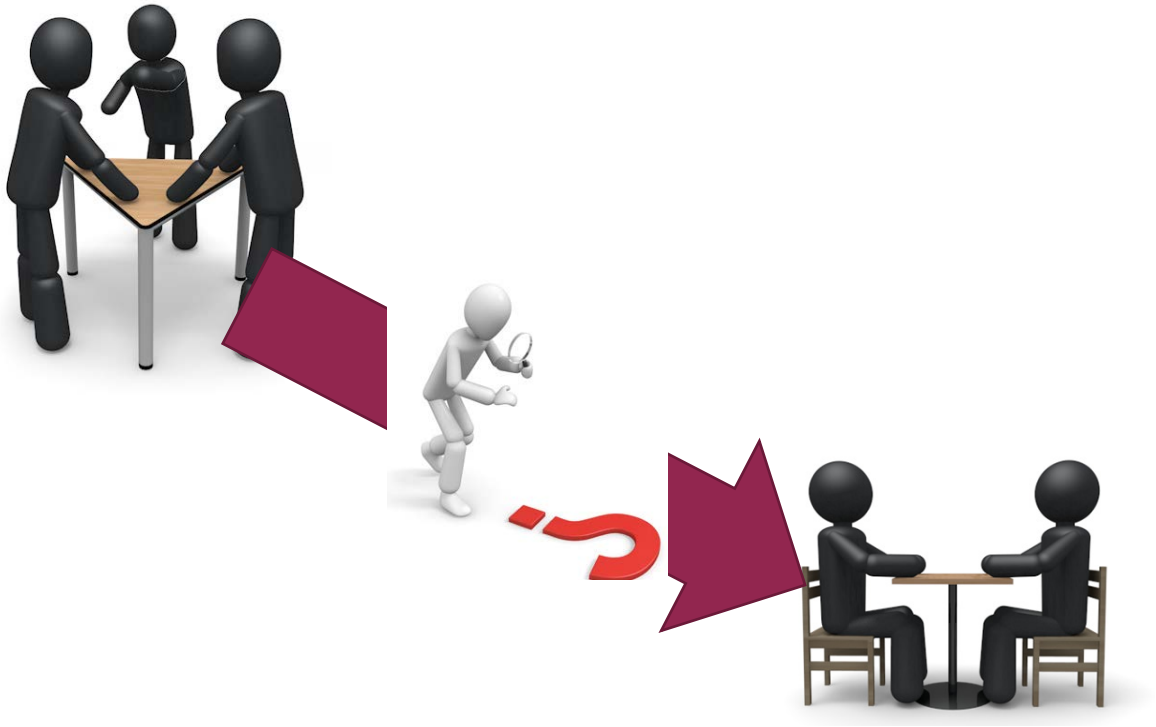
"Direction for Use" section specifies that the patient's smoking status needs to be confirmed prior to the treatment, which will be communicated via the package insert.

Review reports
https://www.pmda.go.jp/files/000238855.pdf

Conclusion



Cooperation between applicants and regulators is an important factor to realize the effective medical device review.



The fast, effective and safe introduction of innovative medical devices needs the CHALLENGE based on regulatory science.

Take home message

The medical device regulation should be an EFFICIENT AND EFFECTIVE ACTION.

- The medical device review needs effective methods to evaluate the efficacy and safety of medical devices , in order to promote the approval of good medical devices as early as possible for patients.

- The pharmaceutical authorities should have clear vision to review medical devices.

Thank you for your kind attention.