REGULATIONS FOR MEDICAL DEVICE CLINICAL TRIAL IN JAPAN

2nd Japan - India Medical Products Regulation Symposium

Yuka Suzuki, Ph.D.
International Coordination Officer
for Medical Device

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Approval Review of Medical Devices

Legal Requirement:
Medical device may be approved in case it doesn't meet any criteria of rejection.

Rejection Criteria of Approval: PMD Act 23-2-5, Paragraph 2

Item 1; it cannot be confirmed that the medical device has claimed efficacy or performance.

Item 2; The medical device has excessively harmful effect, compared to its efficacy or performance. And it is useless as medical device.

Basic Principle on Review

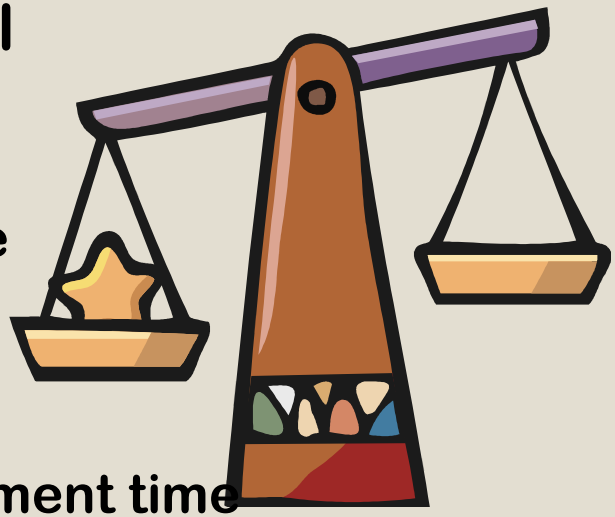
We confirm that the medical device has the claimed effectiveness and doesn't have excessive safety concerns.

Risk & Benefit

➢Balance of Risk / Benefit

Benefit = clinical utility on patient

- Cure from a disease
- Free from pain
- Preventive effect
- Less invasive
- Shortening of treatment time



Risk = harmful effect on patient

- Complication
- Deterioration of disease
- Difficulty of subsequent intervention
- Carcinogenicity
- Allergy

Clinical Evaluation

Research on Human Subjects

Study purpose is other than MA (academic purpose)

Study purpose is to file for MA

Ethical Guidelines for Medical and Health Research Involving Human Subjects	Good Clinical Practice (GCP)
The studies are conducted as a part of daily medical practice. In addition to mutual trust between patient and doctor, requirement of ethical consideration is stipulated by ministerial announcement.	The study sponsors conduct trials for profit (product development). Therefore operating procedures and system are stipulated by ministerial ordinance (GCP) in order to protect study subjects and ensure data reliability.

Purpose of Clinical Trial

- What cannot be confirmed by other than clinical study?
  → If it is confirmed by non-clinical study, clinical trial shouldn't be required.
- Would the mechanical performance be enough?
  → Sometimes it is necessary to evaluate clinical utility.

Once your concerns are specified, appropriate study design would be clarified.

We must be aware that what should be evaluated and what should be statistically guaranteed in a clinical trial!!

Not all medical devices need clinical data

Points to consider the necessity of clinical data:

- What is the difference from existing device or treatment? Will its difference cause too much uncertainty to accept without clinical data?
- Is it necessary to confirm operation procedures by the device in human?
- Should the development concept of the device confirmed by clinical data?
- Is the device high risk to use?
- Is the device permanently implanted in body?
- Is it impossible to clear a specific concern by non-clinical study?

Regulatory measure for clinical trials in Japan

The device hasn't been approved. = The device is investigational and experimental in human use

Its efficacy/safety is unknown.=Risk/benefit balance is uncertain.

→ Safety measures are needed to protect patients.

- **Before clinical trial initiation: Clinical Trial Notification**
- **After clinical trial initiation: Medical Device Vigilance**
- **Throughout clinical trial: Good Clinical Practice (GCP)**
- **During premarket review: GCP Inspection**

What is GCP?

Good Clinical Practice

It is standards to conduct a clinical trial.
The objectives are to assure 1)ethical integrity, 2)data reliability, and 3)patient safety.

These standards have been legalized in Japan (so-called J-GCPs):

- Ministerial Ordinance on Good Clinical Practice for Drugs
- Ministerial Ordinance on Good Clinical Practice for Medical Devices

GCP comparison

- **“GCP Convergence Improves Transportability of Medical Device Clinical Data” in Regulatory Focus 2013 January issue (RAPS)**

REGULATORY FOCUS

GCP Convergence Improves Transportability of Medical Device Clinical Data

By Harmonization-by-Doing Working Group 4

The safety, performance and effectiveness of medical devices are often evaluated by well-controlled clinical investigations before marketing authorization. The integrity of these clinical studies is ensured by compliance with voluntary standards or government regulations known as Good Clinical Practices (GCPs). Four GCPs are most applicable to US and Japanese marketing approvals: US Food and Drug Administration (FDA) regulations and guidance, Japanese GCP ordinances and notifications, ISO14155:2011 *Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice*[1] and ICH E6 (R1) *Guideline for Good Clinical Practice*.[2]

Consistency among GCPs is very important to allow data from a clinical investigation conducted in one country to be used for regulatory marketing approval in another country

Clinical Trial Notification (CTN)

Pharmaceutical and Medical Device Act (PMD Act)

Article 80-2, Paragraph 2: Handling of Clinical Trial

Person who intends to sponsor a clinical trial or person who intends to be a sponsor-investigator shall submit clinical trial plan (Clinical Trial Notification: CTN) to the Minister of Health, Labour and Welfare beforehand, in compliance with ministry ordinance.....

Pharmaceutical and Medical Device Act (PMD Act)

Article 80-2, Paragraph 3: Handling of Clinical Trial

Person who submitted CTN stipulated in the previous paragraph shall not ask or conduct a clinical trial, until it passes at least 30 days after its CTN submission. In this case, the Minister of Health, Labour and Welfare will conduct an inspection of clinical trial plan in order to prevent health hazards.

⇒ 30-day inspection

CTN

Stipulation in subordinate legislation: Ministry ordinance / Its enforcement ordinance

Ordinance for Enforcement of the Pharmaceutical and Medical Device Act, Article 275
Article 269 (CTN for drugs) is applied correspondingly
→ Items to be written in CTN are stipulated.

Ministerial Ordinance on Good Clinical Practice for Medical Devices (J-GCP for MD)
Article 7: Protocol
→ Items to be written in clinical trial protocol are stipulated.

Article 8: Investigator's Brochure (IB)
→ Items to be written in IB are stipulated.

What should be checked in CTN...

Pharmaceutical and Medical Device Act (PMD Act)
Article 80-2, Paragraph 3: Handling of Clinical Trial
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Confirmation of safety of individual study subject, and ethical integrity

Caution: applicant sometimes mistakenly believes that CTN clearance means we endorsed validity of efficacy evaluation in the trial.
In case applicant has a concern about scientific validity of efficacy evaluation , it should be discussed in a clinical trial consultation beforehand.

Medical Device Vigilance before marketing authorization

Reporting of Adverse Drug Reaction (ADR) / Adverse Device Effect (ADE)

- **PMD Act, Article 80-2, Paragraph 6: Handling of Clinical Trial**

Person who sponsored the clinical trial or person who is the sponsor-investigator shall report to the Minister of Health, Labour and Welfare, in case that they recognize any disease, injury, or death which might be caused by study drug/device.

- **PMD Act, Article 80-4: Conduct of inspection by PMDA related to CTN**

The Minister of Health, Labour and Welfare may order PMDA to conduct organized assessment of the reports stipulated in PMD Act, Article 80-2, Paragraph 6.

When the Minister of Health, Labour and Welfare ordered PMDA to conduct organized assessment, the sponsor **shall report ADEs to PMDA.**

ADE reporting in clinical trial for unmarketed device

Expectedness	Seriousness	Domestic	Non-domestic Origin
Unanticipated	Death or life-threatening	Individual Case (within 7days) → Individual (within 7d) & Annual	Individual Case (within 7days) → Individual (within 7d) & Annual
	Other Serious	Individual Case (within 15days) → Individual (within 15d) & Annual	Individual Case (within 15days) → Individual (within 15d) & Annual
Anticipated	Death or life-threatening	Individual Case (within 15days) → Individual (within 15d) & Annual	Individual Case (within 15days) → Individual (Within 15d) & Annual
	Other Serious	none → Annual report	none → Annual report
Malfunction	An incident which may cause serious event	Individual Case (within 7, 15days) → Individual (within 30d) & Annual	Individual Case (within 7, 15days) → Individual (within 30d) & Annual

- "→" denotes that it is not implemented yet but effective from July 1st, 2014.
- Foreign corrective action report: within 15days
- Research report: within 15days

ADE reporting in clinical trial for marketed device

Expectedness	Seriousness	Domestic	Non-domestic Origin
Unanticipated	Death or life-threatening	Individual Case (within 7days) → Individual (within 7d) & Annual	Individual Case (within 7days) → Annual report
	Other Serious	Individual Case (within 15days) → Individual (within 15d) & Annual	Individual Case (within 15days) → Annual report
Anticipated	Death or life-threatening	Individual Case (within 15days) → Individual (within 15d) & Annual	Individual Case (within 15days) → Annual report
	Other Serious	none → Annual report	none → Annual report
Malfunction	An incident which may cause serious event	Individual Case (within 7, 15days) → Individual (within 30d) & Annual	Individual Case (within 7, 15days) → Annual report

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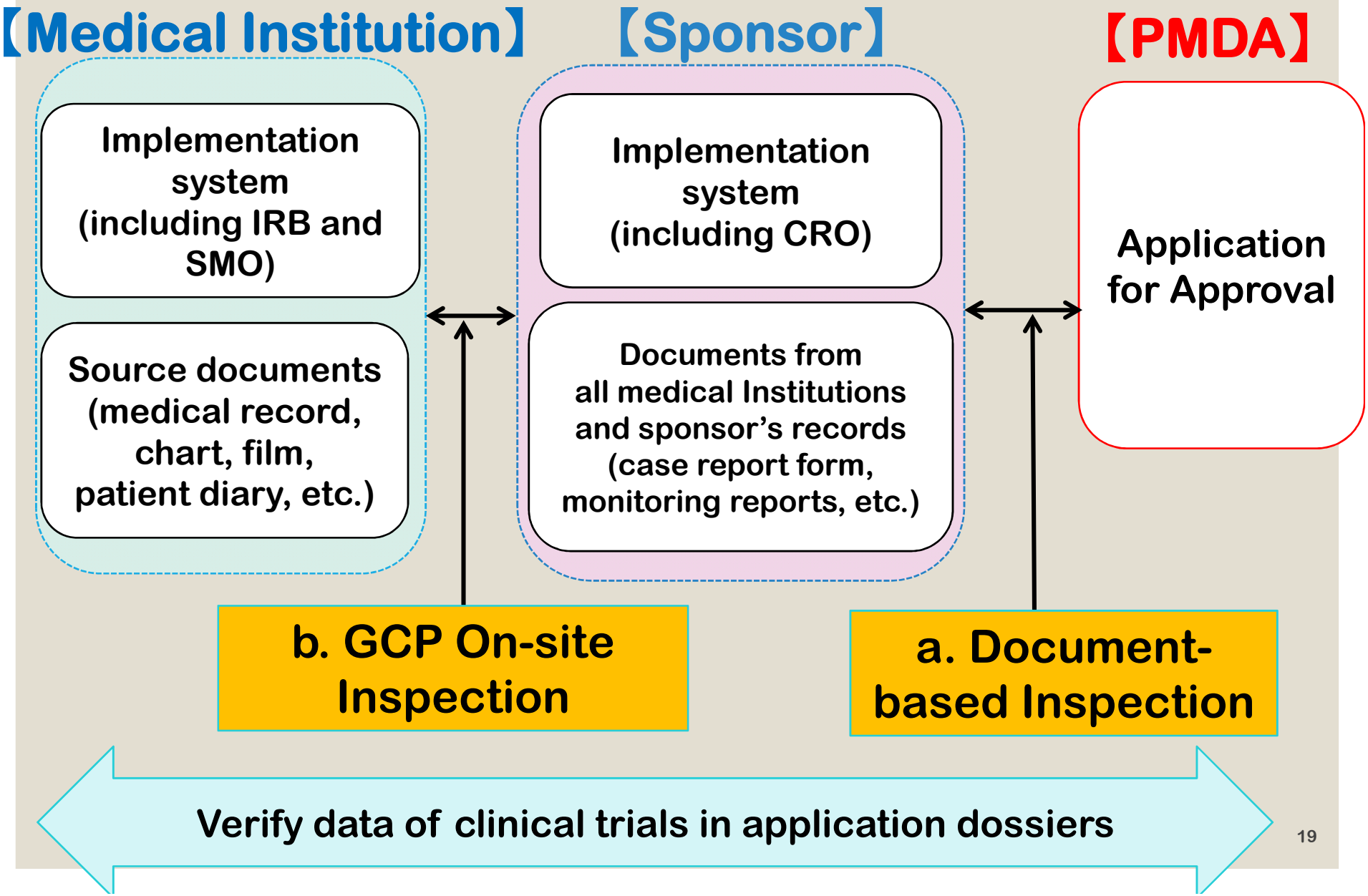
GCP Inspection



Acceptance of Foreign Clinical Data

- **MHLW/PMDA have accepted foreign clinical data for years, as long as it is sufficient enough to evaluate the clinical safety and efficacy of the device on Japanese population under Japanese medical practice/environment.**

Number of devices approved with Clinical Data Review

	2009	2010	2011	2012	2013	2014	2015
Foreign Clinical Data only	32	29	38	23	34	28	23
Both Foreign and Japanese Clinical Data	6	2	5	3	8	2	11
Japanese Clinical Data only	14	19	14	23	24	11	24

(Source: PMDA Annual Report)

Handling of clinical study data on medical devices which was carried out in foreign countries

(Notification No. 0331006 dated March 31, 2006)

<Points>

1. The CT has to be done in a country/jurisdiction which has good quality GCP standards as Japanese device GCP. The CT should be compliant with the local GCP.
2. The trial sites have to be ready for accepting GCP inspection by Japanese authorities.
3. If there are differences between Japanese and local GCPs, an applicant should submit a list of differences and its opinion on influence of the differences on reliability and quality of the data.

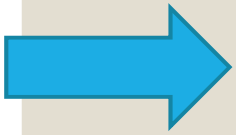
Points of concern to use foreign clinical data

- The clinical positioning of the device should be clarified.
- The efficacy and safety of the device should be assessed by the results of clinical data.
- It is necessary to consider whether the clinical data can be extrapolated to the Japanese population.

Other considerations in using foreign clinical data

- Racial difference
- Existing therapy and its outcome
- Difference of combination therapy
- Healthcare environment

➢ It is necessary to examine how the difference between the foreign country and Japan affects the evaluation of the device.



PMDA provides “Consultation on Clinical Evaluation” for confirmation of abbreviation of clinical trial in Japan before application.

Thank you for your attention!!

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

2nd India – Japan
Medical Products Regulatory Symposium on 24.04.2017
@ Tokyo, Japan

Indian Scenario: Clinical Trials in Medical Devices

V. Sashi Kumar – Managing Director
PHOENIX MEDICAL SYSTEMS PVT LTD. INDIA

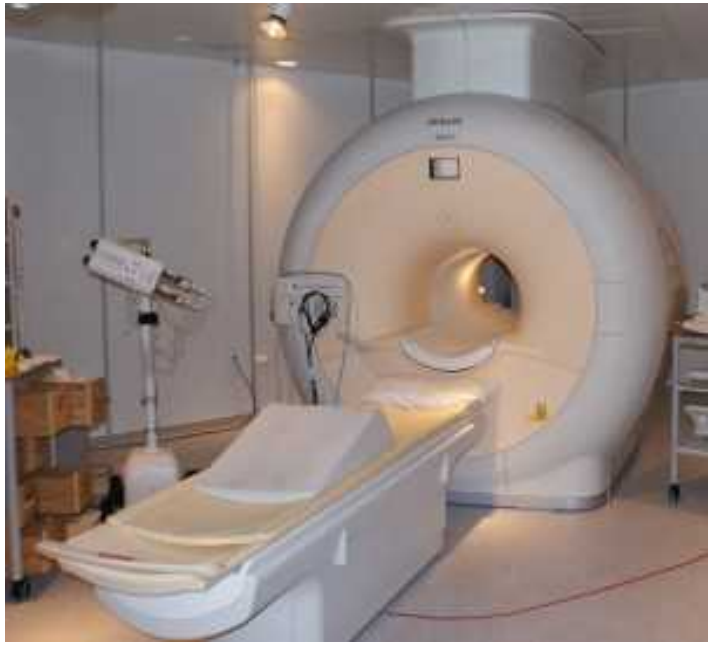
Phoenix Medical Systems

Infant Care

Maternal Care

Assistive Technology

Medical Devices-A mixed Bag..



CE

What makes Device Trials Unique?

- Trials tend to be smaller than drug trials
- Some novel, many “me-too”
- Many difficult to blind, randomize, control
- Many depend on physician technique
- Device modifications occur during trial
- Endpoints highly diverse
- Typically, single pivotal trial follows feasibility stage(s)
- Designed to support a “reasonable assurance of safety and effectiveness” for the marketing application

Clinical Trials, Snapshot – India

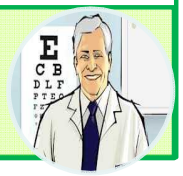
Abundant Patient Pool, High quality talent and best-in class infrastructure

- Treatment Naïve Patients
  - ~2 mio STEMI annually
- Faster completion of the studies
  - ~6 mio recruitment in CV
- Rising Burden of Chronic Diseases
  - ~45-60 mio CHD population

Patient Pool

- Trained & Experienced clinical research professionals
- Well qualified & Trained Physicians
- Medicine, Pharmacy & Science Graduates
- Compliance with Global Ethical & Regulatory Standards

Talent Pool



- World Class Healthcare infrastructure
- JCI NABH Accredited Hospitals
- CAP NABL Accredited labs
- Broadly developed IT Infrastructure
- Core Lab presence
- Cost Effectiveness

Infrastructure

Hot spot for DM

- Highly developed process innovation skills
- Credible data quality
- Software options e.g. Oracle Clinical, BizNet, Clinion etc.
- Range of services like data entry & verification, Statistical analysis, medical writing etc.

Clinical Trials, Snapshot - Medical Devices, India

- Total number of trials: ~40
- Total number of patients: ~16000
- Regulated Trials: 14 %
- Phase IV : 86 %
- Global Trials: 62 %

  - Source – Clinical Trial Registry of India
  - Includes MDT, BSC and ABT

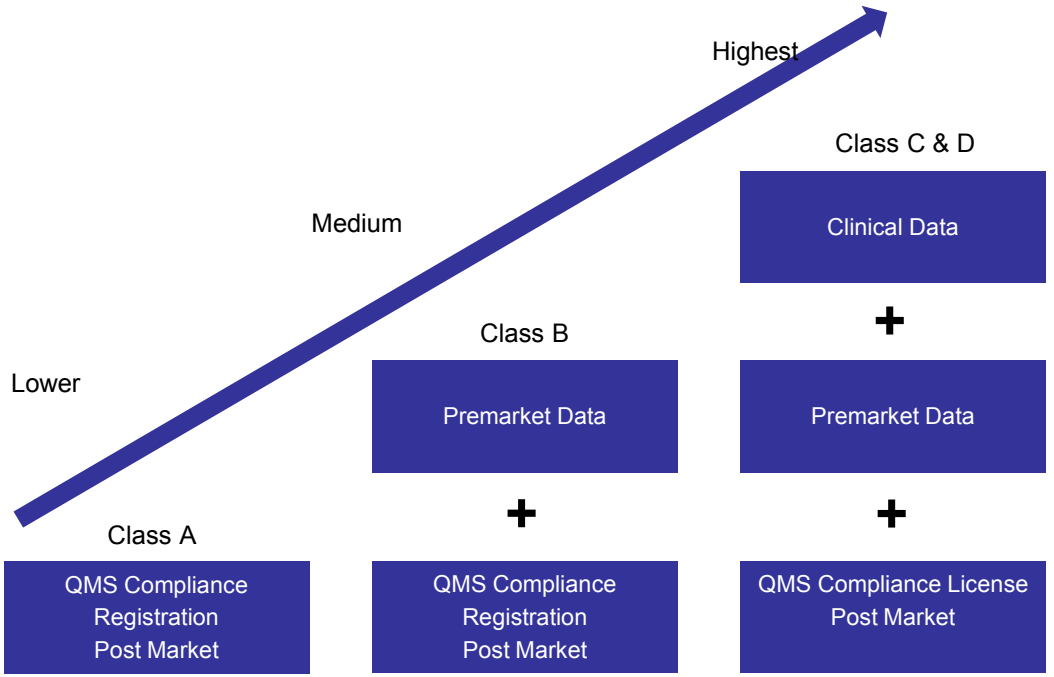
India Regulations

Regulatory Requirements for Approval

Regulatory Compliance	Class A	Class B	Class C	Class D
QMS	√	√	√	√
Device Master File		√	√	√
Biocompatibility Data		√*	√	√
Animal Testing			√	√
Clinical Data			√	√

*Only for invasive and implantable devices

Regulatory Scrutiny Increases with Risk



➢ Medical Device Testing Centre: The Central Government may, by notification, establish or designate Central medical devices testing center or laboratory or any other center for testing and evaluation of medical devices.

Licence to import or manufacture for marketing an Investigational devices / New IVDs

Investigational Medical Device	New IVD
Application to CLA to obtain permission to conduct Clinical Investigation	Application to CLA to obtain permission to conduct Clinical Performance Evaluation
Permission may be granted to conduct	
1. Pilot Clinical Study 2. Pivotal Clinical Study	Clinical Performance Evaluation
Submission of the Clinical data generated	
Submit **CI** data generated in prescribed format to CLA	Submit CPE data generated in prescribed format to CLA
Permission Approval of New or investigational Device / IVD	
On being satisfied with the clinical data generated CLA may approve the product .	
Application to market an approved Investigational device or new IVD	
After above approval, the applicant shall need to apply for grant of Import License or Manufacturing License as per the prescribed procedure.	

CT NOC approval- 90 days + 30 days if query The last step after CT is IL approval- 120 days + 30 days if query

Clinical Investigation of Medical Device (1/3)

- Clinical investigation of investigational medical device in human participants should be conducted in accordance with these rules and with the **permission granted by the Central Licensing Authority (CDSCO).**

- **No permission for conduct of academic clinical study on registered or approved medical device** shall be required, where,-
  - the investigation is approved by the Ethics Committee; and
  - the data generated shall not be used to furnish it to the Central Licensing Authority for manufacture or import to market investigational medical device in the country.

- Medical device requiring clinical investigation but claiming **substantial equivalence to a predicate device shall not be marketed unless the Central Licensing Authority has approved it**.

- Clinical investigation shall be **registered with the Clinical Trial Registry of India** before enrolling the first patient for such clinical investigation

Clinical Investigation of Medical Device (2/3)

- The Central Licensing Authority, will grant permission to conduct clinical investigation:
  - Provided that the Central Licensing Authority may **request additional documents wherever necessary within ninety days (plus extended period of thirty days)** from the date of application
  - Provided that if the applicant has **not furnished** the required information sought by the Central Licensing Authority, **within ninety days from the date of intimation, it may reject the application for reasons to be recorded in writing**.

- Where, a **free sale certificate has already been issued** in respect of any medical device by the national regulatory authority or other competent authority of any of the countries namely, **Australia, Canada, Japan, European Union Countries, or the United States of America, a licence shall be granted under sub-rule (1) to the applicant without carrying out clinical investigation.**

- Results of **clinical investigation may not be required to be submitted where the investigational medical device is approved by the regulatory authorities of either the UK or USA or Australia or Canada or Japan** provided:
  - Device has been marketed for **at least two years** in that country
  - **No evidence of any difference** on performance in Indian population
  - **Mandatory to conduct post marketing clinical investigation** with the objective of safety and performance of such investigational medical device as per protocol approved by CDSCO.

Clinical Investigation of Medical Device (3/3)

- **Annual status report of each clinical investigation**, as to whether it is ongoing, completed or terminated, shall be submitted to the Central Licensing Authority by the sponsor.
- In case of **termination** of any clinical investigation, the detailed reasons for the same shall also be **communicated to the Central Licensing Authority within thirty days of such termination**
- Information about any report of **suspected unexpected serious adverse event occurring during clinical investigation should be submitted to the Central Licensing Authority within 15 days** of the sponsor coming to know about its occurrence
- **In case of an injury or death of the subject during clinical investigation, complete medical management and compensation should be provided to the subject by the applicant as per compensation rules**
- The **first patient should be enrolled in the clinical investigation within one year from the date of grant of permission**, failing which prior permission from the Central Licensing Authority is required

- Ministry of Health and Family Welfare, India has notified Medical Devices Rules, 2017 on 31st January 2017.
- Rules shall come into force with effect from 1st January, 2018.

Our “Ask”

- Definition of Medical devices should include a grandfathering clause “Provided that the Medical Device is already being marketed in India and after new rules being regulated, clinical investigations or evaluations should not be a pre-requisite for grant of registration”
- The wordings used in “Investigational Medical Device” definition is not harmonized with that of global definition. This definition is currently mapping the definition of new drugs under Rule 122(e) – new material and major design change is not explained anywhere
- In case of Devices, approved & marketed in the countries listed (GHTF)- clinical evidence with an undertaking to conduct Post market clinical investigation (PMS) in India should not be mandated- if a substantial global clinical data on safety and performance is available why not a waiver.
- In the list of exempted countries UK, USA, Japan, Canada and Australia included. EU also needs to be included as many advanced technologies are first approved in EU. This can cause potential delay in access to Indian patients.
- Industry seeks development of a Clinical Trial ecosystem through setting up of bovine / porcine animal labs for pre-clinical studies.

Thank you

V. Sashi Kumar – Managing Director

PHOENIX MEDICAL SYSTEMS PVT LTD, INDIA

Email : sashi@pmsind.com

Mobile : +91 9840033951