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Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

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22nd Asian Harmonization Working Party Annual Meeting

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4-8 December, 2017 I New Delhi

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Overview of Medical Device Clinical Investigation Regulations in Korea

5st Dec. 2017

Mi-jung Son

Deputy Director of Medical Devices Policy Division
Korea Ministry of Food and Drug Safety

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Mi-jung Son

Deputy Director
Medical Device Policy Division
Korea MFDS

- In charge of legislating and streamlining laws & regulations on clinical & non-clinical trials for medical devices

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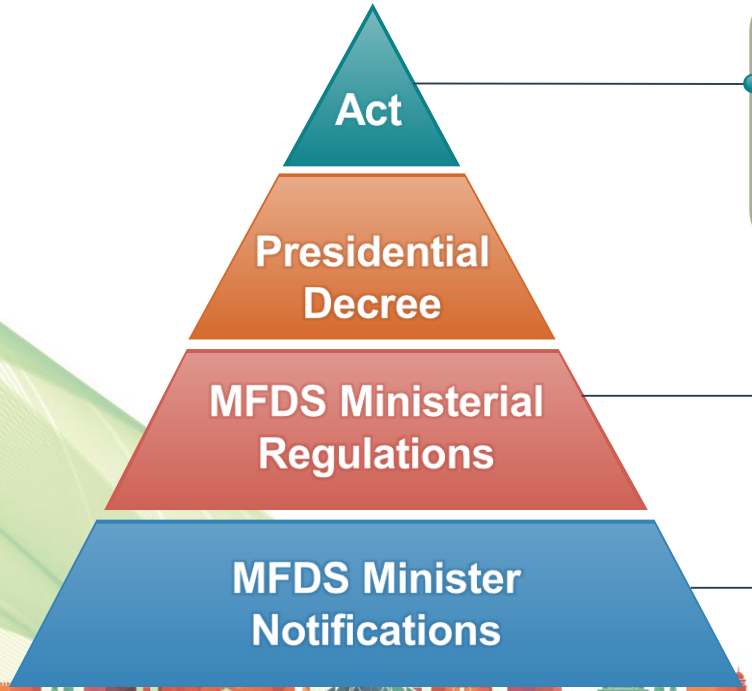
Structure of MFDS Medical Device Regulations



- Medical Device Act Article 10
  - Clinical Study Plan Approval
  - Quality Management System Requirements(GMP)
  - Clinical Study Institutions(Sites) Recognized by MFDS
  - Human Subject Protection, Institutional Review Boards
  - Records and Reports

  } GCP

- Enforcement Article 20, 21, 24
  - Study Plan Approval Elements & Requirement
  - Standards and Procedures, Etc. for Designation of Clinical Trial Institutions
  - GCP Requirements

- Clinical Study Plan Approval
- Clinical Study Institutions Accreditation
- Management of records and documents

Definition and Classification of Clinical Trials for Medical Devices

- A test or a study using human subjects in order to prove safety and effectiveness of the medical device used in a clinical trial/study

Investigator Initiated Trials (IIT)

- Clinical researchers **are performing a clinical trial/study autonomously without sponsors**

Sponsor Initiated Trials (SIT – individual or organization)

Feasibility Study

- **Clinical trial/study with a few subjects during a short period** is done in its early development stage of medical device for investigating safety and effectiveness

Confirmatory Study

- Clinical trial/study is designed and performed with **statistically significant numbers of subjects** for confirming safety and effectiveness

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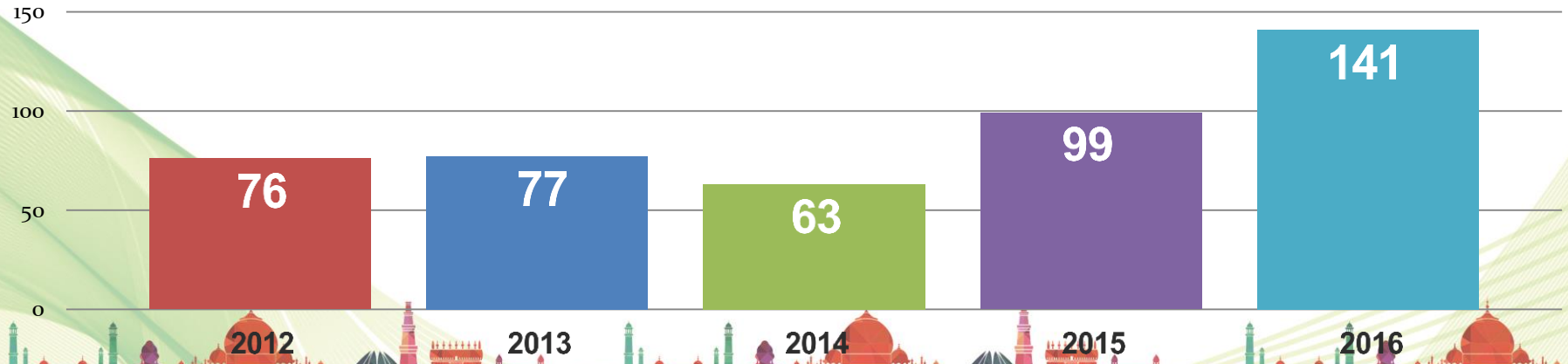
Clinical Trial Approvals by year

Increased number of clinical trial approvals for medical device approved by MFDS

(2012)	(2013)	(2014)	(2015)	(2016)
76	77	63	99	141



Analysis for Clinical Trial Approvals for Medical Devices

Clinical trials for domestically developed products on the rise

- A 60% year-on-year increase in manufacturing
- Feasibility studies (22cases, △83.3%), Confirmatory studies (68cases, △838.8%), investigator-initiated studies (38cases, △100%)
- apparatus·machine(50cases), medical products(30cases), reagents for in-vitro diagnostic use(48cases)

An uplift in clinical trials for IVD products to be regarded as medical devices

- A 43.6% year-on-year increase (manufacture – increased by 60%, import – decreased by 11%)

Anticipated an increase of clinical trials for the applicable devices with the 4th industrial revolution

- Anticipated a rapid increase of clinical trials for the applicable medical devices to rapidly increase for the emergence of AI, Rehabilitation Robots, 3D printed devices
- 3 approval cases for protocol based on artificial intelligence (‘17.9)

Institutions Designated as Clinical Trial Centers for Medical Devices

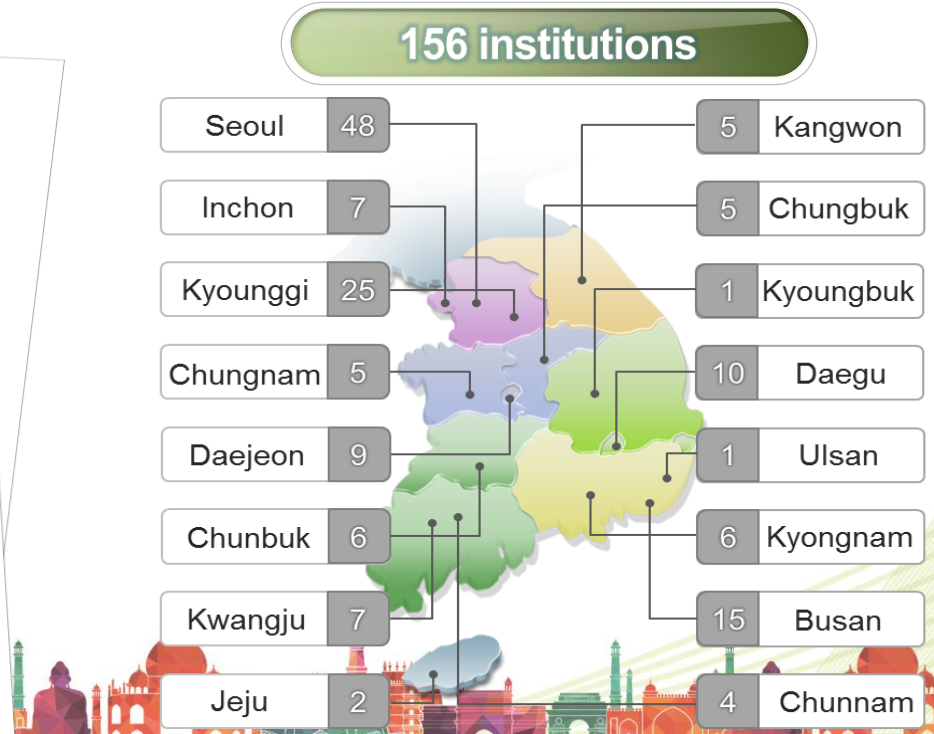
Clinical trial approvals in accordance IRBs

① IRBs	② Shared IRBs	③ Using shared IRBs
134	14	8

① IRBs reviewing clinical trials for medical devices only within the applying institution

② Shared IRBs reviewing clinical trials for medical devices within its own facility and clinical trials in other institutions

③ IRBs which cannot review clinical trials of medical devices in the applicable institution, resulting in reviewing in shared IRBs mentioned above.



Clinical Trials Management Systems

Pre-Approval Management

- Approval of Clinical trials
- Accreditation of Clinical Trial Institutions

Post-Approval Management

- Management of
  - Safety informations and ADE reports
  - Annual reports
  - Termination reports
  - Study reports
- Inspections

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Medical Device Clinical Investigation Process

Sites Accreditations		30 working days	Inspection		
MFDS	GMP Requirements GLP or Testing Institution recognized by MFDS	MFDS Review -Protocol(Informed consent statistical Anal.plan -Data monitoring Plan	MFDS GCP Requirements - Investigation site - IRB - Sponsor - Investigator		Review (80days)
Sponsor (Manufacturer & Investigator)	Conduct Preclinical Studies (In vitro & In vivo testings) - Develop Clinical Strategy - Study Design Investigator /site CRO	Develop Investigation Plan & Submission - Protocol - Preclinical Study data Agreement with site/CRO/vendors IRB Review - Monitoring plan - Clinical GMP certification	Prepare Obtain Approval from MFDS & IRB - Data Mgmt plan - Statistical Anal.Plan	Initiate & Manage Enroll Patients Monitoring QC Audit Record & documents	Study Completion Report -Adverse Events	Submission Product Approval Application with Final clinical Report

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2. Protocol Approvals and Required Documents

Approval Procedure for Clinical Trial Protocol

Application

- Clinical Trial Plan (Protocol)
- Technical Document
- QMS for Clinical Trials

Review & Approval

- Review Period (30 working days)

Clinical Trial

- Approval of clinical trial plans

- **Who Must Apply** : A person who is planning to perform clinical trials for medical devices is required to get an approval from the Minister of KOREA MFDS beforehand.
- **When to Apply** : Prior to initiate studies – MFDS Approvals and IRB Approvals

Approvals for Clinical Trial Protocol

Clinical trials to be approved

- Clinical trials investigating or studying human subjects to prove safety and efficacy of medical devices that are not approved
- Clinical trials investigating and studying human subjects to prove safety and effectiveness of the intended use of devices other than approvals for medical devices on the market (indications, applied region)

Clinical Trials exempted from MFDS approvals

- Clinical Trials to investigate adverse device events and observation of clinical efficacy for approvals of medical devices on the market
- Clinical trials to collect data on safety and efficacy related to approved performance and intended use of medical devices on the market
- Clinical trials for IVD medical devices designated by the ministry of MFDS

Required Materials to Apply for Clinical Trials

Protocols

- Site Selection
- Investigator, sponsor and monitor responsibilities
- Investigational device description and method of use
- Study objects
- Study design and method
- Inclusion/Exclusion Criteria
- Number of Samples, statistical design, analysis plan
- Inspection and observation item
- Evaluation Criteria
- Primary and secondary endpoints
- Expected Adverse Event
- Safety Plan
- Informed Consent from
- Policy for the safety and protection of human subjects

Technical Documents

- Technical Document
  - Intended Use
  - Physical and Chemical properties
  - Electric and Mechanical Safety
  - Biological Safety
  - Radiation Safety
  - Electromagnetic Interference
  - Performance
  - Stability and sterilization
- Safety and Effectiveness Document
  - Origin or Course of development
  - Usage status overseas
  - Comparison with similar medical devices

GMP

GMP Certificate

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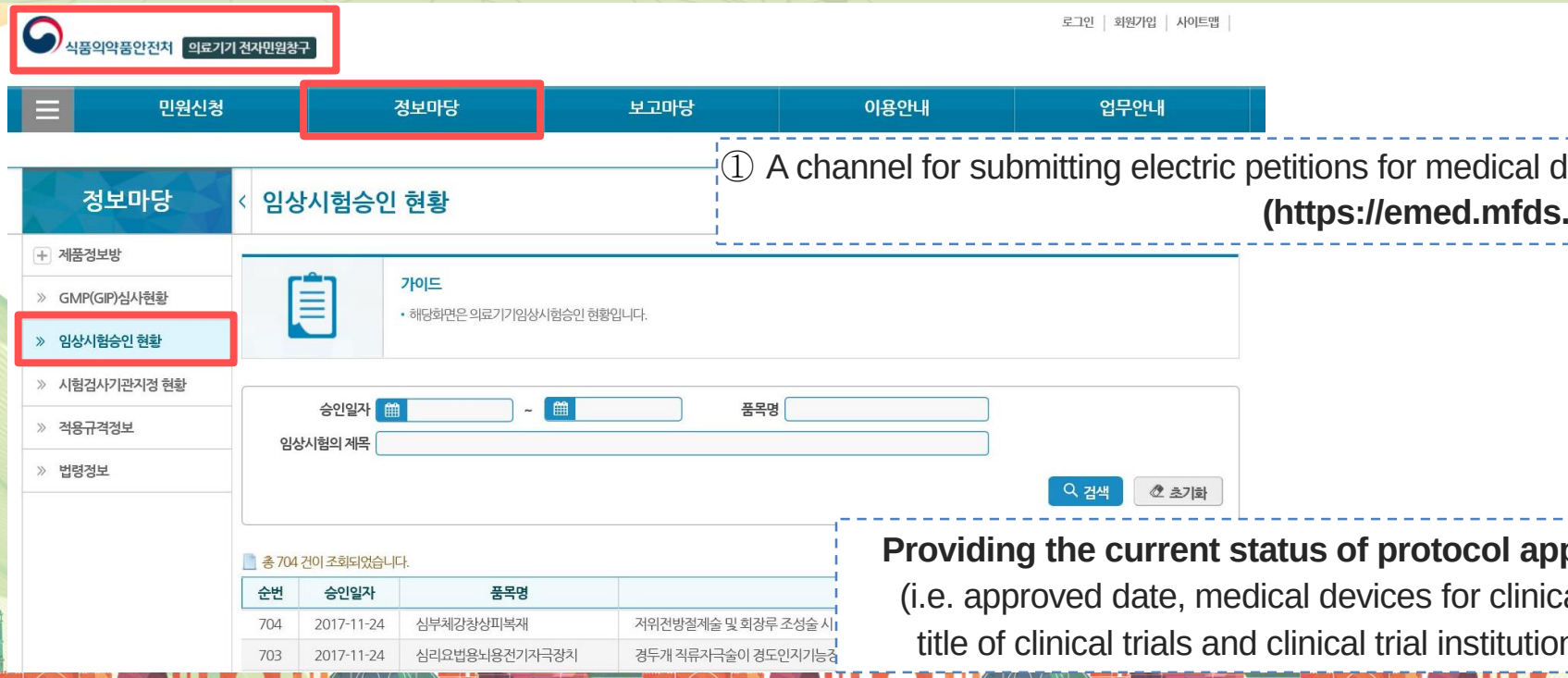
Established a System Publishing Clinical Trials Approved



① A channel for submitting electric petitions for medical devices **(https://emed.mfds.go.kr)**

Providing the current status of protocol approvals
(i.e. approved date, medical devices for clinical trials, title of clinical trials and clinical trial institutions, etc.)

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3. Good Clinical Practice

Good Clinical Practice (General Requirements)

- Comply with approved plan in a safe and scientific manner
- Only at the sites recognized by MFDS
- Select qualified investigator with expertise and ethical qualities
- Informed consents and human subject protection
- Not to be used other than clinical study purpose
- MFDS/IRB Approval
- Initiated within 2 years after approval
- Sponsors should provide investigator with the information to conduct properly
- Annual Reports
- Medical Devices manufactured under GMP
- Adverse Events Report and required records and reports
- Responsibilities of IRB, manufacturer, sponsor, investigator, monitor responsibilities
- Investigational Medical devices and labeling
- Monitoring of study

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Good Clinical Practice

Clinical Trial Institutions & IRBs

Clinical Trial Institutions

- Facilities
- Human Resources
- System
- SOP
- IRBs

IRBs

Protocol Approvals shall remain its independence

- Pre-notified meeting
- SOP renewals
- intensive Review

Sponsors

Plan, Monitor, Audit, Report

- Monitoring & Auditing
  - Same CRF and Source data
  - Correcting protocol violations
  - Training for CRA
- Report on safety issues and take necessary actions
- Quality Management of Study
- Selecting investigator
- Device control & Protect Human subject

GCP

Investigators

Implementing clinical trials

- Qualified by training and experience
- Understand & Follow Protocol
- Assign each role in trials
- Keep subject's agreement procedures
- Strengthening collaboration with IRB
- Protect Human Subject
- Intact relationship with Sponsor
- Informed Consent
- Device Control
- Records & Report

MFDS

Accredited Institutes Approval & Inspection

- Inspections and Corrections, and improving regulations
  - Strengthening pre-, post-inspections
  - Updating related regulations
- Standardization & updating
- IRB-related regulations

Informed Consents and its Exemption (leftover specimens)

- Clinical trials can be performed without written informed consents in case of clinical trials using leftover specimens when it fulfills the following requirements
  - Where it is practically impossible to obtain informed consent from a subject;
  - Where there is no particular reason for subjects to reject consent; and
  - Where the risk to subjects by taking part in the investigation is extremely low

Leftover Specimens

- A human sample left from a use in a medical institution for diagnostic or treatment purposes
- A human sample left from extraction and use for a specific research purpose and for which a comprehensive consent was obtained from its donor on its use for other secondary purposes

Private information of the subject who offered the specimen should be kept in confidential in case of clinical trials using residual specimens without written informed consents

Definition of Adverse Event Reporting

- **Adverse Event, AE**

  It refers to every unintended symptom and disease of subjects during clinical trials (it does not necessarily require to have cause and effect relations with medical devices for clinical trials)

- **Adverse Device Effect, ADE**

  It refers to every harmful and unintended reaction derived from medical devices for clinical trials (it cannot deny the interrelation with medical devices for clinical trials)

- **Serious AE·ADE**

  Adverse Events or Adverse Device Effects caused by medical devices used for clinical trials that fall under any of the followings

  1) In case risks to human lives or death
  2) In case there needs to extend duration of hospitalization or need to be hospitalized
  3) In case of permanent or serious impairment, and malfunction
  4) In case of malformation or abnormality of fetuses

- **Unexpected Adverse Device Effect, UADE**

  Aspects or risk level differs depending on adverse device effect based on relative information on available medical devices such as investigator's brochure or attached documents of medical devices

- **Unexpected serious ADE(Adverse Device Effects)**

  Subject to reporting to the MFDS

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Adverse Event Reporting Process

Approval for Protocol

PI(Principal Investigator)

1

Sponsor

2

MFDS / IRB

Adverse Events

1

- Who to report : Serious Adverse Events (SAE)
- When to report : within period specified in the protocol
- What to report : medical device adverse events

2

- Who to report : Serious and unexpected Adverse Device Effects
- When to report
  - life-threatening cases or death: within 7 days
  otherwise: within 15 days
- What to report : medical device adverse events

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4. Inspections and Designating Clinical Trial Institutions

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Types of Inspections

Periodic Inspection

Periodic post-market inspection for clinical trial centers (evaluated depending on levels)

Product Inspection

Whether to comply with KGCP for the product item applied for approval, etc.

For-cause Inspection

An on-site inspection triggered by social issues, statistical analysis, medical device adverse events and civil petitions, etc.

Strategy of Inspections

- Inspection of on-going and completed clinical trials
- Selection of trials based on risk assessment process and SIT
  - Development phases in the drug or device
  - Product types (Implant, Stent, Bone graft, Electrocardiographs, other)
  - Complexity of the trial design
  - Number of subjects enrolled
  - Therapeutic indications or areas
  - Study population (pediatric, other vulnerable, general)
  - Number of serious unexpected adverse medical device reaction at the clinical trial sites)

Administrative Disposition after Inspections

Violation

Cases that have adversely affected safety, rights and well being of the subjects, and quality and integrity of the clinical trial results

Correction

Cases that might adversely affect safety, rights and well being of the subjects, and quality and integrity of the clinical trial results

Caution

Cases that are not likely to adversely affect safety, rights and well being of the subjects, and quality and integrity of the clinical trial results

Recommendations

Suggestions on how to improve quality of clinical trials for the future and to reduce the potential of deviation

Administrative Disposition / Accusation

Administrative Disposition

: warning, changing PI, suspension on the role of “designated IRB”, 3 to 6 months suspension on implementing the applicable clinical trials, and cancelling the designation, etc.

Accusation

: sentenced to at most 3 years or fined no more than 30million won

Procedure to Designate Institutions for Clinical Trials

- Definition of Clinical Trial Centers for Medical Devices
  - Institutions equipped with required facilities and taskforce for implementing clinical trials among medical institutions

    - Clinical trials for medical devices must be implemented in clinical trial institutions designated by the ministry of MFDS

Application

- License for opening medical institutions
- SOP of clinical trial institutions and IRBs
- materials, etc. on how the IRB is composed

Document Review and Inspections

Processing period
-15 working days

※ institutions designated as clinical trial institutions for drugs
– 12 working days

Designation

Issuing a letter of designation

Required Documents to be Designated as Clinical Trial Institutions

- Required for submissions to be designated as a institution for medical device clinical trials
  - License to launch medical institutions
  - Regulation on administrative procedures, etc. required for clinical trials (taskforce, facilities and equipment, etc.)
  - Regulation on contract inspections
    (only applicable to institutions who intend to operate “Shared IRBs”)
  - Regulations on operation of IRBs and materials of its composition
    - Require to attach contract of consignment to use “Shared IRBs”
  - Materials to prove that it falls under any of the followings
    - General hospitals
    - Teaching hospitals, teaching dental hospitals and teaching oriental medicine hospitals
    - Specialty hospitals
    - Hospitals for teaching singular professional subjects
    - Clinical trial centers in Osong High-tech Composite Medical Complex

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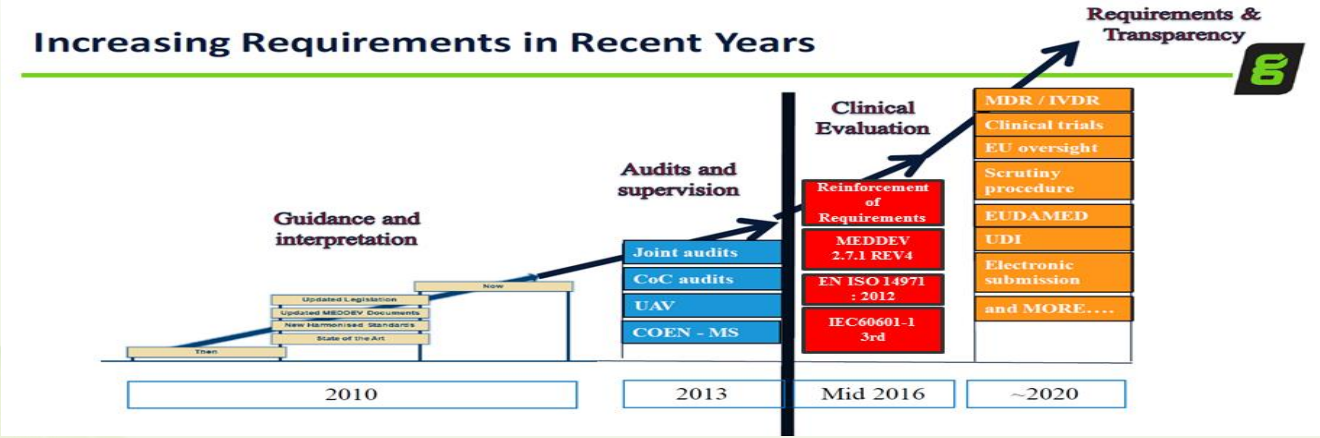
5. Clinical Evaluation

Approval for Medical Devices and Clinical Trials in Europe

- Clinical Evaluation includes contemplating clinical literature, other post-market surveillance and risk management other than simple literature review implemented in pre-market management

Approval for Medical Devices and Clinical Trials in Europe

- Medical Device Directive of the EU was completely revised based on the groundbreaking changes in 2017, and it was transformed from the existing Directive to Regulation



- A guide applying clinical evaluation
  - Medical Devices Directives Clinical Investigations, Clinical Evaluation : A Guide for Manufacturer and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC(MEDDEV 2.7.1)
  ※ MEDDEV 2.7.1 went through **revision in June 2016, applying the 4th revision currently**

Requirements in Europe (Regulatory Authority : Notified Body)

Pre-market

- Clinical evaluation reports for every class of medical devices
- **Class 1, 2**
  - Clinical trial materials and clinical evaluation reports prepared based on the clinical trial materials, or
  - Clinical evaluation reports prepared based on literature materials of equivalent products, or
  - Clinical evaluation reports can be submitted, prepared based on pre-clinical data if there is no equivalent products in case of low risk devices (~2a)
- **Class 2, 3**
  - Clinical evaluation reports including clinical trial materials that have used the applicable medical devices
  - Clinical evaluation reports prepared based on literature materials if there is an approved equivalent product in case of class 2 devices

Post-market

- **PMS(Post-Market Surveillance)**
  - A scheme to make corrective actions by collecting and analyzing post-market information for every class of medical devices
- **PMCF(Post-Market Clinical Follow-up studies)**
  - A scheme to identify clinical safety and efficacy that are not identified when approved
- **EU Surveillance System**
  - A Scheme reporting safety information derived from inside and outside of Europe for all medical devices
  - Clinical evaluation data, PMS and PMCF documents should be updated and go through inspections in case of post-market inspections or renewal inspections for every class of devices
- Actively using DB for adverse event reporting such as MCRA and BfArm, and EUDAMED to be publicly available

US standards (Regulatory Authority : FDA)

Pre-market

- Clinical Data submission requirements varies depending on risk levels of devices and whether it is a substantially equivalent product
  - Class 1 & 2 (510(k)) : exempted from submitting clinical data if it is substantially equivalent, and requires clinical data if it is not substantially equivalent
  - Most Class 3 and some Class 2 Devices (PMA) : risk-benefit analysis on clinical safety and efficacy
  - De Novo : clinical data and risk-benefit analysis on safety and efficacy

Post-market

- PMS (Post-Market Surveillance)
  - A scheme investigating information on adverse events using implantable and high-risk devices and effects on patients
- PAS (Post-Approval Studies)
  - A scheme consistently evaluating safety and efficacy based on results of long-term monitoring on some PMA medical products subject to PMA
- RWE(Real World Evidence) : Identify clinical safety and efficacy using Real World Data
  - Can help expanding clinical indications, be used as PMS and PAS materials, replaced as control group materials for clinical studies, used as supplementary data for post-market safety information, etc. and used as objective performance standards and information on intended use (released a guideline in Aug 31st in 2017)
- Encouraging DB of MAUDE and MEDSUN and then will be available on NEST

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Considerations in Clinical Evaluation

- Should consider Clinical Evaluation of Europe and clinical inspection system of the US (considering real world data) in terms of managing the whole life-cycle of medical devices
- Should analyze the meaning of clinical evaluation in terms of post-market management including post-market surveillance, adverse event reporting as well as pre-market management of medical devices
- Should contemplate specific inspection method for clinical evaluation reports as well as streamlining laws and regulations
- Should come up with improvement plans for effective safety management system of medical devices leading to preemptively respond to global regulatory changes
- Need capacity building of medical device inspectors

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Thank you for your attention

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