INTRODUCTION TO ELEMENTS OF REGULATORY SYSTEMS

Elements of Regulatory Systems

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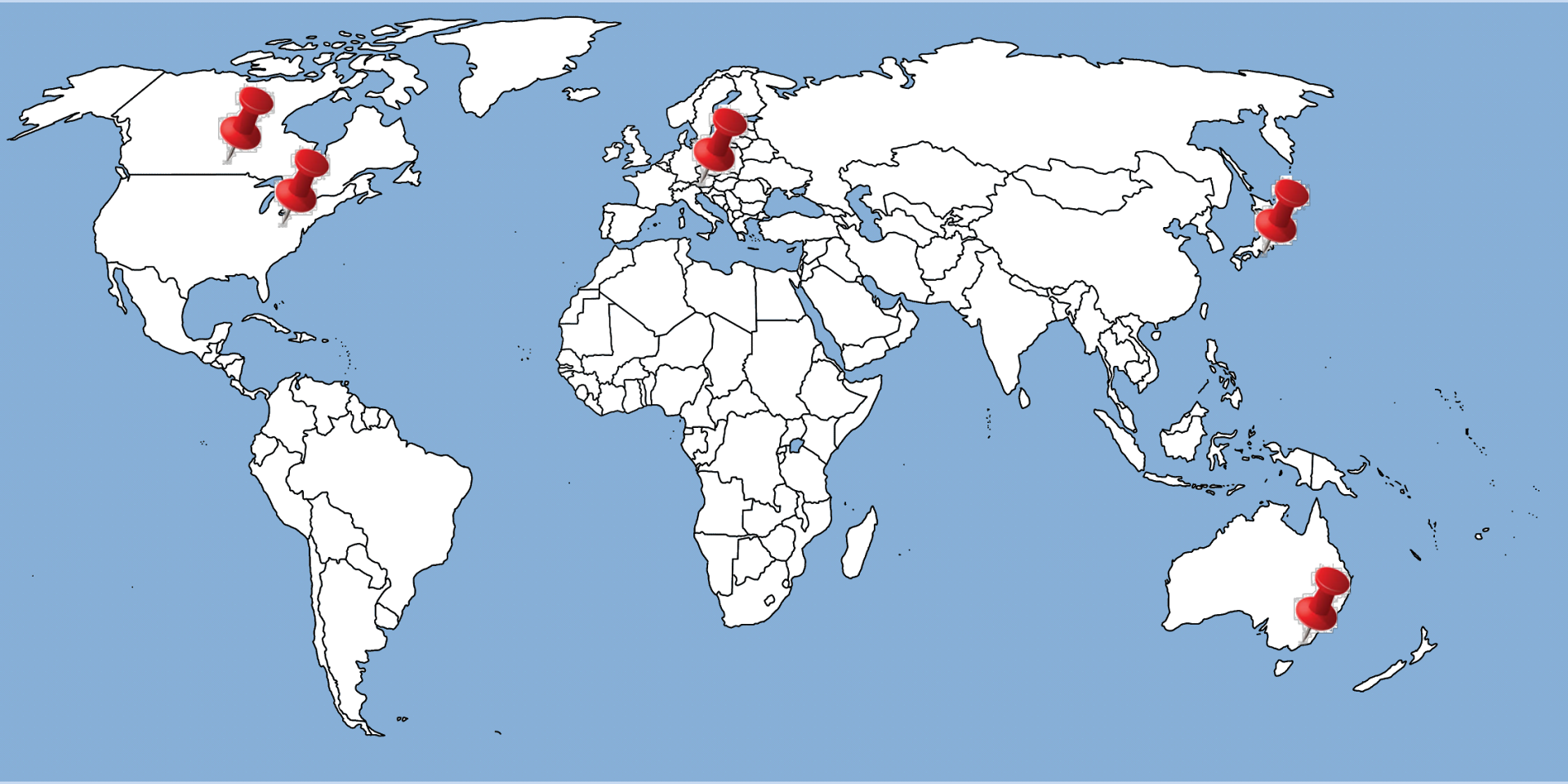
Purpose of this Session

- To show how existing regulatory systems have converged on a common basic set of principles
- To understand briefly the principles
- To explain the elements of good review practice
- To discuss how to think about implementing a regulatory system for IVDs

The Concept of Convergence

Medical Device Regulatory Authorities: 1992



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Medical Device Regulatory Authorities: 1992

GLOBAL HARMONIZATION TASK FORCE

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GHTF

- Best practice assessment principles
  - Group of representatives from global national medical device regulatory authorities (Australia, Canada, EU, Japan and US) and from industry
  - Purpose: Convergence of regulatory practice and identification of best regulatory practice

Structure and Products of GHTF

Study Group 1
Premarket Evaluation

Study Group 2
Post-Market Surveillance/Vigilance

Study Group 3
Quality Systems

Study Group 4
Clinical Safety/Performance

FINAL DOCUMENT

Global Harmonization Task Force

(revision of GHTF/SG1/N41:2005)

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 Asanuma, GHTF Chair

Overview

- Manufacturer of a medical device is expected to **DESIGN** and **MANUFACTURE** a product that is **SAFE** and **PERFORMS AS INTENDED**
- Document describes fundamental design and manufacturing requirements (*the Essential Principles of Safety and Performance*) to ensure this outcome

Essential Principles Applicable to All Medical Devices

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Essential Principles Applicable to All Medical Devices (1)

- Medical devices should be designed and manufactured in such a way that, when used as intended by intended users, will perform as intended by the manufacturer and that the benefits of its use will outweigh the risks, consistent with a high level of protection of health and safety.

Essential Principles Applicable to All Medical Devices (2)

- Design and manufacture of devices should conform to state-of-the-art safety principles and risk should be minimized, as follows (in priority order)
  - Estimate risks from known or foreseeable hazards from intended use and foreseeable misuse
  - Eliminate risks as much as possible through safe design and manufacture
  - Reduce remaining risk as much as possible by taking adequate protection measures (e.g., alarms)
  - Inform users of any residual risks

Essential Principles Applicable to All Medical Devices (3)

- Medical devices should achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.
- During the lifetime of the device, its safety and performance should not be compromised by stresses that can occur during normal conditions of use

Essential Principles Applicable to All Medical Devices (4)

- Medical devices should be designed, manufactured and packaged in such a way that their characteristics and performance during their intended use will not be adversely affected by transport and storage conditions (e.g., temperature, humidity), based on manufacture information
- Risks should be minimized and be acceptable when weighed against the benefits of the intended performance of medical devices during normal conditions of use.

Essential Principles Specific for IVDs

Essential Principles Specific for IVDs (1)

- Chemical, physical and biological properties
  - Meet the general characteristics and performance, taking into account possible impairment of analytical performance due to incompatibility between the device materials and the specimen or analyte
  - Minimize risk posed to intended users and patients
- Infection and microbial contamination
  - Minimize risks by allowing easy and safe handling, reducing leakage, preventing contamination of the IVD

Essential Principles Specific for IVDs (2)

- IVD medical devices incorporating materials of biological origin
  - Use manufacturing methods that optimize safety for the manufacturer, the user, and the patient (e.g., use validated methods to eliminate or inactivate infectious agents)
- Minimize risks arising from the environment in which the IVD is used

Essential Principles Specific for IVDs (3)

- Performance characteristics
  - Must support intended use, with design addressing sensitivity, specificity, accuracy, control of relevant interference, and limits of detection, and be maintained over lifetime of IVD
  - Traceability of calibrators and control materials (as applicable)
  - Use commonly accepted, standardized units for IVDs with numerical readout

Essential Principles Specific for IVDs (4)

- Software associated with the IVD must be validated (development lifecycle, risk management, verification, validation)
- User must be protected from risks associated with using the device (mechanical, electrical, etc.)

Essential Principles Specific for IVDs (5)

- Protection from risks posed by IVDs for self-testing
  - Designed and manufactured for the intended use taking into account use by untrained users, with information and instructions appropriate for the lay person, to reduce the risk of error
  - Procedure or design feature to allow the lay person to verify product performs as intended

Essential Principles Specific for IVDs (6)

- Label and instructions for use should be provided to users with the information needed to identify the manufacturer, to use the device safely and to ensure the intended performance, taking account of their training and knowledge

Essential Principles Specific for IVDs (7)

- Performance evaluation including analytical performance and, where appropriate, clinical performance
  - According to GHTF guidance, to establish that IVD achieves its intended performance, and any undesirable effects are minimized and acceptable such that the benefits outweigh the risks
  - Clinical performance studies using human specimens should be carried out according to the Declaration of Helsinki (patient rights) and specific regulatory requirements for a given country

General Elements of a Regulatory System

An Introduction to a More Detailed Discussion

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General Elements of a Regulatory System

1. The IVD must meet accepted levels of safety and performance (at FDA: safety and effectiveness)

General Elements of a Regulatory System

2. Safety and performance of IVDs can be assessed through a balance of:
   - Premarket scrutiny
   - Adequate manufacturer quality management systems (QMS)
   - Implementation of effective post-market surveillance (PMS)

General Elements of a Regulatory System

3. Risk classification provides a rational approach to the assessment process.
   - Many IVDs, limited resources
   - Increased risk = Increased oversight
   - Public health risk vs. individual health risk
   - Risk classification may differ depending upon intended use setting

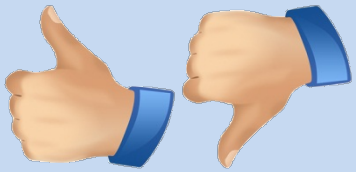
General Elements of a Regulatory System

4. Assessment bodies are most effective when there are consequences that discourage inappropriate activity.

Applying Regulations: Enforcement

QA → **PRODUCT** →

- Consistent performance
- Trust in results
- Public health benefit
- Optimized use of resources



DISINCENTIVES
CONSEQUENCES

REGULATIONS → **Legal action**
Removal from list
Etc.

How to Review: Good Review Practice

(From: WHO and Asia Pacific Economic Cooperation Regulatory Harmonization Steering Committee)

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Good Review Practices

- Definition
  - Documented best practices for any aspect related to the process, format, content, and/or management of a medical product review
- Goal
  - Promote timeliness, predictability, consistency, transparency, clarity, efficiency, and high quality of the content and the management of reviews
- Mechanism
  - Development of review tools (e.g., SOPs, templates) and reviewer learning activities (e.g., training courses, mentoring, orientation packages, discussion sections)
  - Evaluate and update on an ongoing basis

Principles of a Good Review (1)

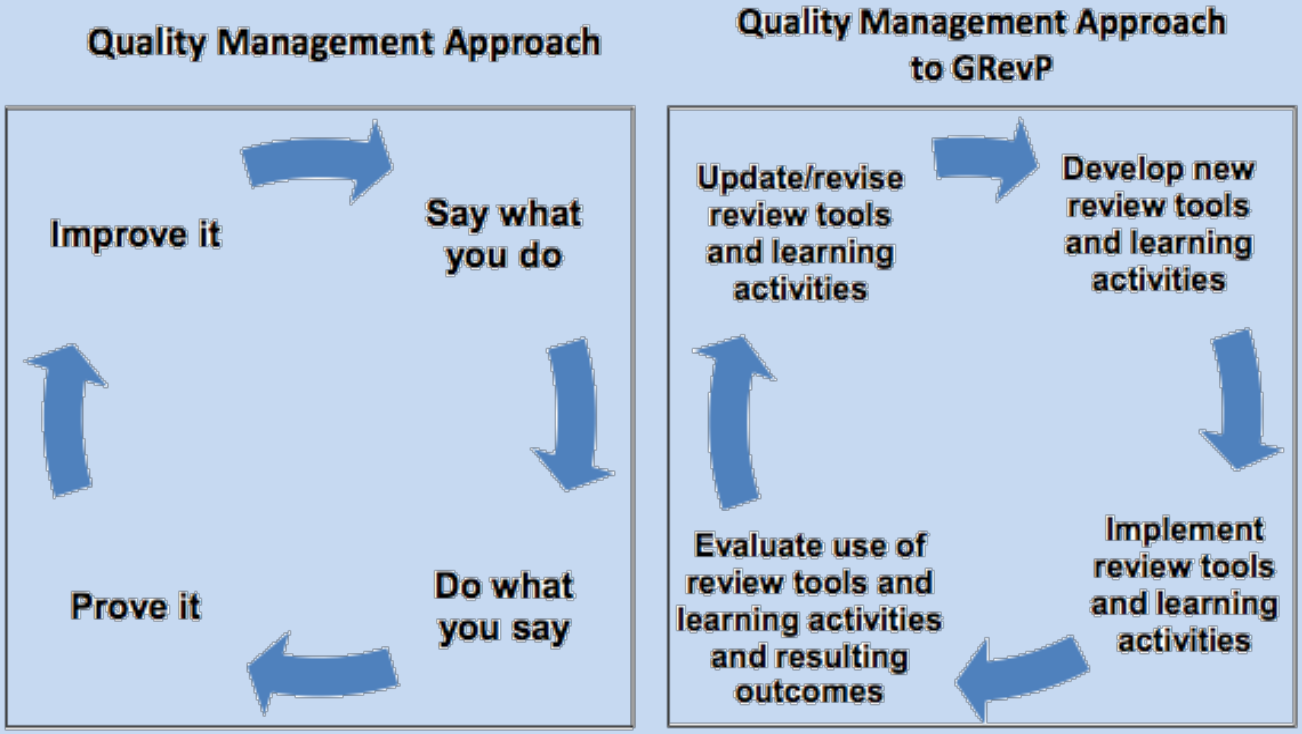
- Evidence-based
  - Scientific and state-of-the-art
- Utilizes critical analyses
  - Assesses scientific integrity, relevance, and completeness of data, labeling, and interpretation
- Identifies signals
  - Highlights areas of concern
- Investigates and problem-solves
  - Devise and recommend critical solutions and efficient alternatives where needed
- Makes linkages
  - Integrated analysis across all aspects of an application

Principles of a Good Review (2)

- Considers context
  - Proposed conditions of use and storage, including perspectives from healthcare professionals and other RAs
- Involves consultation
  - Internal and external
- Balanced
  - Objective and unbiased
- Thorough
- Well-documented
  - Professional, well-written, clear, neutral, respectful

Activities Critical to Good Review Practice: Managing the Review (1)

- Project management
- Quality management



Activities Critical to Good Review Practice: Managing the Review (2)

- SOPs, guidances, checklists, and templates
- Communication
  - Intra-agency
  - Inter-agency
  - With the applicant
  - With the public

Activities Critical to Good Review Practice: Other (1)

- Personnel competencies and training
  - Reviewer training
  - Critical thinking
  - External experts
  - Collaboration and leveraging
  - Evidence-based review with a risk-benefit result

Activities Critical to Good Review Practice: Other (2)

- Conducting the review
  - Defining a review strategy
    - Public health priority of product
    - Understanding other RAs action on the application
    - Understanding specific intrinsic and extrinsic factors
    - Assessment of submission quality
    - Identification of major scientific questions and their possible resolution

More on Convergence

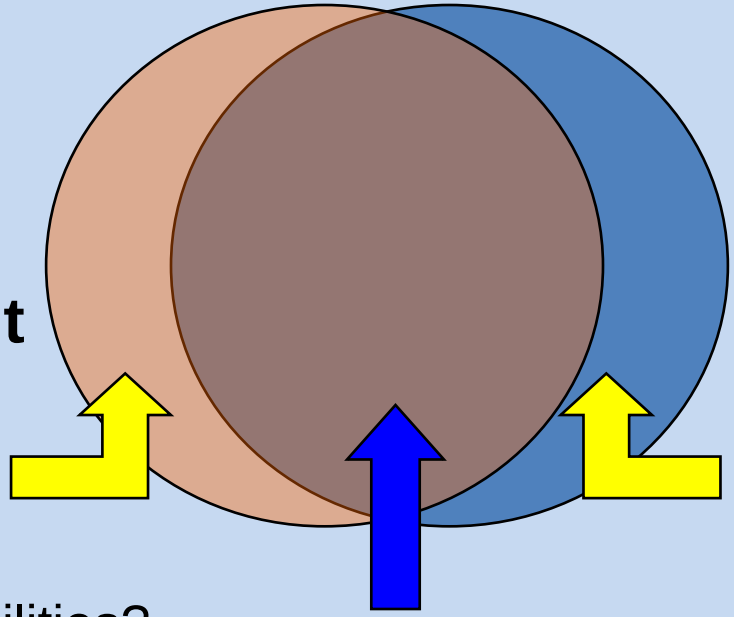
Convergence Q&A

If mature regulatory bodies are converging their practice, does that mean a test approved by any of those bodies could be accepted anywhere without any additional review?

It depends…

Considering Tests Approved by a Mature Regulatory Authority

MRA IVD Assessment



Country Needs

VARIABLES

- Clinical studies
- Manufacturing facilities?

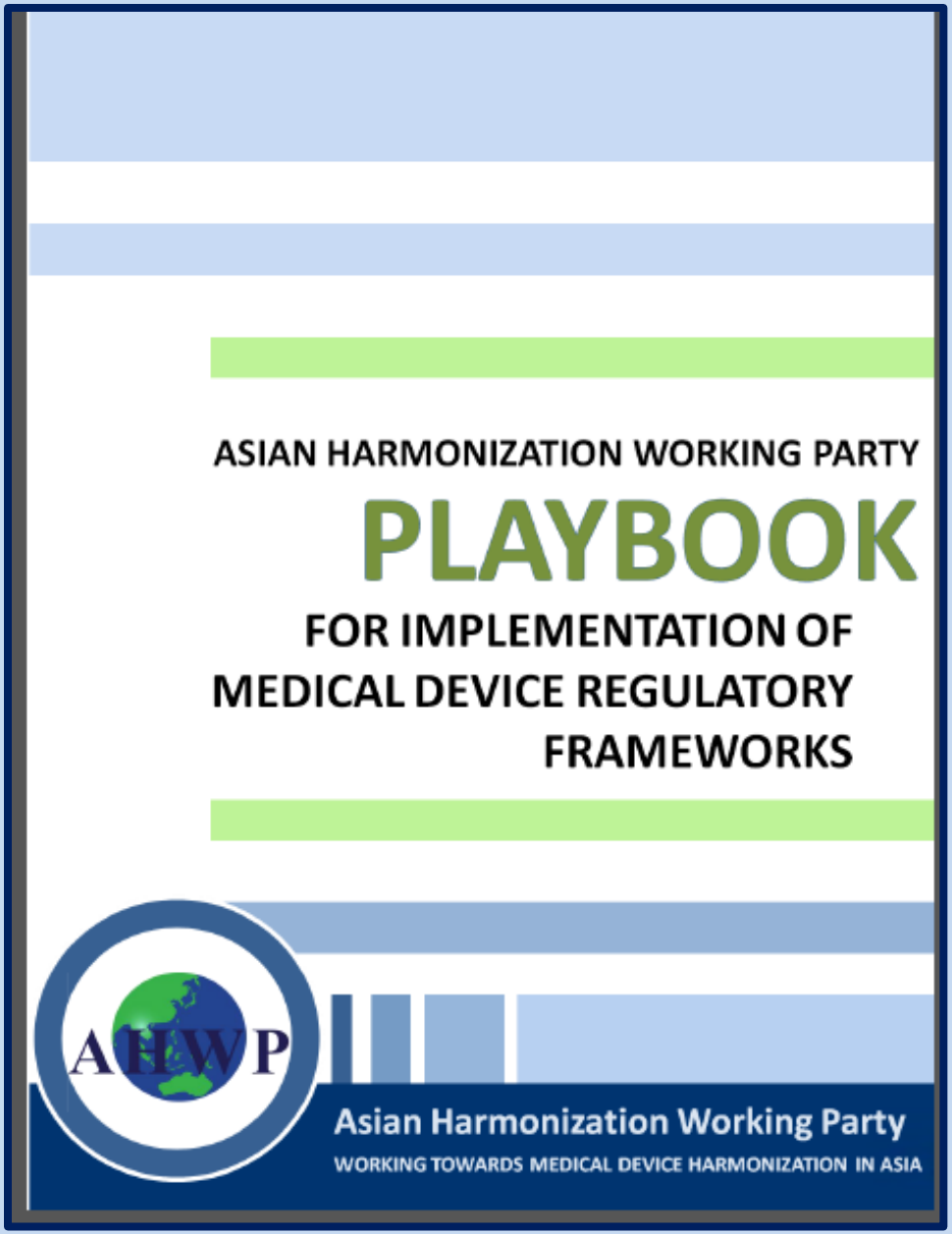
VARIABLES

- Design?
- Risk/benefit

CONSTANTS

- Analytical studies
- Manufacturing
- Quality Management System
- Inspection

Building a Regulatory System



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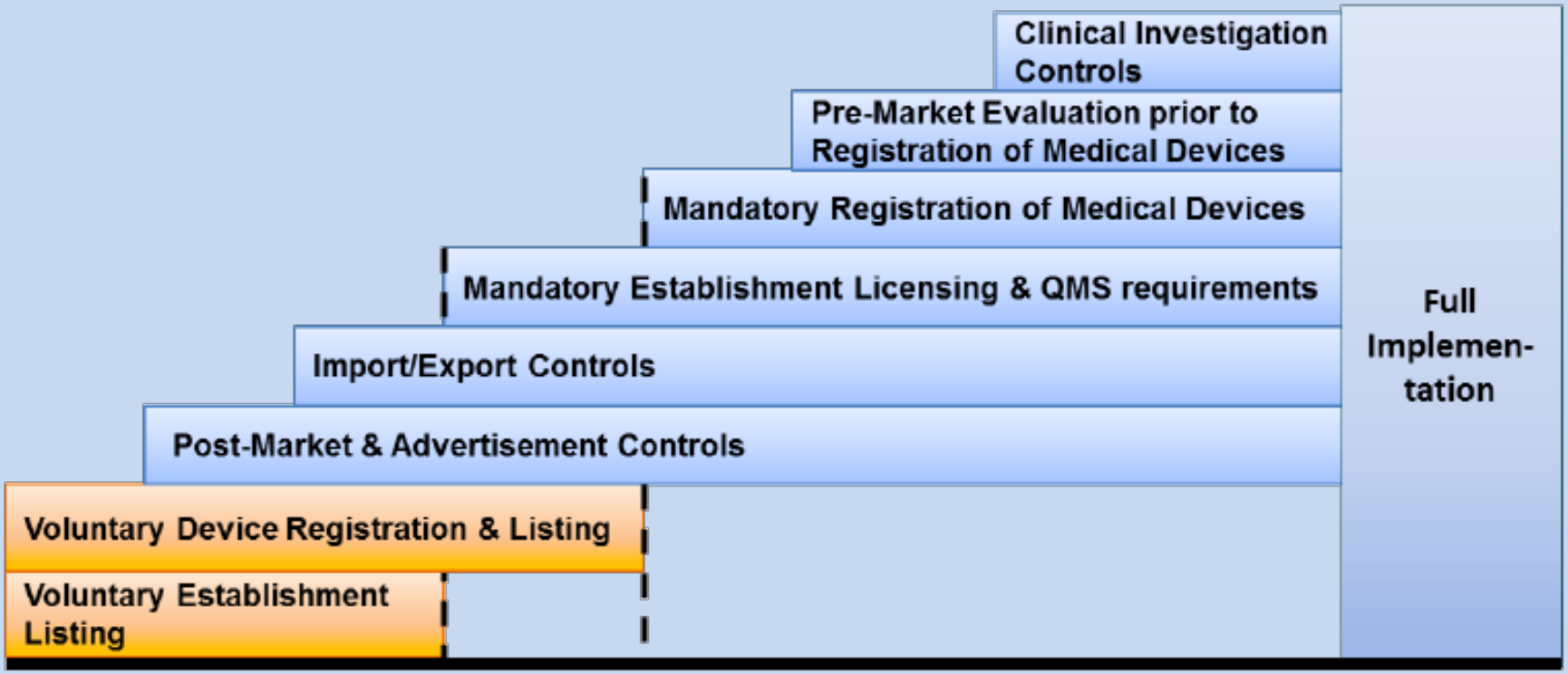

Figure 6: Possible phased implementation plan for a medical device framework

Coming Up

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Thank You