Study Group 1

IVD Medical Devices – the GHTF Guidance Documents

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Overview of presentation

- IVDs as a sub-set of medical devices
- Essential Principles
- Classification
- Summary Technical Documentation (STED)
- Conformity Assessment

What is an IVD?

'Medical device' means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- control of conception,
- disinfection of medical devices,
- providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body,
- and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

What is an IVD?

- **IVD medical device:** A device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.
- Note: In some jurisdictions, some IVD medical devices may be covered by separate regulations.

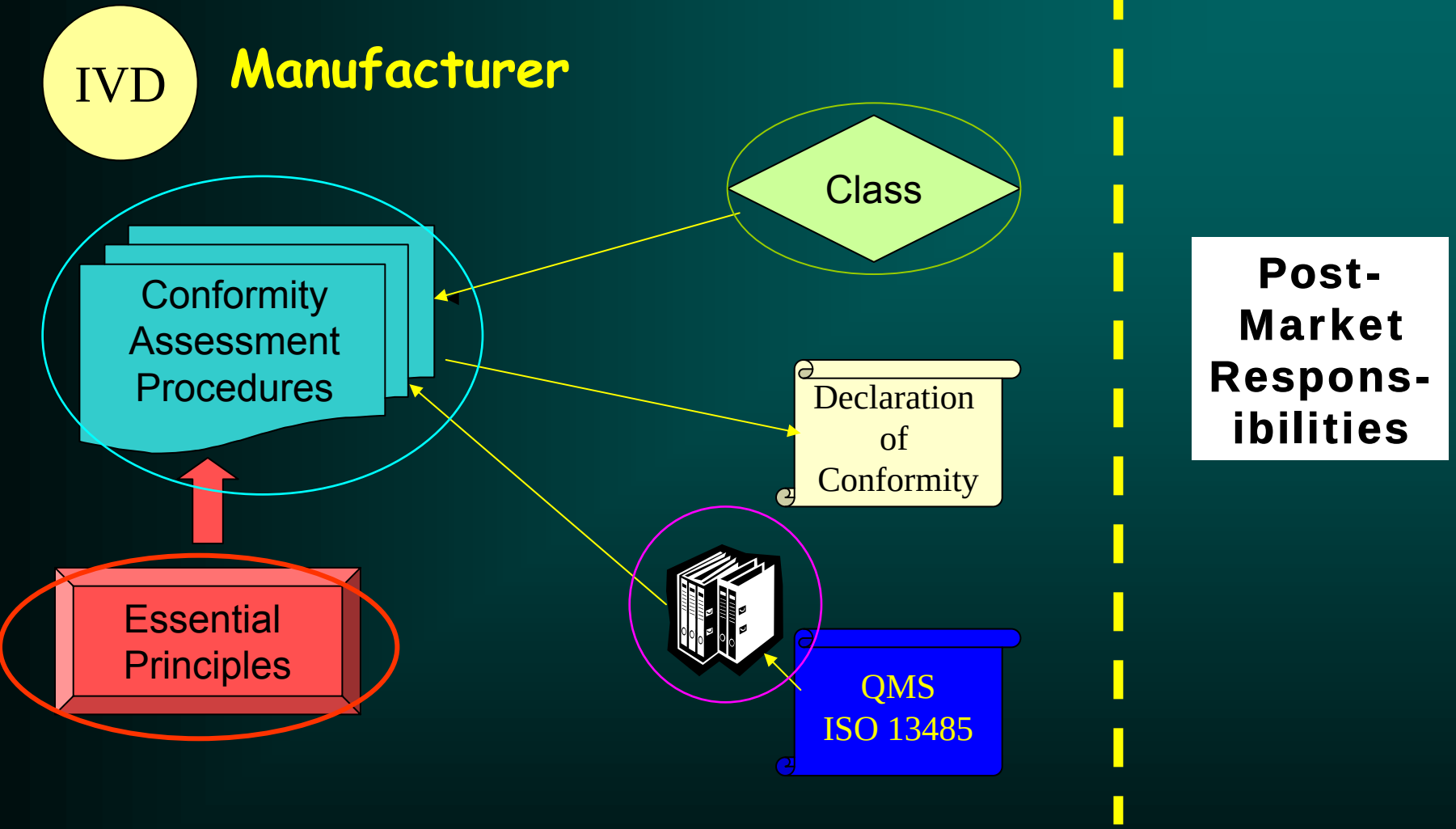
GHTF documents on IVDs - General

- SG1/N012 *Role of Standards in the Assessment of Medical Devices.*
- SG1/N029 *Information Document Concerning the Definition of the Term 'Medical Device'.*
- SG1/N041 *Essential Principles of Safety and Performance of Medical Devices.*
- SG1/N043 *Labelling for Medical Devices.*

GHTF documents on IVDs - Specific

- SG1(PD)/N045R13 *Principles of In Vitro Diagnostic (IVD) medical devices Classification*
- SG1(PD)/N046R4 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) medical devices*
- SG1(PD)/N063 (early Draft) *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices (STED)*

The Roadmap

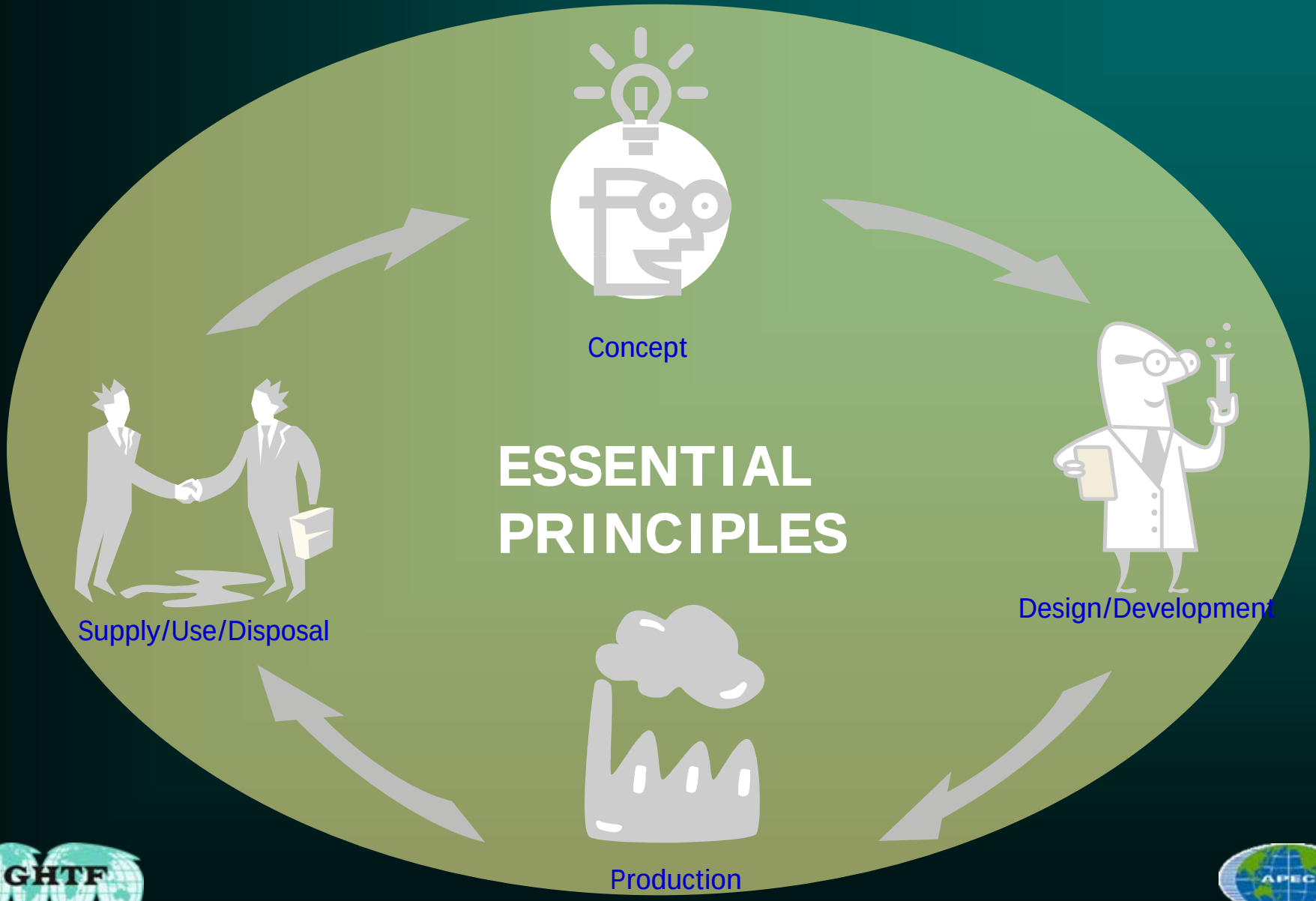

IVD
Manufacturer
Class
Conformity Assessment Procedures
Declaration of Conformity
Essential Principles
QMS ISO 13485
Post-Market Respons-ibilities

Essential Principles

Essential Principles

- All IVDs must meet the Essential Principles for quality, safety and performance
- EPs underpin the regulatory framework
- Compliance with EPs may be demonstrated by use of standards – see GHTF SG1-N012R10 *Role of Standards in the Assessment of Medical Devices*

Essential Principles



Essential Principles

- EPs cover design, manufacture, clinical performance, and overall safety to user and person being tested
- EPs define risks to be managed/ results to be achieved, but do not specify how
- Manufacturers determine which EPs are applicable
- Compliance with EPs is the manufacturer's responsibility

Essential Principles

- GHTF document on Essential Principles includes IVDs in its scope.
- Six general EPs – apply to all medical devices, including IVDs
- 11 specific EPs, which may or may not apply to a particular device, depending upon its type and construction

General Essential Principles

- Must not compromise health and safety
- Conforms to safety principles, taking into account the general state-of-the-art
- Suitable for intended purpose
- Performs as intended during determined shelf life under normal conditions of use
- Performs as intended when subjected to prescribed conditions of transport and storage
- Benefits outweigh risk

Specific Essential Principles

Devices with a diagnostic or measuring function (5.10)

- Sensitivity, specificity, trueness, repeatability, reproducibility, control of interference, and limits of detection
- Traceability of controls and calibrators

Self-Testing (5.15)

- Consider the user of the test - easy to use instructions/protocol
- Reduce risk of error in use and interpretation
- Design allows for verification by user

Specific Essential Principles (cont)

- Performance evaluation (5.17) – “all data generated in support of performance evaluation should be obtained in accordance with the relevant requirements applicable in each jurisdiction”...
- Just what is required in relation to clinical evidence for IVDs not yet determined in GHTF guidance.

Classification

Classification

- The GHTF framework proposes a risk based classification system for all IVDs

- The determination of classification will be based on a set of rules derived from those features that create the risk associated with an IVD

Why classify?

Class determines level of regulatory oversight

- Class determines the relevant conformity assessment procedures
- The class is determined by applying a set of rules
- Rules based classification allows greater flexibility
  - New diseases, emerging technologies
- Classification is the responsibility of the manufacturer

How to determine class?

Responsibility of the manufacturer

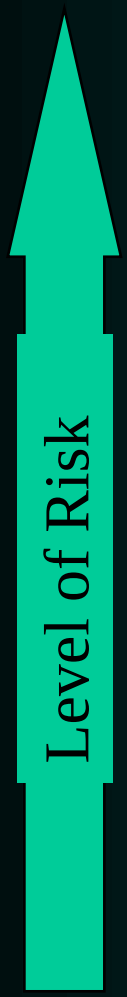
- Decide if the product is an IVD, based on intended use and using the definition
- Consider the Rules. An IVD with multiple intended purposes will be placed in the highest applicable class
- Determine that special national rules do not apply
- Where more than one Rule applies, the Rule which places the IVD in the highest class applies

Classification

Risk Factors

- The intended use and indications for use
  - Specific disorder, population, condition or risk factor for which the test is intended
- The technical/scientific/medical expertise of the intended user
- The importance of the information to the diagnosis
  - Sole determinant or one of several
- The impact of the result (true or false)

Risk Classes



Class D IVD - High Individual Risk and High Public Health Risk

E.G. HIV blood donor screening, HIV blood diagnostic

Class C IVD – High Individual and/or Moderate Public Health Risk

E.G. Blood glucose self-testing, HLA typing, PSA screening, Rubella

Class B IVD – Moderate Individual and/or Low Public Health Risk

E.G. Vitamin B12, pregnancy self-testing, Anti-Nuclear Antibody, Urine test strips

Class A IVD – Low Personal/No Public Health Risk

E.G. Clinical Chemistry Analyser, prepared selective culture media

Class D IVD

High Public Health Risk
and/or
High Individual Risk

Includes IVDs that are used for

- screening of the blood supply and organ and tissue donations for pathogens , eg IVDs used for screening for infection with HIV, HCV, HBV, HTLV
- Detecting the presence of a transmissible agent likely to cause a life-threatening illness with a threat to public health – example as above
- Blood grouping or tissue typing to ensure compatibility where there is an individual high risk, eg ABO, rhesus, Kell, Kidd and Duffy

Class C IVD

High Individual Risk and/or Moderate Public Health Risk

Includes IVDs that are used for

- Blood grouping, tissue typing, not in Class D
- Detection of transmissible agents
  - Sexually transmitted
  - In CSF or blood (limited risk of propagation)
  - Likely to cause death or severe disability
- Immune status in pregnancy
- Human genetic testing
- Detection of congenital diseases in the foetus

Class C IVD (cont...)

High Individual Risk and/or Moderate Public Health Risk

Includes IVDs that are used for

- Infective disease status in high individual risk situations
- Screening for selective therapy and management, for disease staging, or diagnosis of cancer
- Monitor levels of medicines etc, in high-risk patient management situations (cardiac markers, prothrombin time testing)
- Management of patients with life-threatening infectious disease (HCV/HIV viral load, genotyping or subtyping)
- Self-testing, in determining a medically critical status.

Class B IVD

Moderate Individual Risk and/or Low Public Health Risk

Includes IVDs that

- are used for self-testing, where results are not medically critical or require confirmation (pregnancy testing, fertility testing, urine test strips)
- Are not covered by other Rules (blood gases, hormones, vitamins, enzymes, metabolic markers)
- Are intended to be used as controls without a quantitative or qualitative assigned value (do not validate the decision on the release of patient results)

Class A IVD

Low Individual Risk and/or Low Public Health Risk

Includes IVDs that are

- Reagents or other articles used in in vitro diagnostic procedures (selective/differential microbiological media, identification kits for cultured micro-organisms, wash solutions)
- Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures
- Specimen receptacles

STED-
Summary Technical Documentation

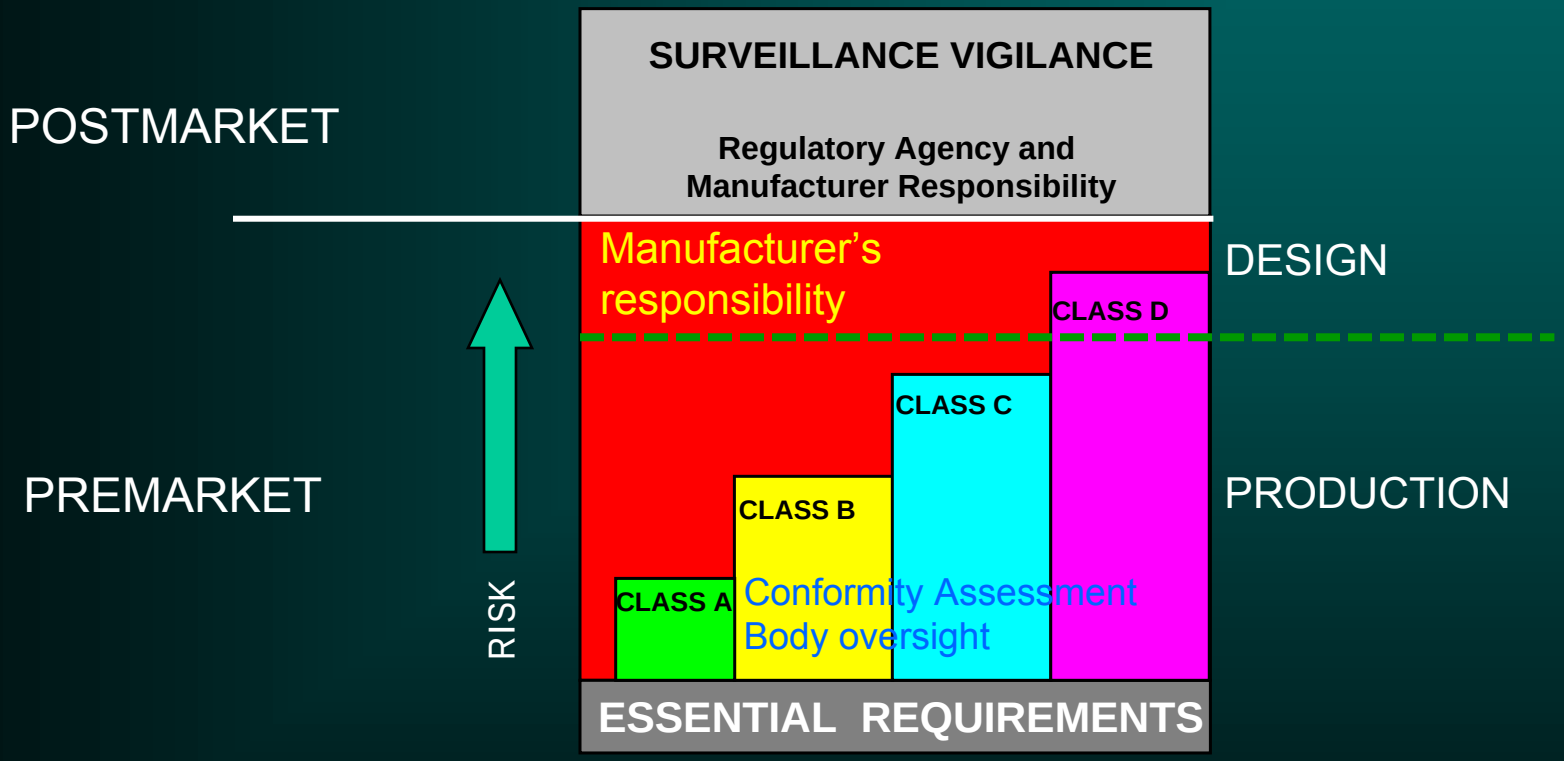
Content of STED

- Preface:
  - The STED does not represent the full technical documentation which is controlled under the Quality System
  - STED should be in a language acceptable to the reviewing organization
  - Depth and detail may be dependant on classification and risk, whether it is novel technology or already marketed

Content of STED

- General description and list of specified features
- Set of labels and list of language variants
- Summary of technical documentation concerning design and manufacturing
- Essential Requirement Checklist
- Summary of risk analysis and mode of control
- Summary of verification and validation studies – Performance Evaluation

Conformity Assessment


SURVEILLANCE VIGILANCE
Regulatory Agency and Manufacturer Responsibility
POSTMARKET
Manufacturer's responsibility
DESIGN
CLASS D
CLASS C
PREMARKET
CLASS B
PRODUCTION
RISK
CLASS A
Conformity Assessment Body oversight
ESSENTIAL REQUIREMENTS

Conformity Assessment - Elements

- Quality Management System
- Documentation (STED= Summary Technical Documentation)
- Declaration of Conformity
- Registration of Manufacturer and their Products
- Systematic Post-Market Surveillance System

Type of Quality System

- ISO 13485 — Certified full Quality System with design Control
- ISO 13485 — Certified full Quality system **except** design control (alternative for Class A and B products only)

- In assessing the Quality Management System for Class B to D IVDs, the Regulatory Authority or Conformity Assessment Body will take into account relevant existing certification and conduct on-site audit only with reasoned justification.

STED = Summary Technical Documentation

- Technical documentation is to be prepared for all IVDs according SG1(PD)/N063 (early draft)
- Submission and review by the authorities not required for Class A and B, but if in justified cases may be submitted on request.
- Review by the authorities for Class C and D, based on risk of the products and experience of the manufacturer

Declaration of Conformity

- A declaration made by the manufacturer
- Name and address of the responsible manufacturer
- Identification of the device (product name, product number, GMDN code)
- Statement that the device complies with
  - The Essential Principles of Safety and Performance
  - The Classification and Conformity Assessment Procedure
  - List standards used in the Conformity Assessment Procedure
- Dated and signed by the manufacturer (appropriate senior personnel)

Registration of Manufacturer and Their IVD Products

- At minimum the Regulatory Authority maintains a registrar of products marketed in their country (manufacturer and product listing, and maybe importers)

Systematic Post-Market Surveillance

- Manufacturer holds a complaint handling systems and initiates appropriate investigations
- Manufacturer captures information learnt from the market and the users and takes actions if required
- Manufacturer reports any potential medical events to the authority, where the event occurred
- Regulatory Authority may request information or audit the manufacturer in justified cases

Quality System or Surveillance Audits

- It is not passing an exam!!!!
- Demonstration of continual operation and compliance
- Supports continuous improvement of products and processes

Conformity Assessment

- Considerations for Regulatory Authorities
  - Public health protection priorities (risked based, not every product has the same risk)
  - Proportionality of methods to public health benefits
  - Access to market to ensure efficient diagnosis of patients and state-of-the-art products
  - Relevant existing certification
  - Resources
    - Funding
    - Expertise
    - Efficient use
    - Timeliness (eg - impact on market viability)

In Practice

- Class D
  - The manufacturer has a full Quality System certificate which includes design control according ISO 14835
  - Submission of the STED and Declaration of Conformity
  - Pre-Market Review by the Regulatory Authority or the Conformity Assessment Body (3rd party) of documentation and performance of the product to ensure that the Essential Principles are fulfilled and the claims of the products are met
  - Review Adverse Event Reporting process and procedure
  - Open questions to be discussed with the manufacturer and/ or representative
  - Add product to registrar

In Practice

- Class C
  - The manufacturer has a full Quality System certificate which includes design control according ISO 14835
  - Submission of the STED and Declaration of Conformity
  - Review by the Regulatory Authority or the Conformity Assessment Body (3rd party) of documentation and performance of the product to ensure that the Essential Principles are fulfilled and the claims of the products are met (maybe done during a pre-market audit on-site)
  - Review Adverse Event Reporting process and procedure
  - Open questions to be discussed with the manufacturer and/ or representative
  - Add product to registrar

In Practice

- Class B
  - The manufacturer has a Quality System certificate according ISO 14835, which need not include design control
  - Preparation of STED and maintained by the manufacturer, pre-market submission is not required, but in justified cases may be reviewed
  - Declaration of Conformity is prepared by the manufacturer and submitted to the Regulatory Authority
  - Verify that Declaration of Conformity is appropriate
  - Ensure Adverse Event Reporting process and procedure is in place
  - Add product to registrar

In Practice

- Class A
  - The manufacturer has a Quality System certificate according ISO 14835, which need not include design control
  - Preparation of STED and maintained by the manufacturer, pre-market submission is not required, may be reviewed during surveillance audits or if there are regulatory concerns
  - Declaration of Conformity is prepared by the manufacturer, not submitted to Regulatory Authorities
  - Ensure Adverse Event Reporting process and procedure is in place
  - Add product to registrar

Any Questions?