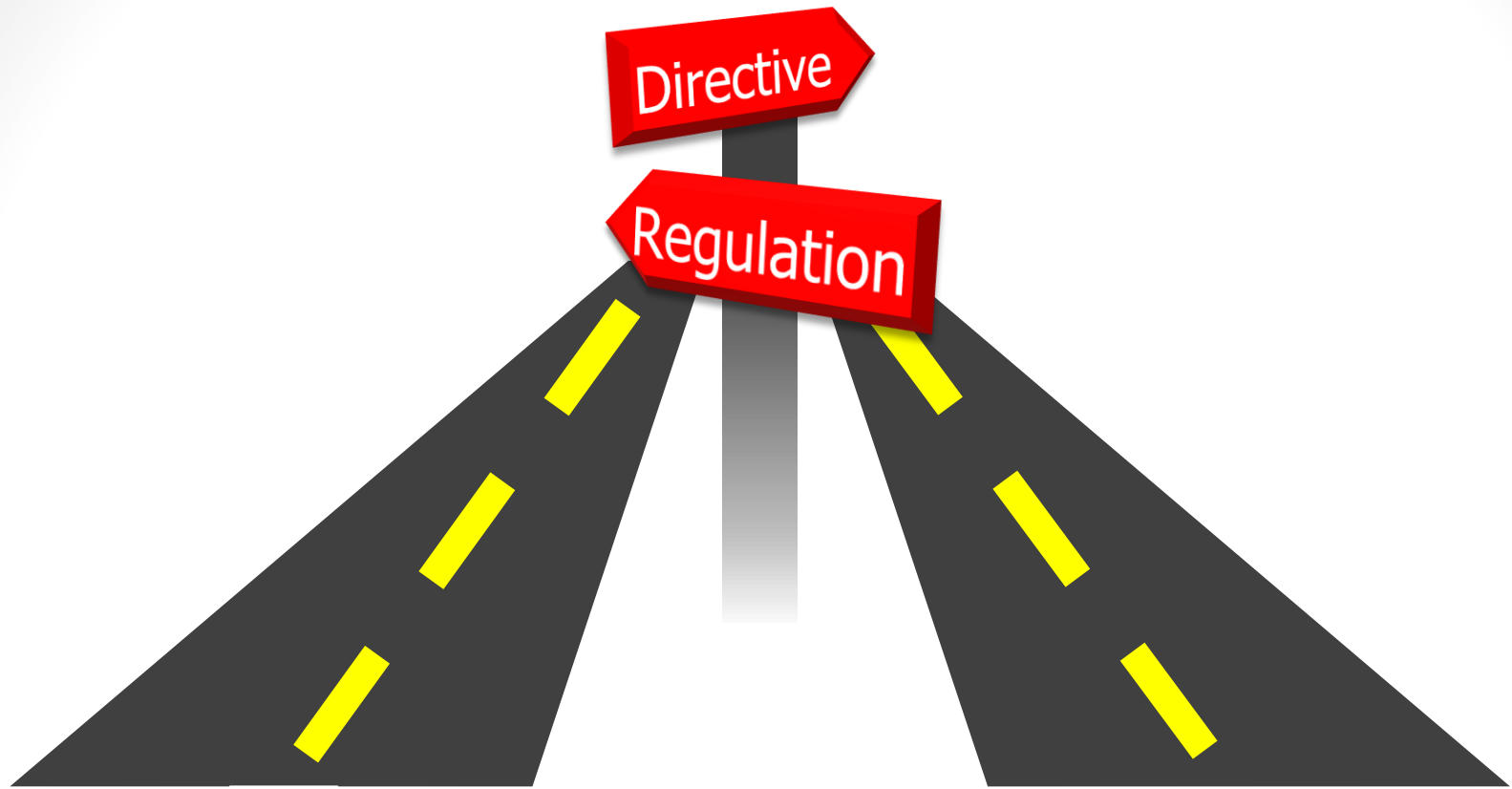


IVD REGULATION IN THE EU

CE Mark your IVDs in compliance with the European IVD
Regulation

Agenda

- Regulatory background and definition of an IVD
- Product Classification & Conformity Assessment Routes
- Product Design and Development
- Performance Evaluation
- Technical Documentation
- Post-Market Responsibilities
- Placing on the Market



Times are changing.....

REGULATORY FRAMEWORK

Background to European IVD regulation

- IVD Directive 98/79/EC came into force in 2003.
 - Standardised regulation of, and access to, IVDs throughout those countries in the EU Single Market.
 - Amended *once* to include vCJD in the high risk group of IVD analytes
- IVD Regulation 2017/746 issued in 2017 and will replace the IVDD in 2022.
 - Date of publication in European Journal 5 May 2017
 - Entry into force 25 May 2017
 - Transition period (+ 5 yrs) ends 25 May 2022
 - Date of application 26 May 2022

Background to European IVD regulation

Up to 25 May 2022, IVDs may comply with either the IVDD or the IVDR.

From 26 May 2022, IVDs on the market must be in compliance with the IVDR. NO grandfathering

This presentation will focus on the requirements under the IVD Regulation.

Other EU Regulations relevant to IVDs

Regulation / Directive

- CLP
- REACH
- Animal by-products
- RoHS 2 and 3
- WEEE
- EMC Directive
- Machinery Directive
- Biocides

Impacts

- All hazardous safety labelling/MSDS
- Controls use of chemicals
- Controls import and use in EU
- Hazardous substances blocked
- Disposal of electrical equipment
- Instrumentation with EMC
- Equipment defined as a machine
- Used in interim product or research

...and what is not!

WHAT IS AN IVD?

In vitro diagnostic medical device

in vitro diagnostic medical device' means:

any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system,

whether used alone or in combination,

intended by the manufacturer **to be used in vitro for the examination of specimens**, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- (a) concerning a physiological or pathological process or state;*
- (b) concerning congenital physical or mental impairments;*
- (c) concerning the predisposition to a medical condition or a disease;*
- (d) to determine the safety and compatibility with potential recipients;*
- (e) to predict treatment response or reactions;*
- (f) to define or monitoring therapeutic measures.*

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;

What is not an IVD

- X **Sample not removed from body - medical device regulation**
- X Sample collectors that are considered invasive (oral swabs)
- X Diagnostics for veterinary use
- X Device for performance evaluation
- X Software apps that collect and trend lifestyle data with no specific medical purpose
- X Product used for research – with no medical purpose

...and conformity assessment

PRODUCT CLASSIFICATION

IVDD Product Classification - List based

- Annex II of the Directive comprises of two lists: A and B
- High Risk IVDs named in Annex II List A
 - Examples include HIV, Hepatitis B and C, TB not included.
 - Document review and approval required by a Notified Body (NB)
- Moderate Risk IVDs named in Annex II List B.
 - Infection markers/conditions listed are CMV, chlamydia, rubella, toxoplasmosis.
 - Document review and approval required by a NB
- All other IVDs considered Low Risk General IVDs
 - Self certified by manufacturer – No NB required)
- Self test IVDs require some NB involvement. **POC or Near Patient Tests do not.**

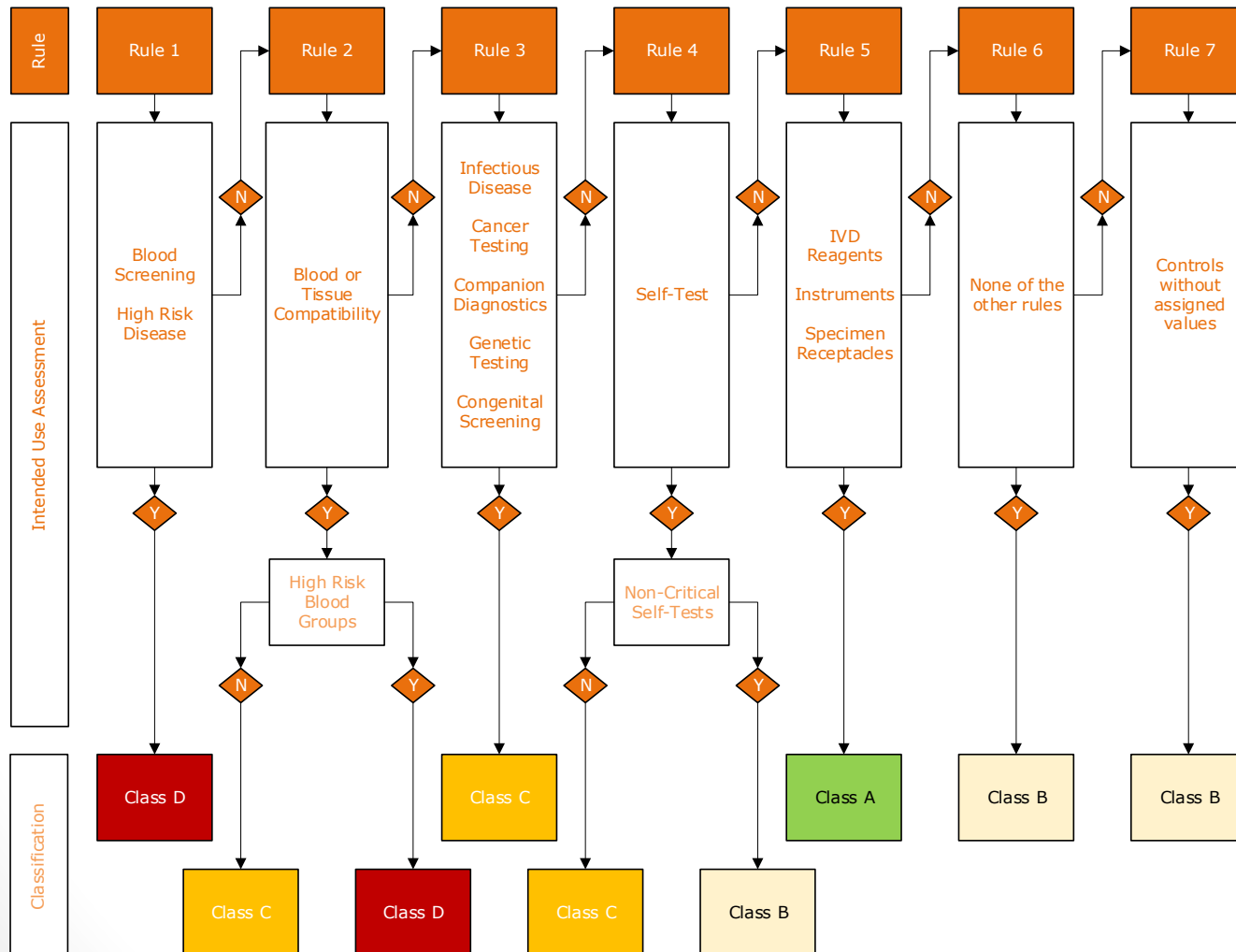
IVDR Product Classification – Rules based

- FOUR risk classes: D highest risk and A lowest risk.
- Governed by intended purpose. Manufacturer responsible for determining Class and associated Rule.
- Annex VIII details the seven Classification Rules



IVDR Product Classification

Annex VIII



Annex VIII, Rule 1

Rule 1 Devices intended to be used for the following purposes are classified as class D:

- detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation;
- determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management.

Annex VIII, Rule 3

Rule 3 Devices are classified as Class C if they are intended:

- (b) for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation;
- (c) for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring;
- (e) for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;
- (k) for management of patients suffering from a life-threatening disease or condition;

IVD Product Classification

Directive versus Regulation

IVD Directive Classification

Highest Risk
High Notified Body
Interaction

Annex II
List A

Significant Risk
Notified Body Interaction

Annex II
List B

Self test

Low Risk

General
IVD

IVD Regulation Classification

Class D

Highest Risk
High Notified Body
Interaction

Class C

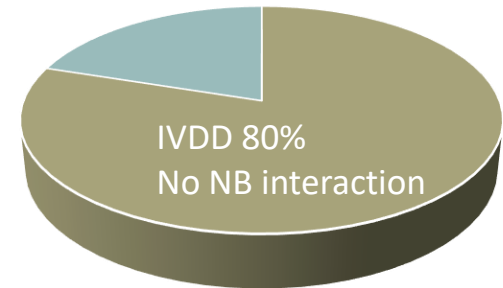
Significant Risk
Notified Body Interaction

Class B

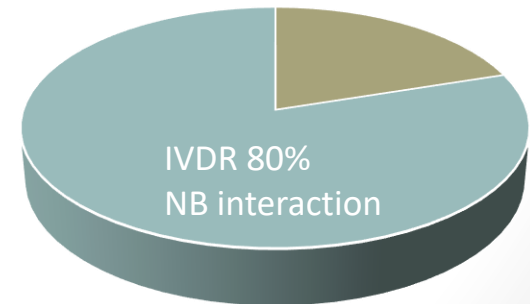
Medium Risk
Limited Notified Body
Interaction

Class A

Low Risk



■ General ■ Annex II



■ Class A ■ Class B, C, D

Conformity Assessment

Article 48

Class A

- *Annex IV Declaration of Conformity. Tech Documentation Annexes II and III. No NB involvement.*
- *Sterile Class A devices. Annex IX or Annex XI. NB involvement for sterile component only*

Class B

- *Annex IX Quality and technical assessment Ch I and Ch III. Tech Documentation Ch II Section 4.1-4.8.*
- *Self-test and Near Patient test Ch II Section 5.1*
- *Companion Dx Ch II Section 5.2*

Conformity Assessment

Class C

- *Annex IX Quality and technical assessment Ch I and Ch III. Tech Documentation Section Ch II 4.1-4.8.*
 - *Self-test and Near Patient test Ch II Section 5.1*
 - *Companion Dx Ch II Section 5.2*
- *Annex X Type Examination (relevant sections) + Annex XI Production quality assessment (except Section 5)*
 - *Companion Diagnostics Annex X includes Section 3k*

Conformity Assessment

Class D

- *Annex IX Quality and technical assessment*
 - *Self-test and Near Patient test Section 5.1*
 - *Companion Dx Section 5.2*
- *Annex X Type Examination + Annex XI Production quality assessment*
- *Batch verification and EU Ref Lab confirmation of performance characteristics*

Annex IX, Section 5.1

The manufacturer of class B, C and D devices for near-patient testing shall lodge with the notified body an application for the assessment of the technical documentation.

- The application shall enable the design of the device characteristics and performance(s) to be understood and shall enable conformity with the design-related requirements of this Regulation to be assessed. It shall include:
 - (i) test reports, including results of studies carried out with intended users;
 - (ii) where practicable, an example of the device; if required, the device shall be returned on completion of the technical documentation assessment;
 - (iii) data showing the suitability of the device in view of its intended purpose for self-testing or near patient- testing;
 - (iv) the information to be provided with the device on its label and its instructions for use.
- Changes to the approved device may require approval from the notified body

...from idea to finished article

PRODUCT DESIGN AND DEVELOPMENT

Placing on the Market

Article 5

- A device may be placed on the market or put into service only if it complies with this Regulation when duly supplied and properly installed, maintained and used in accordance with its intended purpose.
- A device shall meet the **general safety and performance requirements** set out in Annex I which apply to it, taking into account its **intended purpose**.
- Demonstration of conformity with the general safety and performance requirements shall include a performance evaluation in accordance with Article 56.

What is the Intended Purpose?

- IVDR Article 2.12 Intended purpose means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements, or as specified by the manufacturer in the performance evaluation.
- Intended Purpose defines:
 - *Who the test will be used on (intended use population)*
 - *What sample (type/matrix) will be required*
 - *Who will use it (lay person, professional, level of training)*
 - *What setting (home, near patient, laboratory)*
 - *What clinical/medical outcome can be expected (aid to diagnosis, monitoring etc)*

General Safety and Performance Requirements

- A device shall meet the **general safety and performance requirements** set out in Annex I which apply to it, taking into account its intended purpose.
- Annex 1 is divided into 3 chapters
 - Chapter I: General Requirements – ALL IVDs must comply with these 8 GRs;
 - Chapter II: Requirements regarding performance, design and manufacture – IVDs must comply with those requirements that apply;
 - *Chapter III: Requirements regarding information supplied with the device*

Annex I, Chapter I – ALL IVDS

- Devices achieve intended performance and are suitable for their intended purpose. Safe and effective
- Reduce risks as far as possible without adversely affecting the benefit-risk ratio
- Establish, implement, document and maintain a risk management system
- Risk control measures conform to safety principles; state of the art
- Risk controls to consider ergonomics, environment, user skills
- Safe under normal conditions of use
- Safety and performance not impacted by shipping and storage
- All risks minimized and acceptable when weighed against the benefits

Annex I, Chapter I – ALL IVDS

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ISO 14971: 2012 Risk Management System

- Risk Management Plan should cover all parts of product lifecycle – including product development, through commercial phase to decommissioning.
- Annexes of ISO 14971 are helpful when thinking about potential hazards linked to IVDs.
- Several risk management tools available – choice is up to manufacturer (FMEA/FTA/HAZOP)
- Notified Body will be looking for evidence that risk management was integrated into product design and development.
- Risk management teams should be cross functional and have documented expertise in this area.

Annex I, Chapter II

- Chapter II details requirements for:
 - Performance characteristics
 - Chemical, physical and biological properties
 - Infection and microbial contamination
 - Incorporating materials of biological origin
 - Construction of devices and interaction with their environment
 - Devices with a measuring function
 - Protection against radiation
 - Electronic programmable systems
 - Devices connected to or equipped with an energy source
 - Protection against mechanical and thermal risks
 - **Protection against risks posed by devices intended for self-testing or near-patient testing**

Annex I, Chapter II

Performance 9.1 and 9.2

- **Devices shall be designed and manufactured in such a way** that they are suitable for the purposes ... specified by the manufacturer, and suitable with regard to the performance they are intended to achieve, taking account of the generally acknowledged state of the art. **They shall achieve the performances, as stated by the manufacturer** and in particular, where applicable:
 - (a) the analytical performance, such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross- reactions; and
 - (b) the clinical performance, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.
- The performance characteristics of the device shall be maintained during the lifetime of the device as indicated by the manufacturer.

Annex I, Chapter II 16.3 and 16.4 (Part of Electronic programmable systems)

- Software referred to in this Section that is intended to be used in combination with mobile computing platforms shall be designed and manufactured taking into account the specific features of the mobile platform (e.g. size and contrast ratio of the screen) and the external factors related to their use (varying environment as regards level of light or noise).
- Manufacturers shall set out minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.

Annex I, Chapter II 19 Protection against risks posed by devices intended for self testing or near patient testing

- 19.1. Devices intended for self-testing or near-patient testing shall **be designed and manufactured** in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to the intended user and the influence resulting from variation that can be reasonably anticipated in the intended user's technique and environment.....

Annex I, Chapter II 19 Protection against risks posed by devices intended for self testing or near patient testing

-The information and instructions provided by the manufacturer shall be easy for the intended user to understand and apply in order to correctly interpret the result provided by the device and to avoid misleading information. **In the case of near-patient testing**, the information and the instructions provided by the manufacturer shall make clear the level of training, qualifications and/or experience required by the user.

Quality System ISO 13485:2016

Section 7 Product Realization

7.1 Planning of Product Realization

- The organization shall plan and develop the processes needed for product realization.....
- *The organization shall document one or more processes for risk management in product realization.*
- Records of risk management activities shall be maintained.
- In planning product realization, the organization shall determine:
 - quality objectives and requirements for the product;
 -
 - required verification, validation, monitoring, measurement, inspection and test, handling, storage, distribution and traceability activities specific to the product together with the criteria for product acceptance;
 - records needed to provide evidence that the realization processes and resulting product meet requirements.

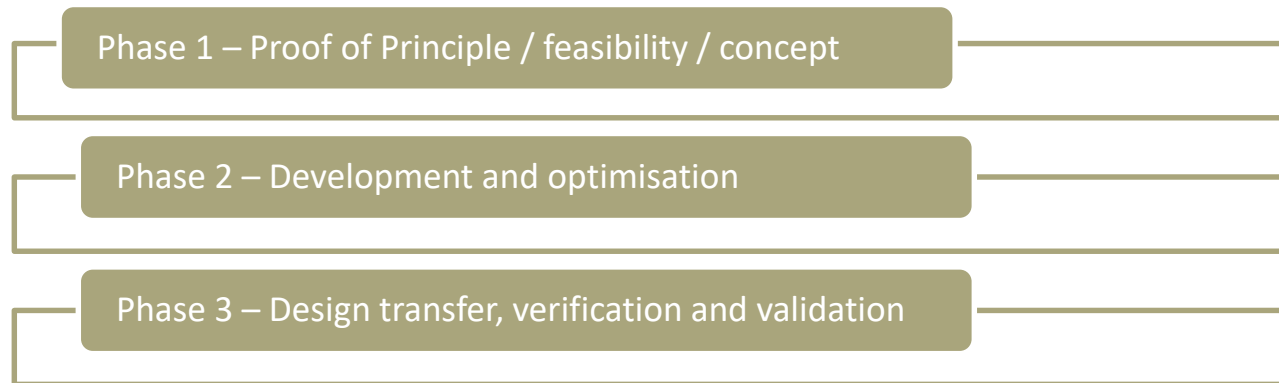
Quality System ISO 13485:2016

Section 7 Product Realization

- 7.3 Requires a Design and Development Procedure describing
 - Development Plan with phases of development
 - Design Inputs
 - Design Outputs
 - Design Reviews
 - Design Verification
 - Design Validation
 - Design Transfer to Production
 - Control of changes
 - Documentation requirements

Phases of Development

- *Development Plan*



Phase 1 PROOF OF CONCEPT

- Planning phase
 - Business case, route to market, commercial issues, customer needs and input, product definition.
 - Generate product specification and design inputs.
 - Define intended purpose, intended use population and intended users.
 - Development plan with estimates of costs, time, resources and activities for all phases.
- Early risk assessments
 - Business risks
 - Raw material and component risks
 - Supply chain issues
 - User needs and limitations
- Generate early data for proof of principle
 - Retrospective banked samples. Prove test will distinguish between disease and no disease state or e.g. increases/decreases with disease stage.
- End of Phase review
 - Do the early data suggest the product can be made?
 - Have you identified any major or business critical risks?



Phase 2 SAMPLE

- Sample type - any patient preparation or sample processing required
- Sample volume - minimum volume required for test
- Consistency / uniformity of sample – sputum, urine, swabs
- How collected and stored post collection – time limit on storage
- Different requirements for different sample types



Phase 2 Risk Points to Consider for POC / NPT

- Internal / external control system
 - Proof that device is functioning correctly each time when used
- User education / qualification / skills /age
 - Potential impact on reproducibility of result
 - Dexterity
- Use environment
 - Temperature / humidity fluctuations
 - Electrical connectivity and power surges / interruptions
 - Wifi connectivity
 - Battery life
 - Cleanliness of work space
 - Light levels - to read displays

Phase 2 VARIABLE DESIGN PHASE

- Development
 - Iterative process to identify a pilot product that appears at an early stage to be likely to deliver the design inputs / product specifications
 - Documentation of iterations, analysis of data and conclusions drawn, and decisions taken including reasons why a particular route was not taken.
 - Are GSPRs being addressed
- Optimisation
 - Adjustments to raw materials / components / protocol or instructions of use etc to deliver the best possible test performance while still maintaining safety profile.
 - Bench top data to demonstrate design inputs have been or are on track to be achieved.
- Risk assessments
 - ISO 14971 annex checklists
 - Ergonomics and human factors – ensure product is appropriate for intended users and use location
 - Risks to production and supply chain
- End of Phase review
 - Are GSPRs addressed or being addressed?
 - Compare design outputs to inputs. Can the design be locked down?
 - Is the business case still valid? Are all risks manageable?



Phase 3 LOCK DOWN PHASE

- Design Transfer to Production
 - Components and raw materials, specifications and suppliers
 - Manufacturing batch records and procedures
 - Incoming controls, in process controls and final product testing
 - Validation test batches – these re used for V & V
- Verification
 - Gather data to support product claims and intended purpose.
 - Gather data to comply with GSPRs.
 - Statistically relevant data, ethically generated
- Validation
 - Gather data to support clinical performance and safety profile
 - Gather data to support intended purpose statement in target population.
 - Gather data in the hands of the intended user.
 - Statistically relevant data, ethically generated
- Risk Management
 - Residual risks. Risk : benefit analysis and report.
- End of Phase review
 - Do data support product claims? Are all design inputs/goals achieved? Is risk : benefit analysis acceptable? Are technical file documentation and QMS documentation in place to support product development and the GSPRs.
 - Have risks been addressed, and controlled, are risk assessments in risk management file?



Phase 3 V & V

- **Verification**

- Analytical performance tests will confirm whether the device meets documented design specifications – including:
- Analytical sensitivity, Analytical specificity, Accuracy , Assay range and cut off, Repeatability and reproducibility, Control of known relevant interference, Impact of co-morbidities, Limits of detection.
- Stability testing (open and unopened), instrument life time.
- Depending on type, other 'bench tests' may include: software validation; electronic/electrical safety and usability testing

- **Validation**

- Clinical performance may include expected values, diagnostic sensitivity and diagnostic specificity based on the known clinical/physiological state of the individual, and negative and positive predictive values based on the prevalence of the disease.
- Clinical performance will also confirm sample collection and handling requirements – under normal conditions of use

Quality System ISO 13485:2016 = Good Laboratory Practice

- The R&D lab has responsibilities under the Quality Management System to operate to relevant GLP standards including:
 - Standard Operating Procedures for instrumentation and equipment.
 - IQ, OQ, PQ for instruments and equipment.
 - Instruments and equipment maintained, serviced and calibrated to a pre-defined schedule and status clearly labelled (in service / out of service)
 - Incoming acceptance procedures for raw materials, with clear labelling of status (accepted, awaiting testing / rejected)
 - Clear labelling of opened and unopened reagents, with date of opening and in-use shelf life.
 - Standard procedures with batch records for mixing reagents e.g. instrument calibration curve solutions.
 - Lab notebooks reviewed and approved.
 - Calculations double checked
 - Protocols written with acceptance criteria before conducting certain types of experiment and reports inclusive of all data
 - Laboratory cleaning and environmental monitoring defined and documented.

...an introduction to harmonised standards and other guidance

HOW TO DEMONSTRATE CONFORMITY TO THE GSPR

Harmonised Standards

Article 8

https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices_en

ISO13485

ISO15223

ISO13532

ISO18113

ISO14971

ISO13612

EN 62366

EN61010

EN62304

- Harmonised standards listed for IVD Directive 98/79/EC
- New harmonised list will be published for IVDR later

ISO 13485:2016

- Globally recognised QMS standard to demonstrate conformity assessment for manufacture of IVDs

IVDR Annex IX

- 2.1 The manufacturer shall lodge an application for assessment of its quality management system with a notified body.
- 2.2(c) the procedures and techniques for monitoring, verifying, validating and controlling the design of the device and the corresponding documentation as well as the data and records arising from those procedures and techniques.

ISO 14971:2012

- Globally recognised approach to risk management for medical devices
- Key overarching principle of ISO13485 and IVD Regulation
- Not certified by a Notified Body but they will review and assess the Risk Management File for compliance.

OTHERS COMMONLY USED

- BS EN 62304: 2006 Medical device software — Software life-cycle processes
- BS EN 62366-1: 2015 Medical devices Part 1: Application of usability engineering to medical devices
- BS EN ISO 18113 – X: 2011 In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling)
 - Part 2: In vitro diagnostic reagents for professional use
 - Part 4: In vitro diagnostic reagents for self-testing.
- BS EN ISO 15223-1 2012 Medical devices — Symbols to be used with medical device

Common Specifications

Article 9

- Class D IVDs will be required to follow the Common Specifications (CS) relevant to their analyte.
- CS are proscriptive about sample types, numbers and performance values that must be achieved

HIV	
Diagnostic sensitivity Positive samples	400 HIV-1 100 HIV-2 including 40 non-B subtypes, all available HIV/1 subtypes should be represented by at least 3 samples per subtype
Diagnostic sensitivity Seroconversion	20 panels 10 further panels (at Notified Body or manufacturer)
Diagnostic specificity	Unselected donors (including first-time donors) 5 000 Hospitalised patients 200 Potentially cross-reacting blood-specimens (RF+, related viruses, pregnant women, etc.) 100

Other guidance and help

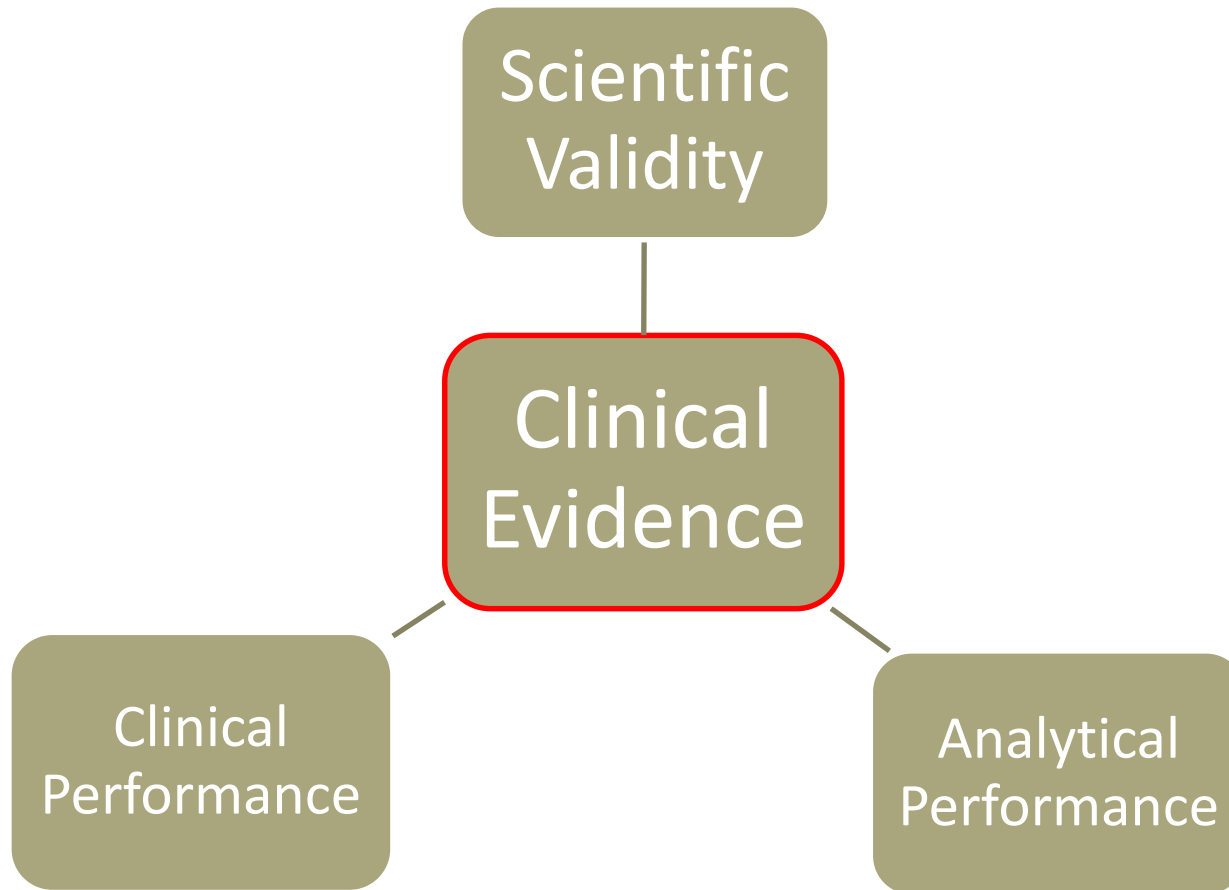
- National, regional and international standards that are not harmonised to the IVD Directive or Regulation.
- CLSI documents – typically used by R&D during product development and verification.
 - EP 25-A 2009 Evaluation of Stability of *In Vitro* Diagnostic Method Products
 - <https://clsi.org/standards/products/method-evaluation/>
- Global Harmonisation Task Force documents (Now IMDRF)
- WHO documents
- FDA guidance documents

And the importance of Clinical Evidence

PERFORMANCE EVALUATION

Clinical Evidence

Article 56



Scientific Validity

- Scientific validity is the association of an analyte with a clinical condition or a physiological state.
- Scientific Validity Plan and Report are required
- Potential sources of scientific validity (depending upon whether your analyte or marker is new, or use of novel technology).
 - Scientific peer reviewed literature
 - Relevant data / information from devices measuring same analyte or marker
 - Expert opinion / consensus opinion / position of professional associations
 - Pre-clinical data
 - Proof of concept data

Analytical Performance

- Analytical performance means the ability of a device to correctly detect or measure a particular analyte.
- Analytical Performance Plan and Report are required
- Analytical studies may include:
 - Analytical sensitivity and specificity, limits of blank, detection and quantitation, reproducibility and reliability, precision, bias and accuracy, upper and lower levels of quantitation and linear range, clinical cut-offs, analyte recovery, exogenous and endogenous interferences, analyte stability, sample collection and handling, sample matrix studies, freeze-thaw cycles of sample and critical reagents.

Clinical Performance

- Clinical performance means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.
- Clinical Performance Plan and Report are required.
- Clinical performance data may include diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.

Performance Evaluation

- Performance Evaluation is the process of collecting your clinical evidence.
 - An assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device.
- Performance Evaluation Plan and Report are required
- **Class C and D – A Post Market Performance Follow Up plan will be required**
- Device for performance study means a device intended by the manufacturer to be used in a performance study.
 - must be labelled For Performance Evaluation Only,
 - should be manufactured to final product specifications and released in accordance with final product release criteria.

Performance Evaluation Studies

Article 57 and Annex XIII

- Requires a Performance Evaluation Study Plan and Report
- Designed and conducted to ensure:
 - Safety of subjects and users
 - The clinical data are reliable and robust (statistically derived)
- Usually requires ethical approval, may require additional regulatory approvals
- Requires study protocols and data collection forms
- Trial subjects must be representative of the European population
- EN 13612 performance evaluation of in vitro diagnostic medical devices.

...including Summary Technical Documentation - STED

TECHNICAL DOCUMENTATION

Technical Documentation File

- Start from the IVD Regulation
 - Annex I - GSPR checklist
 - Annex II - Structure of the Technical Documentation
 - Annex III – Post Market Surveillance requirements
- Recommended use of GHTF format GHTF/SG1/N063:2011 Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices

<http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n063-2011-summary-technical-documentation-ivd-safety-conformity-110317.pdf>

- Cross-functional team effort – Regulatory, Quality, Manufacturing, R&D, Project Managers, Marketing and Clinical input is essential
- Start early in the design process
 - Build design file using GSPR as a backbone
 - Recommended start = end of feasibility (Phase 1)

Annex I: General Safety and Performance Requirements Checklist

- Checklist of Annex I GSPRs to confirm product meets the requirements of the regulation
- Any requirement determined not applicable should be justified
- Notified Body will request this checklist

Section	Requirement	Method to demonstrate conformity	Reference to Technical Document
I.1.	Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that....	ISO13485:2016 ISO14971:2012	Section xxx / SOP Section xxx / RM documents
I.2.	The requirements in this Annex to reduce risks as far as possible means the reduction of risks ...	ISO14971:2012	Section xxx / RM documents Risk/benefit report
I.3.	Manufacturers shall establish.....a risk management system	ISO13485:2016 ISO14971:2012	Risk management SOP Section xxx / RM documents
I.4.	Risk control procedures.....safety principles	ISO14971:2012 BS EN 62366: 2015	Relevant RM documents

Technical Documentation

Sections (Annex II and III)



... it does not end there...

POST-MARKET RESPONSIBILITIES

Post Market Surveillance

Chapter VII

- Post Market Surveillance procedure
 - How PMS is defined and implemented within manufacturer
- Post Market Surveillance Plan (Article 79)
 - Device/group/type strategy for implementation of process
 - Where? What? Who? How? When?
 - Meet requirements of IVDR annex III, section 1
 - Use a risk-based approach – one size does not fit all
- Post Market Surveillance Report (Class A and B)
- Periodic Safety Update Report (Class C and D)

Post Market Surveillance Reporting

Class A

Post Market Surveillance Report

- Summary of results & conclusions of analysis as a result of the PMS plan
- Available on request to notified body and competent authority
- Part of Technical Documentation

Class B

Post Market Surveillance Report

- Summary of result & conclusions of analysis as a result of the PMS plan
- Available on request to notified body and competent authority
- Part of Technical Documentation

Class C

Periodic Safety Update Report

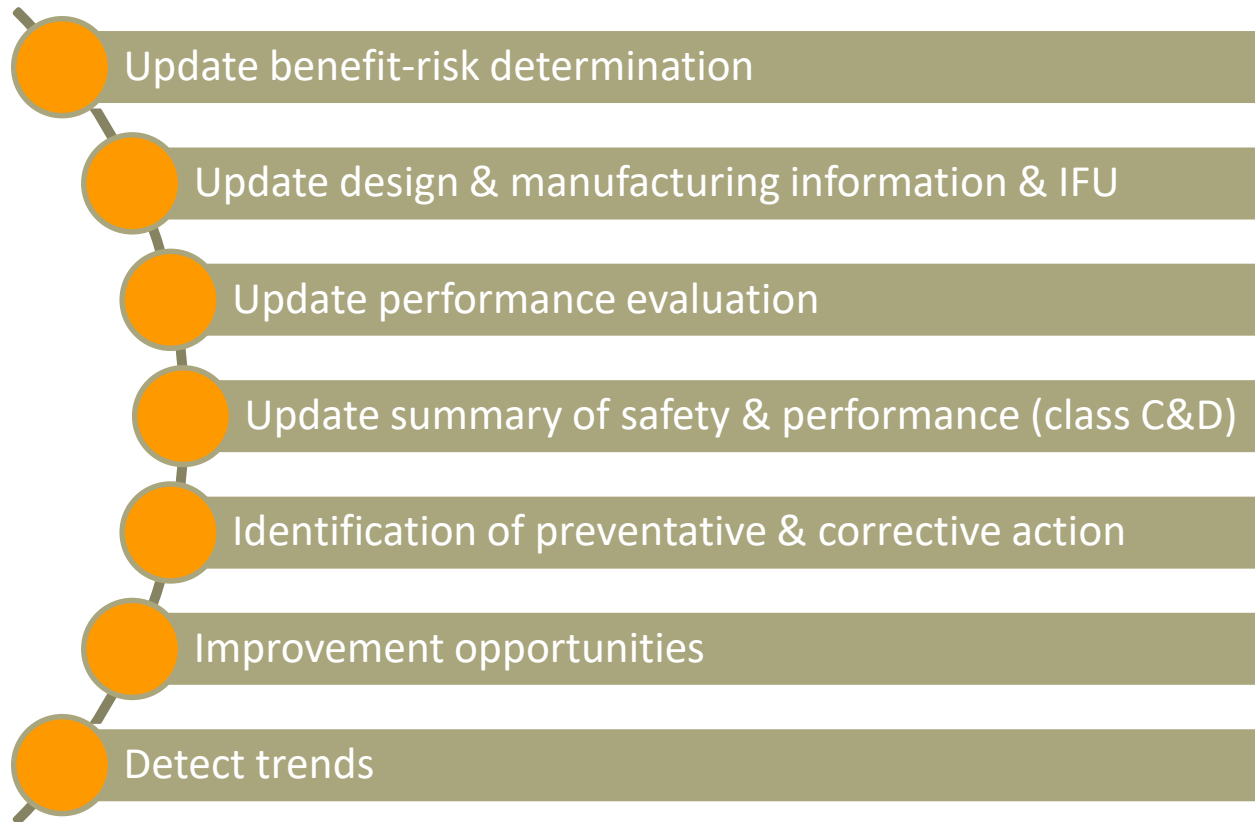
- Summary & conclusions of PMS activities including preventative & corrective action, Risk-benefit determination, Volume of sales and population information of device users
- Updated Annually and included as part of Technical Documentation
- Made available to Notified Body on request

Class D

Periodic Safety Update Report

- As above
- Manufacturer to submit to Notified Body
- Notified Body to review, evaluate and upload into Eudamed

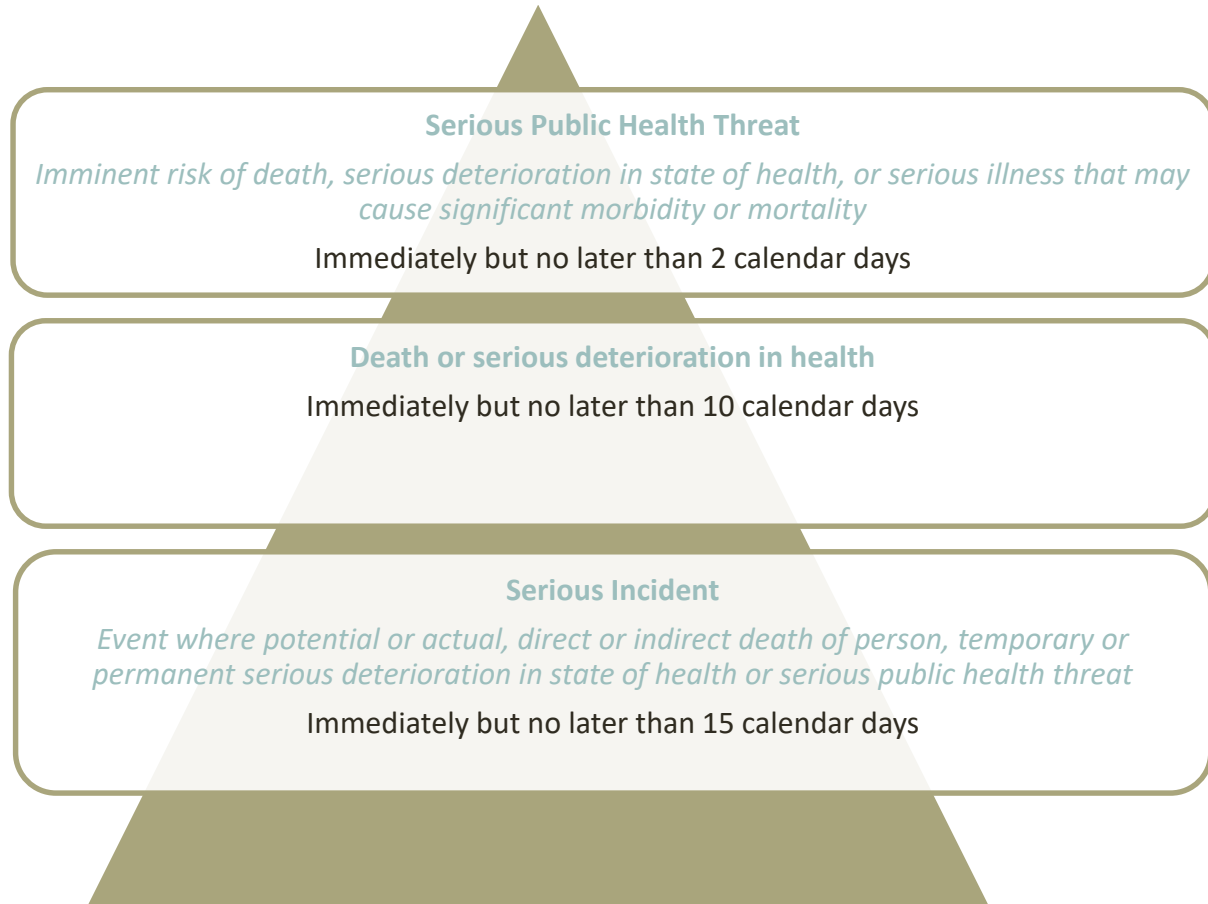
Post Market Surveillance



Complaints & Vigilance

- All economic operators (importers, distributors) must have complaint handling procedures in place and share relevant information with the legal manufacturer and/or the authorised representative.
- All economic operators must cooperate with relevant Vigilance investigations and Field Safety Corrective Actions.
- Contractual agreements in place between the Legal Manufacturer and economic operators should include these obligations.
- Notified Bodies will review these as part of Supplier Control during the QMS audits.

Vigilance – reporting timelines



Trend Reporting

- Manufacturer must report via Eudamed when
 - Significant increase in severity or frequency of non serious incidents that could have
 - Adverse impact on benefit-risk analysis of product
 - Which have led to unacceptable risk to persons
 - Or any significant increase in erroneous results compared to stated performance
- Manufacturer will determine method to identify statistical significance – PMS Plan
- Effective risk management is key
 - Closely tied with complaint and market data

...Roles and responsibilities

PLACING ON THE MARKET – KEY PLAYERS

Economic Operators

Manufacturer

Legal person who manufactures or refurbishes the device under its own name

Virtual Manufacturer

Legal person who does not design and develop product but places own name on the device

Authorised Representative

Within EU who acts on behalf of non-EU manufacturer for responsibilities within EU

Importer

Within EU who first places a non-EU device within the EU market

- Identify roles early in development
- Understand the responsibilities

Distributor

Person in the supply chain, other than manufacturer or importer that makes a device available within the EU market

Legal Manufacturers

Art. 10 - General Obligations of Manufacturers

- Design and manufactured in accordance with requirements of regulation
- Risk Management
- Completed performance evaluation
- Compilation of technical documentation
- Conformity assessment of Quality Management System
- Unique Device Identification (UDI) and Information for Use (IFU)
- Product liability insurance
- Person with Responsibility for Regulatory Compliance If third country – establish an Authorised Representative

Virtual Manufacturers

Article 16

- Must hold and take full legal responsibility of technical documentation for any product under their name
- Requires a Quality Management System subject to review by notified body
- Sign an EU declaration of conformity
- Clear contractual agreements with 3rd part manufacturer

MHRA Guidance: Medical Devices: Virtual Manufacturing replaces Own Brand Labelling

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/604371/Own-Brand-Labelling-toVirtual-Manufacturing-Final.pdf

Authorised Representative

Art. 11 – Authorised Representative

- Third country must appoint one AR within EU
- Documented mandate of responsibilities agreed
- Ensure technical documentation and conformity assessment completed
- Maintain current versions of technical documentation and certification
- Registration obligations
- Vigilance reporting
- Product liability insurance
- Person with Responsibility for Regulatory Compliance

Importers

Art. 13 – General obligations of importers

- Ensures that devices are in conformity to the regulation
- Ensures device is CE marked and registered in Eudamed
- Declaration of conformity is available
- Authorised representative is appointed by manufacturer and listed within packaging
- Device is labelled in accordance with the regulation and accompanied by IFU
- UDI has been assigned
- Packaging contains importer name and address
- Maintain stability of product throughout transport and storage
- Maintain and provide complaint and non-conformance data

Distributors

Art. 14 – General obligations of distributors

- Ensure that device is CE marked and Declaration of conformity is available
- Device is accompanied by IFU
- Importers name and address on the packaging
- UDI is assigned

- Establish sampling method to check the above
- Maintain device stability during transport and storage
- Maintain and provide complaint data to manufacturer

Person with Responsibility for Regulatory Compliance (PRRC)

A new role under the IVDR – described in Article 15.

Qualifications: PRRC must have either

- A degree in a relevant subject and 1 year experience in RA or QMS with *in vitro* diagnostic medical devices; or
- Four years experience in RA or QMS with *in vitro* diagnostic medical devices

Job description: Role of PRRC includes

- The conformity of the device checked, in accordance with the quality management system under which they are manufactured, before a device is released
- The technical documentation and the EU DoC are drawn up and kept up-to-date
- The PMS obligations are complied with
- The reporting obligations are fulfilled
- A statement is issued for interventional studies that devices meet the GSPRs

Notified Bodies

Chapter IV and Annex VII

- ❖ Designated by the Commission
 - ❖ *Designations expected for IVDR end 2019 / early 2020*
- ❖ Scope of designation published on NANDO database
 - ❖ <http://ec.europa.eu/growth/tools-databases/nando/>
- ❖ Manufacturer can choose any from designated list that has relevant scope
 - ❖ e.g. National Standards Authority of Ireland not designated under IVDD for Annex II List A devices
- ❖ Contractual agreement between Notified Body and Manufacturer

European Reference Laboratory

Article 100

- ❖ Designated by the Commission
 - ❖ *Designations expected after 2020*
- ❖ Class D devices within their designated scope – verify performance claims and compliance to common specifications as part of conformity assessment
- ❖ Notified Bodies cannot issue certificate if EU Reference Lab test report is unfavourable
- ❖ Batch release for all Class D devices.
- ❖ Note: Member states may request EU Reference Labs also verify performance of Class C devices.

... packaging and labelling requirements

UDI AND LABELLING

UDI

Article 24 and Annex VI

Gives traceability of production



UDI comprises a fixed part (manufacturer and product code) and variable part (batch/serial number)

UDI issuers will be designated by European Commission. Manufacturer must enter into a contract with their selected issuer.

Basic UDI will be entered on Eudamed

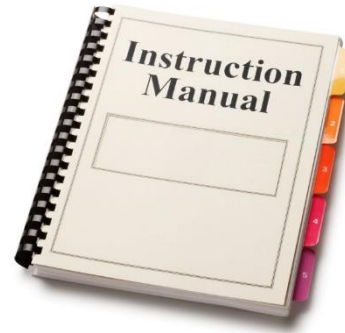
UDI will be phased in over 4 years. Class D devices require UDI labelling by 2023 and Class A by 2027

Labelling

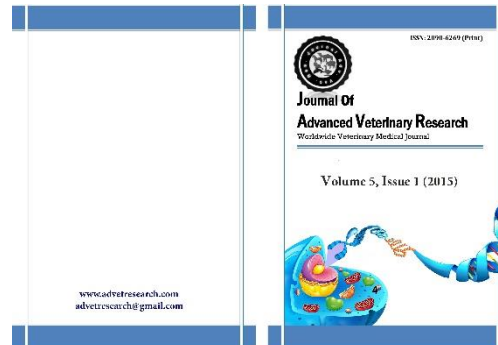
Product labels



Instructions for Use /
package inserts / user
manuals



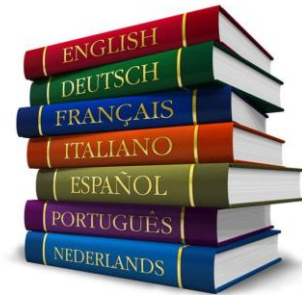
Marketing and sales
materials (including
verbal statements)



Labelling

Annex I, Chapter III

Most EU countries require their national language(s)



Use of harmonised symbols permitted

Symbols that are not harmonised (BS EN 15223) must be described and translated somewhere in the labelling

IVDR Annex I, Ch III and Labelling standards give detail of minimum information required on labels and details about information required in the Instructions for Use / User manuals.

EUDAMED

Article 30

European Database on Medical Devices

Manufacturers will upload information

Modules for

- UDI
- Registration of devices
- Registration of manufacturers, authorised representatives and importers
- Notified Body certificates
- Performance studies
- Vigilance
- Market surveillance

- *Certain modules will have public access*





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I hope that was helpful.....

THANK YOU