THE IN-VITRO DIAGNOSTICS REGULATION (IVDR):

UNRAVELLING THE CHALLENGES OF THE TRANSITION

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This whitepaper discusses the new European in vitro Diagnostic Medical Devices Regulation, **EU-IVDR 2017/746**, and the increased requirements it introduces to the IVD Industry. The IVDR-specific provisions with respect to classification, General Safety and Performance Requirements (GSRs), Technical Documentation, Economic Operators (EOs), Conformity Assessment and clinical data/performance evaluations are presented and discussed.

We outline:

- The IVD Regulation and its main differences from the IVD Directive
- The new, risk-based classification system and how it changes interventions of Notified Bodies
- The changes in Conformity Assessment
- The increased requirements for clinical evidence and the respective changes in performance evaluations
- The changes introduced in the Quality Management system (QMS), and therefore to Post-Market Surveillance (PMS) and Risk Management (RM) activities, which must now cover the entire lifetime of IVDs

IVDR requires Notified Body intervention for 80-90% of IVDs sold in Europe, compared to 10-20% that were evaluated under IVDD, which automatically translates into a need for QMS remediation, if not design from scratch, and Technical Documentation. In addition, just like in EU-MDR, there have been no grandfathering provisions, which combined with a new risk-based classification system, adds further challenges for manufacturers.

Software as part of IVD instruments (SaMD), single-use IVDs, companion diagnostics (CDx), and genetic tests are oversighted in a new perspective, while at the same time, vigilance and Post-market Surveillance requirements become more stringent aiming to cover the entire lifetime of IVDs.

Along with safety and performance requirements, IVDR launches a new understanding of traceability and calls for a revised role of Economic Operators by the introduction of the Person Responsible for Regulatory Compliance (PRRC) and the increased preconditions for Authorized Representatives and Importers.

DISCLAIMER | This white paper is issued for information only. It does not substitute In-vitro Medical Device Regulations, Directives, official Guidance(s) and/or official or agreed advice from designated Notified Bodies. The views expressed are entirely those of its authors. All rights reserved. Except as permitted under the Copyright, Designs and Patents Act 1988, no part of this publication may be reproduced without prior permission in writing from Evnia. Whilst every care has been taken in developing and compiling this publication, Evnia accepts no liability for any loss or damage caused, arising directly or indirectly in connection with reliance on its contents except to the extent that such liability may not be excluded in law. Whilst every effort has been made to trace all copyright holders, anyone claiming copyright should get in touch with Evnia at any of the addresses of the last page.

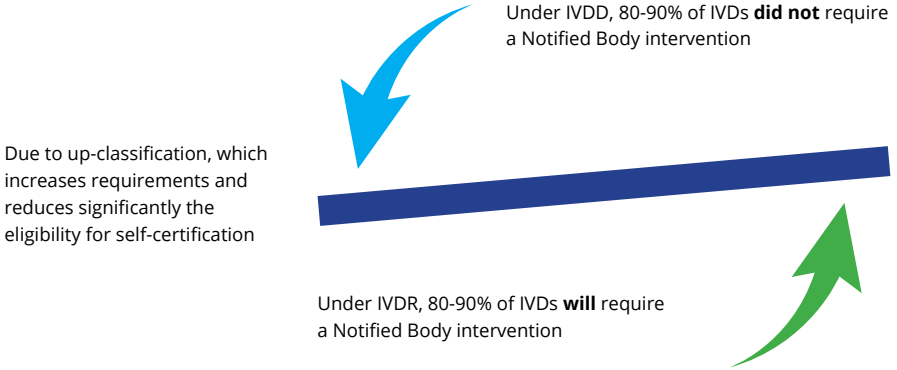
INTRODUCTION

THE CHANGING LEGAL FRAMEWORK FOR THE IN-VITRO DIAGNOSTICS INDUSTRY

The increased needs for early and accurate diagnosis along with the expanding field of personalized medicine have triggered the demand for in-vitro diagnostics with higher sensitivity and specificity.

For this reason, the new IVD Regulation published in May 2017, tries to align more with the life-cycle perception for diagnostics promoted by the FDA and takes a distance from the simplified views of the 98/79/EC Directive. Yet this strategic decision has come with numerous challenges for the European market as it introduces significantly more requirements in almost all regulatory aspects ranging from Notified Bodies to manufacturers and Economic Operators.

The adoption of the risk-based conception has resulted in the overnight up-classification of almost 90% of marketed IVDs!



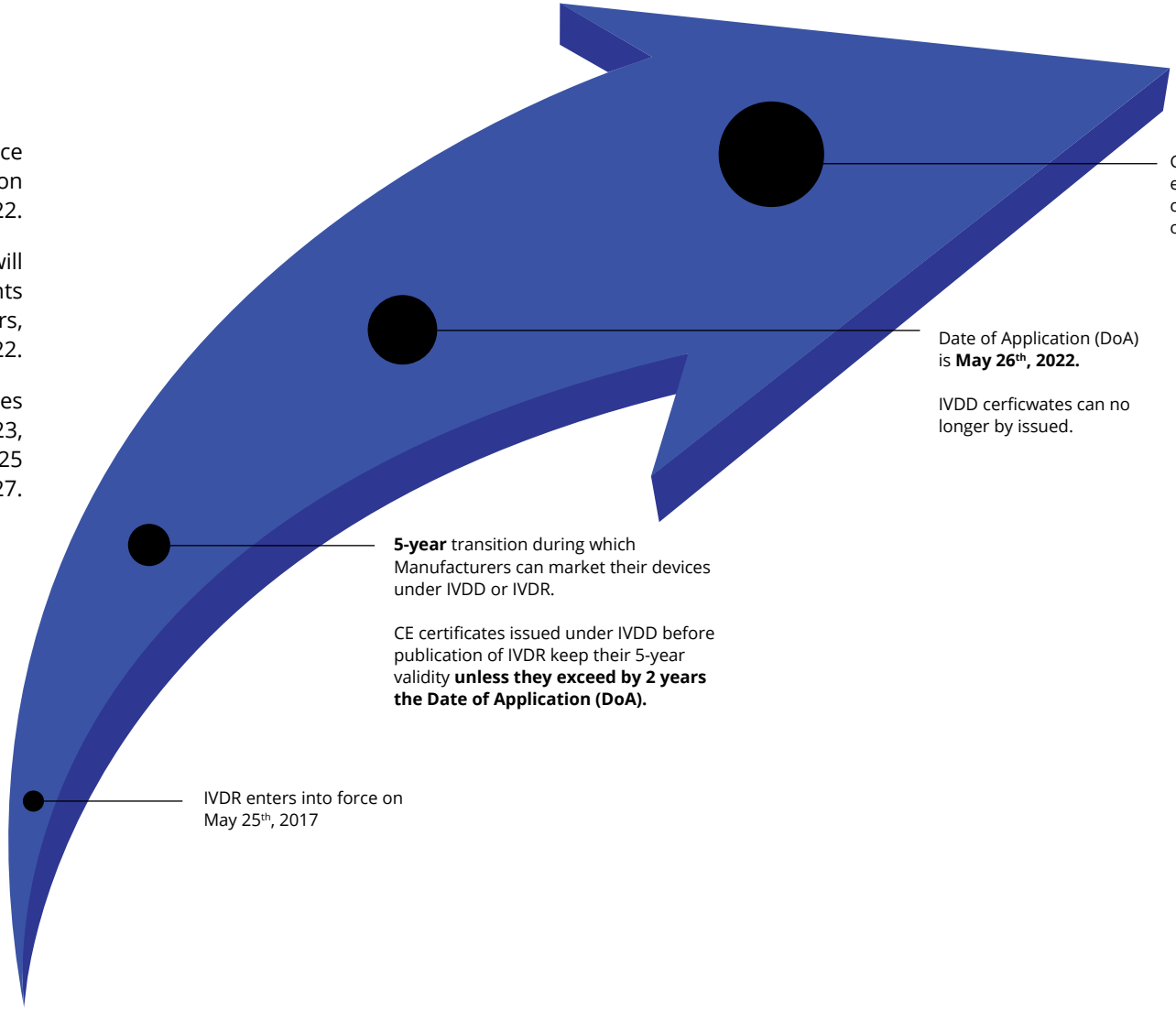
DEFINITION OF IN-VITRO DIAGNOSTICS - ART.2	SCOPE - WHAT IS NOT AN IVD
Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used 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	The scope of the new IVD Regulation does not include: • products for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination; • invasive sampling devices or those which are directly applied to the human body for the purpose of obtaining a specimen; • internationally certified reference materials; • materials used for external quality assessment schemes.

DATES OF APPLICATION AND TRANSITIONAL PROVISIONS

The Regulation has been formally adopted and into force since May 27th, 2017. Currently, it is under a 5-year transition period and will be fully applicable from May 26th, 2022.

Certificates issued prior to May 25th, 2017 will become void by 27 May 2024. However, requirements with respect to registration of Economic Operators, QMS and PMS and QMS will apply since May 2022.

With respect to UDI, requirements for class D devices should be implemented on or before May 26th, 2023, for class B and C the deadline is on May 26th, 2025 whereas class A IVDs must conform by May 26th, 2027.



OVERVIEW OF THE 2017/746 REGULATION

The Regulation is organized in 10 chapters containing 113 Articles and 15 Annexes.

THE STRUCTURE OF THE NEW IVD REGULATION	
CHAPTERS	**ANNEXES**
Chapter I (Art. 1-4): Introductory provisions	Annex I: General safety and performance requirements
Chapter II (Art. 5-21): Making available on the market and putting into service of devices, obligations of economic operators, CE marking, free movement	Annex II: Technical documentation
Chapter III (Art. 22-30): Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance (SSCP), European database on medical devices	Annex III: Technical documentation on post-market surveillance
Chapter IV (Art. 31-46): Notified bodies	Annex IV: EU Declaration of conformity (DoC)
Chapter V (Art. 47-55): Classification and conformity assessment	Annex V: CE marking of conformity
Chapter VI (Art. 56-77): Clinical evidence, performance evaluation and performance studies	Annex VI: Information to be submitted upon the registration of devices and economic operators in Accordance with Art. 26(3) and 28, core data elements to be provided to the UDI database together with the UDI-DI in accordance with Art. 25 and 26 and the UDI system
Chapter VII (Art. 78-95): Post-market surveillance (PMS), vigilance, market surveillance	Annex VII: Requirements to be met by notified bodies
Chapter VIII (Art. 96- 101): Cooperation between member states, medical device coordination group, EU reference laboratories and device registers	Annex VIII: Classification rules
Chapter IX (Art. 102- 106): Confidentiality, data protection, funding and penalties	Annex IX: Conformity assessment based on a quality management system and assessment of the technical documentation
Chapter X (Art. 107- 113): Final provisions	Annex X: Conformity assessment based on type examination
	Annex XI: Conformity assessment based on production quality assurance
	Annex XII: Certificates issued by a notified body
	Annex XIII: Performance evaluation, performance studies and postmarket performance follow-up
	Annex XIV: Interventional clinical performance studies and certain other performance studies
	Annex XV: Correlation table

MAJOR CHANGES IN COMPARISON TO DIRECTIVE 98/79/EC (IVDD)

Evidently, the most significant change introduced by IVDR lies in the new classification system, which transits from the list-based to a risk-based approach of 4 categories (classes A, B, C, D) and transforms the whole regulatory framework for IVDs (see below for a presentation of the new classification system).

On top of this, there are no grandfathering provisions. Moderate and high-risk IVDs must be certified to meet the IVDR by May 2022 (unless a delay is dictated), while low risk IVDs may profit from the grace period until May 2024 but still must meet IVDR QMS requirements since the DoA.

As already discussed, the new IVD Regulation tries to align with the FDA perception of IVDs and aims to serve the emerging needs of genetic diagnostic and precision medicine. This is why several terms of these fields are introduced and defined (see below), and focus is shifted towards companion diagnostics.

Companion diagnostic	means a device which is essential for the safe and effective use of a corresponding medicinal product to: (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;
Device for near-patient testing	any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional;
Falsified device	any device with a false presentation of its identity and/or of its source and/or its CE marking certificates or documents relating to CE marking procedures. This definition does not include unintentional non-compliance and is without prejudice to infringements of intellectual property rights
Genetic testing	introduced as "concerning the predisposition to a medical condition or a disease." Although with some bending of rules these tests are currently overseen by the IVDD, they will now be formally defined as IVDs.
Kit	a set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic examination, or a part thereof;
Single-use device	device that is intended to be used during a single procedure

ECONOMIC OPERATORS

IVDR brings in more stringent and concrete requirements for authorized representatives (see Art. 12), importers (see Art. 13) and distributors (see Art. 14). As described in Art. 16. These stakeholders should ensure that

- ❑ The IVD is properly CE marked and there is an available EU DOC at all times
- ❑ The manufacturer is identified and the authorized representative (where applicable) is designated
- ❑ They hold active participation in post-market surveillance and complaint handling
- ❑ Process for storage and transportation without compromising the intended use of the device is in place
- ❑ The manufacturer has liability insurance to provide sufficient financial coverage to the natural or legal persons who claim compensation for damage caused due to a defective device

Of note
The retention period for Technical Documentation, Declaration of Conformity and relevant certificates, including amendments and supplements is at least 10 years after the last device covered by the EU declaration of conformity (DOC) has been placed on the market.

The 'Article 15' man

Manufacturers shall have available within their organization at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of medical devices.

The Person Responsible for Regulatory Compliance (PRRC) is introduced in Chapter II and is explicitly responsible for safeguarding regulatory compliance within the manufacturer and Authorized Representative as ARs must also appoint a PRRC. In particular, the PRRC is responsible for

- ❑ The compliance of the medical devices is suitably checked, in line with the quality management system (QMS) under which the devices are produced, and this should be done before the product is released.
- ❑ The EU declaration of conformity and EU technical documentation are managed and maintained with the incorporation of all the necessary updates.
- ❑ The post-market surveillance responsibilities are fulfilled consistently with the MDR requirements.
- ❑ Reporting requirements to regulatory authorities and others are well managed including those of the vigilance and analysis reporting, serious incident reporting, field safety corrective measures and the trend analysis etc.
- ❑ For the devices involved within investigation, a statement signed should be available demonstrating that the devices meet the requirements of the General Safety and Performance Requirements (GSPR).

This new requirement is turning out to be particularly challenging for non-EU manufacturers entering the EU market for the first time as the profile of the PRRC is very specific and his appointment a difficult task.

UNIQUE DEVICE IDENTIFIERS AND TRACEABILITY

Unique Device Identifiers (UDIs) are […] *a series of numeric or alphanumeric characters . . . created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market.* […].

Mandatory Unique Device Identification is introduced as mandatory requirement with the intention to facilitate device traceability and to enhance transparency. IVDs will be allocated device identifiers, and batches or production series will be identified with production identifiers respectively. The basic device identifier (Basic UDI-DI) must be included in the information provided with the Declaration of Conformity and should be available on the certificates of class B, C, and D IVDs.

In the same context, EUDAMED will contain the "summary of safety and performance" for Class D IVDs. For its purposes, the manufacturer is required to prepare a clearly readable document for the intended user and, when applicable, the patient, which is why the summary of safety and performance will be translated into all languages of the Member States where the device is marketed. The Notified Body will be assessing this document and uploading it to EUDAMED together with their assessment report. The launch of EUDAMED was initially targeted for MDR's DoA, i.e, May 26th, 2020. However, due to various reasons, its launch has now been pushed out to coincide with IVDR DoA in May 2022.

As per Art. 22 […] *Distributors and importers* ***shall*** *co-operate with manufacturers or authorised representatives to achieve an appropriate level of traceability of devices.* […] and in addition *[…] Economic operators shall store and keep, preferably by electronic means, the UDI of the devices which they have supplied or with which they have been supplied. […]* (see Art. 24(8)).

IMPACT ON QUALITY MANAGEMENT SYSTEMS (QMS)

As explicitly mentioned in preliminary statement (1), IVDR aims to establish

> *a robust, transparent, predictable and sustainable regulatory framework for in vitro diagnostic medical devices which ensures a high level of safety and health whilst supporting innovation*

This is translated into new various requirements but mainly focuses on the aspects discussed in Art. 10(8), i.e.

- ❑ Design changes
- ❑ Process verification/validation
- ❑ Production process controls
- ❑ Regulatory compliance
- ❑ Risk management
- ❑ Performance evaluation
- ❑ Post-Market Surveillance

Although many of these are not at all new entries for the Industry, and are aligning with EN ISO 13485:2016 requirements, IVDR upgrades the importance of documentation, implementation and maintenance of QMS (see Annex II, section 3.2 & Annex IX, section 2) in comparison to the Directive as it shall now include a thorough strategy for regulatory compliance taking into account GSPRs, PMS and RM requirements.

After the DoA, QMS assessment will be performed by Notified Bodies.

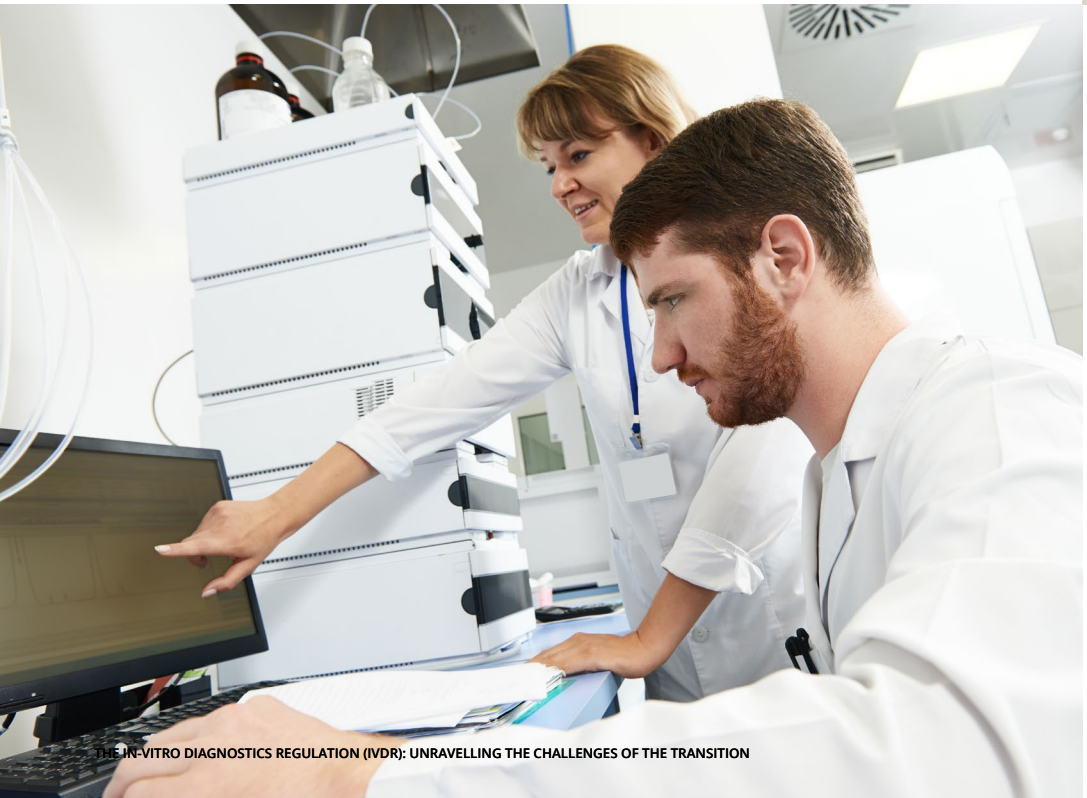
OVERVIEW OF THE MAIN CHANGES INTRODUCED BY THE IVDR IN COMPARISON TO THE 98/79/EC DIRECTIVE

DEFINITION & SCOPE	REGULATORY STAKEHOLDERS	ESSENTIAL REQUIREMENTS
❑ Applies to all IVDs & accessories ❑ New definitions & rules for companion diagnostics, in-house tests, kits, single-use IVDs, distance sales	❑ Apart from Manufacturers, Notified Bodies (see Chpt IV) & Competent Authorities, there are explicit roles for distributors and importers	❑ More detailed description of GSPRs (see Annex I) ❑ Harmonized Standards & Common Specifications expected to play key role ❑ Specific rules: self-testing & NPT IVDs, CDx, genetic tests, in-house tests
PERFORMANCE EVOLUTION	**CLINICAL STUDIES**	**CONFORMITY ASSESSMENT**
❑ Clarification of performance indicators (scientific validity, analytical & clinical performance) ❑ Explicit requirement to collect analyse clinical evidence throughout the life-cycle of a IVD ❑ Process of performance evaluation defined ❑ Required throughout the lifetime of the device ❑ Plan for performance evaluation	❑ Clinical performance studies required although some exceptions apply ❑ Focus on transparency of data from clinical performance studies (see Chpt VI) ❑ Provision for interventional performance studies	❑ Amended to reflect the new classification rules ❑ NB involvement in all classes except class A, non-sterile ❑ Involvement of EMA & reference laboratories (see Chpt V, section 2 and Annexes IX, X, XI)
MOST-MARKET REQUIREMENTS	**TRANSPARENCY & TRACEABILITY**	**MANUFACTURER OBLIGATIONS**
❑ Definition of PMS activity with PMPF (see Art.10(3)) ❑ Post-market follow-up plan (PMPF) requirements (see Chpt VII) ❑ Continuous updates of the PER (see Art. 56) ❑ Incident reporting and trending	❑ EUDAMED will be accessible to public and stakeholders ❑ Unique Device Identifier (UDI) for traceability in the supply chain (see Art. 10(4) & 24)	❑ Every manufacturer shall have a designated person responsible for regulatory compliance (see Art.15) ❑ Manufacturers outside the EU/EEA shall have an appropriate contract with an authorised representative based inside the EU/ EEA (see Art. 11)
TECHNICAL DOCUMENTATION	**QUALITY MANAGEMENT SYSTEM**	**RISK MANAGEMENT ACTIVITIES**
❑ Development of a Technical Documentation (TD) file in compliance with Annexes II & III is mandatory (see Art. 10(4)) ❑ Significant changes in comparison to IVDD that add workload and requirements	❑ Implementation of QMS (see Art. 10(8)) with increased requirements on creation, maintenance ❑ Focus on risk management (see Annex I, section 3)	❑ Requirements for maintaining a risk management system (see Art. 10(2)) differs based on device classification and has to take to cover the entire lifetime of the device (see Annex I)

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

The juxtaposition of IVD Essential Requirements with IVDR GSPRs clearly illustrates the extra workload with respect to safety and performance requirements; the new list now has more than 190 items to review, while [...] taking into account the generally acknowledged state of the art.[...]

Introduction of post-market surveillance throughout the lifetime of the IVD as well as the reduction of risks “as far as possible” but “without adversely affecting the risk-benefit ratio” calls for an entirely new structure and evaluation of GSPRs including new sections for requirements for performance characteristics, [...] electronic programmable systems, [...] and self-testing and near-patient testing.



TECHNICAL DOCUMENTATION

The juxtaposition of IVD Essential Requirements with IVDR GSPRs clearly illustrates the extra workload with respect to safety and performance requirements; the new list now has more than 190 items to review, while [...] taking into account the generally acknowledged state of the art.[...]

Introduction of post-market surveillance throughout the lifetime of the IVD as well as the reduction of risks “as far as possible” but “without adversely affecting the risk-benefit ratio” calls for an entirely new structure and evaluation of GSPRs including new sections for requirements for performance characteristics, [...] electronic programmable systems, [...] and self-testing and near-patient testing.

IVDR requirements for Technical Documentation	REF	IVDD requirements - Annex III
Device description and specification including variants and accessories Reference to previous and similar generations of the device	Annex II Section 1 - 28 points	The technical documentation must allow assessment of the conformity of the product with the requirements of the Directive. It must include in particular: ❑ a general description of the product, including any variants planned, ❑ the documentation of the quality system, ❑ design information, including the determination of the characteristics of the basic materials, characteristics and limitation of the performance of the devices, methods of manufacture and, in the case of instruments, design drawings, diagrams of components, sub-assemblies, circuits, etc., ❑ in the case of devices containing tissues of human origin or substances derived from such tissue, information on the origin of such material and on the conditions in which it was collected, ❑ the descriptions and explanations necessary to understand the abovementioned characteristics, drawings and diagrams and the operation of the product, ❑ the results of the risk analysis and, where appropriate, a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the Directive if the standards referred to in Article 5 have not been applied in full, ❑ in the case of sterile products or products with a special microbiological state or state of cleanliness, a description of the procedures used, ❑ the results of the design calculations and of the inspections carried out, etc., ❑ if the device is to be combined with other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when combined with any such device(s) having the characteristics specified by the manufacturer, ❑ the test reports, ❑ adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available), with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used; such data should originate from studies in a clinical or other appropriate environment or result from relevant biographical references, ❑ the labels and instructions for use, ❑ the results of stability studies. ❑ The manufacturer shall take necessary measures to ensure that the manufacturing process follows the principles of quality assurance as appropriate for the products manufactured. The system shall address: ❑ the organizational structure and responsibilities, ❑ the manufacturing processes and systematic quality control of production, ❑ the means to monitor the performance of the quality system. ❑ The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the competent authorities of the following incidents immediately on learning of them: ❑ any malfunction, failure or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to, or might have led to, the death of a patient or user or other persons or to a serious deterioration in his or their state of health; ❑ (ii) any technical or medical reason connected with the characteristics or the performance of a device for the reasons referred to in subparagraph (i) leading to systematic recall of devices of the same type by the manufacturer. ❑ For devices for self-testing the manufacturer shall lodge an application for examination of the design with a notified body. ❑ The application shall enable the design of the device to be understood and shall enable conformity with the design-related requirements of the directive to be assessed. ❑ It shall include: ❑ test reports including, where appropriate, results of studies carried out with lay persons, ❑ data showing the handling suitability of the device in view of its intended purpose for self-testing, ❑ the information to be provided with the device on its label and its instructions for use.
Information to be supplied by the manufacturer	Annex II Section 2 - 3 points	
Design and manufacturing information Design information Manufacturing information	Annex II Section 3 - 9 points	
General safety and performance requirements	Annex II Section 4 - 5 points	
Benefit-Risk Analysis and Risk Management	Annex II Section 5 - 3 points	
Product verification and validation Information on analytical performance of the device	Annex II Section 6.1- 17 points	
Product verification and validation Information on analytical performance of the device	Annex II Section 6.2- 1 point introducing PER requirements	
Product verification and validation Stability	Annex II Section 6.3- 14 points	
Product verification and validation Software verification and validation	Annex II Section 6.4-1 point; new requirement	
Product verification and validation. Additional information required in specific cases	Annex II Section 6.5-4 points	
Technical Documentation on post-market surveillance	Annex III -21 points	
Declaration of Conformity	Annex IV	

CLASSIFICATION

IVDR introduced 7 new, risk-based rules as per the classification scheme below. For IVDs with multiple intended purposes, all purposes must be classified and the highest risk class is applicable.

Of note that in IVDR,

- The only self-certified devices are the ones falling under Rule 5 (e.g. products for general laboratory use, buffers, general culture media, histological stains, instruments for IVD procedures and specimen receptacles)
- Products falling under rule 6 (i.e. the ones not covered by any other Rule) require Notified Body certification
- Manufacturer proposes the classification based on the intended purpose. A notified body shall verify this proposal for classes A sterile, B, C, and D. In case of a dispute, national Competent Authorities arbitrate
- Software, which drives a device or influences the use of the device shall fall within the same class as the device. If the software is independent of any other device, it shall be classified in its own right (Annex VIII(1.4)). Also refer to MDCG 2019-11

As understood, there will be significantly more products in class D in comparison to IVDD's Annex II List A. Nevertheless, the largest proportion of IVDs will fall into class B, while companion and cancer diagnostics as well as those for infectious diseases will be falling into class C. The recent Guidance MDCG 2020-16 provides concrete examples of classification.

Only instruments and simple devices, such as wash solutions, will remain in Class A and continue to be self-declared.

RULE 1 - BLOOD SCREENING / HIGH-RISK DISEASES

- Transmissible agents in substances, cells, tissues, organs, etc. intended for donation
- Transmissible life-threatening agents with high-risk of propagation
- Monitoring infectious load of life-threatening diseases

CLASS D

Rule 1 does not apply? → **NO** → Consider Rule 2

RULE 2 - BLOOD OR TISSUE COMPATIBILITY

Devices intended to be used for blood grouping, or tissue typing as part of transfusion, transplantation, or administration.

Except when intended to determine any of the following, high-risk markers: ABO system [A (ABO1), B (ABO2), AB (ABO3)] ; Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)] ; nKell system [Kel1 (K)] ; Kidd system [JK1 Jka), JK2 (Jkb)] ; Duffy system [FYl (Fya), FY2 (Fyb)].

CLASS C | **CLASS D**

Rule 2 does not apply? → **NO** → Consider Rule 3

RULE 3 - INFECTIOUS DISEASES - CANCER TESTING - COMPANION DIAGNOSTICS - GENETIC TESTING - CONGENITAL SCREENING

- Infectious diseases, including sexually transmitted agents
- Pre-natal screening, congenital disorders in embryo, fetus, or newborn
- Companion diagnostics
- Disease staging
- Screening, diagnostics, and staging of cancer
- Genetic testing

CLASS A

Rule 3 does not apply? → **NO** → Consider Rule 4

RULE 4 - SELF-TESTING / NEAR-PATIENT TESTING

- Devices intended for self-testing
- Devices intended for near-patient testing are classified in their own right.

Devices intended for self-testing except for devices for the detection of pregnancy; fertility testing; determining cholesterol level; detection of glucose, erythrocytes, leucocytes and bacteria in urine.

CLASS C | **CLASS B**

Rule 4 does not apply? → **NO** → Consider Rule 5

RULE 5 - THE ONLY SELF-CERTIFIED DEVICES!

- Products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, general culture media and histological stains, intended for IVD procedures relating to a specific examination
- Instruments intended for IVD procedures
- Specimen receptacles

CLASS A

None of the other Rules apply?
Classify per Rule 6 in class B

RULE 6 - NONE OF THE OTHER APPLY

Devices not covered by the above-mentioned classification rules are classified as class b.

CLASS B

RULE 7

Devices which are controls without a quantitative or qualitative assigned value.

CLASS B

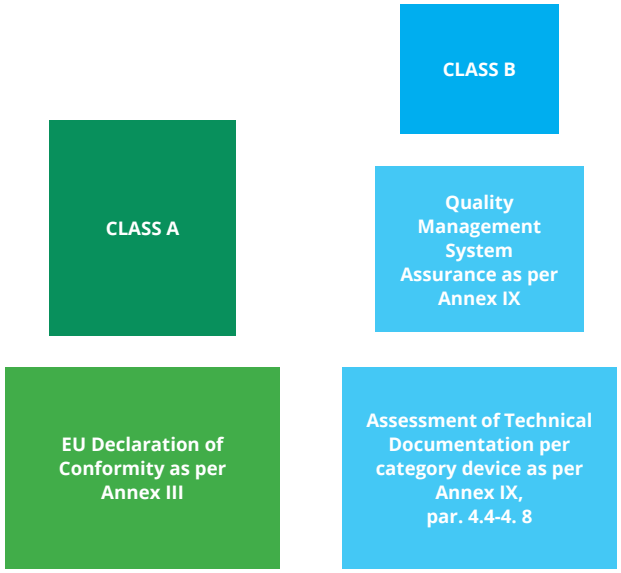
CONFORMITY ASSESSMENT

The conformity assessment concept outlined in IVDR is not new but is largely affected by the up-classification of the vast majority of IVDs, which inevitably results in the involvement of a Notified Body and the assessment of the manufacturer's Quality Management System.

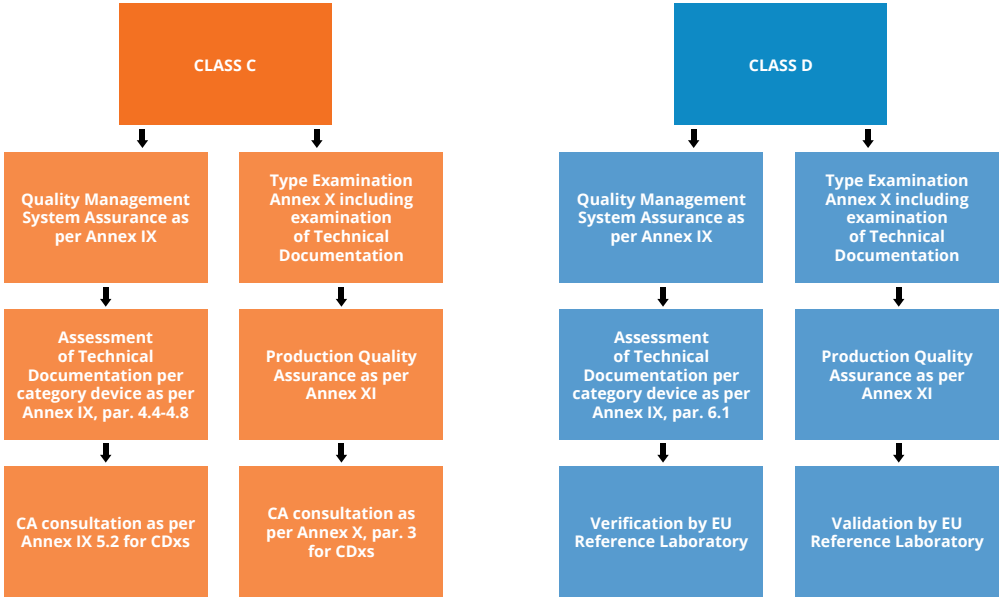
IVD manufacturers must select an appropriate route to conformity assessment as per Annexes IX through XI but the route is essentially determined by the device's classification. Art. 9 of IVDD has been replaced by Art.48 in the new IVDR.

The general conformity routes are:

- ❑ Class A (may self-certify): Declaration of Conformity. Technical documentation must include risk-benefit analysis, risk management, product verification and validation.
- ❑ Class A sterile: per Annex IX or XI, assessment of the sterile aspects
- ❑ Class B: per Annex IX or XI & X with full QMS audit and Technical Documentation assessment by sampling
- ❑ Class C: per Annex IX or XI & X with full QMS audit and Technical Documentation assessment by sampling
- ❑ Class D: per Annex IX with full QMS audit and Technical Documentation assessment for every device.



Most Class A devices can be self-certified by their manufacturers if they are not sold sterile. Devices in classes B, C and D will require a conformity assessment by a Notified Body. The conformity assessment of Class D devices will require the involvement of a designated EU Reference Laboratory to verify performance claims and compliance with the applicable Common Specifications (IVDR Art. 48(5)). For innovative Class D devices where no Common Specifications are yet available, an independent expert panel must provide its opinion on the performance evaluation report (Art. 48(6)).



EU Reference Laboratories are new regulatory stakeholders intended to be part of conformity assessments for IVDs. The European Commission designates EU Reference Laboratories to help assess specific devices, a category or group of devices or specific hazards related to a category or group of devices. With respect to IVDs, EU Reference Laboratories are called to verify class D claimed performances and carry out testing on samples.

Eligibility Criteria

- ❑ Horizontal roles: provision of scientific guidance, contribution to development of analytical methods
- ❑ Regulatory responsibilities: verification of performance, compliance with Common Specifications and batch testing for class D devices
- ❑ To be designated by the Commission
- ❑ Subject to on-site audits by the Commission

PERFORMANCE EVALUATION PLAN AND REPORT

IVDR, Art. 2 defines various aspects of performance

- **Performance evaluation** means 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 of a device** means the ability of a device to achieve its intended purpose as claimed by the manufacturer. It consists of the analytical and, where applicable, the clinical performance supporting that intended purpose
- **Analytical performance** means the ability of a device to correctly detect or measure a particular analyte.
- **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;

Annex XIII defines the requirements for a **Performance Evaluation Plan (PEP)**, which should describe how the performance evaluation will be carried out to show conformity with requirements of Annexes I, II and III. If an element is deemed as not appropriate, a justification shall be provided

- a specification of the intended purpose of the device;
- a specification of the characteristics of the device as described in Section 9 of Chapter II of Annex I and in point (c) of Section 20.4.1. of Chapter III of Annex I;
- a specification of the analyte or marker to be determined by the device;
- a specification of the intended use of the device;
- identification of certified reference materials or reference measurement procedures to allow for metrological traceability;
- a clear identification of specified target patient groups with clear indications, limitations and contra-indications;
- an identification of the general safety and performance requirements as laid down in Sections 1 to 9 of Annex I that require support from relevant scientific validity and analytical and clinical performance data;
- a specification of methods, including the appropriate statistical tools, used for the examination of the analytical and clinical performance of the device and of the limitations of the device and information provided by it;
- a description of the state of the art, including an identification of existing relevant standards, CS, guidance or best practices documents;
- an indication and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the intended purpose or purposes and for the analytical and clinical performance of the device;
- for software qualified as a device, an identification and specification of reference databases and other sources of data used as the basis for its decision-making;
- an outline of the different development phases including the sequence and means of determination of the scientific validity, the analytical and clinical performance, including an indication of milestones and a description of potential acceptance criteria;
- the PMPF planning as referred to in Part B of Annex XIII

The **Performance Evaluation** is a continuous process to demonstrate the scientific validity, analytical performance and clinical performance of an in vitro diagnostic medical device (IVD). The performance evaluation is conducted according to a **Performance Evaluation Plan (PEP)**. The clinical evidence from the performance evaluation is documented in a Performance Evaluation Report (PER) as per **Art. 56** of the IVDR.

> ***There are NO grandfathering provisions in IVDR. Therefore the transition from IVDD to IVDR shall be based on a thorough redesign of available documentation and creation of new according to the revised GSPRs***

According to Annex XIII, part A, par 1.3.2, the performance evaluation report shall include:

- ❑ The justification for the approach taken to gather the clinical evidence;
- ❑ The literature search methodology and the literature search protocol and literature search report of a literature review;
- ❑ The technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety;
- ❑ The nature and extent of the scientific validity and the analytical and clinical performance data that has been evaluated;
- ❑ The clinical evidence as the acceptable performances against the state of the art in medicine;
- ❑ Any new conclusions derived from PMPF reports in accordance with Part B of Annex XIII

The 3 pillars of performance evaluation are

- ❑ **Scientific Validity:** The association of an analyte to a clinical condition or a physiological state, i.e. what is the evidence for the association between the analyte/biomarker and the clinical condition?

Answer to be extracted from/ based on: literature review, internal studies (e.g. proof of concept studies), information from similar devices.

- ❑ **Analytical Performance:** The ability of a device to correctly detect or measure a particular analyte, i.e. How good is the device at detecting the analyte/ biomarker?

Answer to extracted from/ based on: literature review, internal study reports (e.g. analytical specificity, sensitivity, trueness/bias, precision, accuracy, limits of detection & quantitation, measuring range, linearity, thresholds/cut-off, interfering substances, cross-reactions, criteria for specimen collection and handling).

- ❑ **Clinical Performance:** The ability of a device to yield results that are associated with a particular clinical condition or a physiological process or state in accordance with the target population and intended user, i.e. How good is the device at determining who is positive with the clinical condition?

Answer extracted from/ based on: literature review, internal studies (on e.g. diagnostic sensitivity, diagnostic specificity, predictive values, likelihood ratio, expected population values), routine diagnostic testing, equivalent devices (if applicable).

CLINICAL EVIDENCE IN IVDR

Clinical Evidence in IVDR should be seen as the sum of evidence collected when evaluating **Scientific Validity AND Analytical Performance AND Clinical Performance**. The total findings will stand for the pool of clinical data and performance evaluation results, pertaining to a device and will be used to assess whether the IVD achieves its intended clinical benefit and safety, when used as intended by the manufacturer.

Clinical evidence is likely to be the greatest challenge IVD manufacturers while transitioning to the new Regulation because even if the latter have at their disposal data needed to show compliance with IVDR, they will still need to prepare a scientific validity, analytical and clinical performance reports, plus a performance evaluation report. Of note here, that many IVDs might have undergone significant changes since the collection of their initial data. Therefore, careful consideration and justification must be provided for the relevance of these data to the IVD currently on the market and submitted for CE marking.

POST-MARKET SURVEILLANCE

IVDR has introduced dynamic PMS requirements for all IVDs and requires manufacturers to have a post-market surveillance plan and proactively collect and evaluate performance and relevant scientific data from the use of an IVD. **Post-market performance follow-up (PMPF)** must be performed during the entire lifetime of an IVD in order to "feed" the Performance Evaluation Report updates and to demonstrate the scientific validity, analytical performance and clinical performance (where applicable) for the IVD.

PMPF is intended to

- ❑ confirm the safety and performance of the IVD,
- ❑ identify previously unknown risks or limits to performance and contra-indications,
- ❑ identify and analyze emerging risks on the basis of factual evidence,
- ❑ ensure the continued acceptability of the clinical evidence and of the risk-benefit ratio, and to
- ❑ identify possible systemic off-label uses.

The manufacturer **shall** be updating **Post-Market Surveillance Reports** for class A and B devices and **Periodic Safety Update Reports (PSURs)** for class C and D devices at least annually. Manufacturers **shall** be updating the safety and performance summary report of class C and D IVDS at least annually.

Note: ***A PMPF plan is mandatory for all IVDs and yearly updates are required for classes C and D***

COMPANION DIAGNOSTICS

Personalized medicine has made significant progress in the last 20 years, following the approval of trastuzumab for HER2 positive breast cancer and the corresponding diagnostic assay for the detection of HER2 overexpression in 1998.

Cancer patients, but not exclusively them, often present with similar diagnosis yet very different response to therapeutic schemes, which may result in degradation of the effectiveness and safety of any given treatment. Companion diagnostics (CDxs) are used to enhance the use of therapeutic treatment by identifying the individuals who are most likely to respond positively. These tests are considered in vitro diagnostic devices directly related to the corresponding therapeutic product.

As understood, the success of precision medicine is directly dependent on the performance of the diagnostic test (i.e. its sensitivity, specificity, accuracy and precision). However, up to now, the regulatory 'approval' process in the EU for a diagnostic test and a corresponding medicine was disconnected. The new IVD Regulation aims to counterbalance this regulatory gap.

The conformity assessment for CDxs, foresees a consultation procedure between a Notified Body and a medicine authority, depending on who is responsible for the authorization of the corresponding medicinal product. Examples of products, which should undergo EMA consultation include:

- Recombinant DNA
- Advanced therapy (gene therapy, somatic cell therapy)
- Products containing substance not yet authorised in EU
- Orphan medicinal products

Manufacturers are expected to provide a summary of safety and performance and a draft IFU and to evaluate the IVD with respect to the associated medicinal product. Competent Authority must provide its opinion within 60 days but may be extended once for a further 60 days for a justifiable reason, which is why manufacturers of CDxs should allow for 120 days. Unlike reference laboratory testing, if scientific opinion is negative, the certification process may carry on based on the recommendation of the NB, provided there is a sufficient justification of the reason.

CONCLUDING REMARKS

The new IVD Regulation has introduced various new or updated requirements in an effort to ensure the continued safety of end users and patients. However, by doing so, it requires from all stakeholders of the IVD Industry, both regulatory and economic operators, to implement effective transition strategies.

The shortage of Notified Bodies is alarming for the IVD Industry but it should not halt the remediation activities of manufacturers. The new conformity assessments, the risk-based up-classification of a huge number of IVDs as well as the lifetime - long PMS activities are expected to add a considerable workload to the Industry.

The new and stringent requirements on clinical evidence is putting extra pressure on all stakeholders but should be treated as a motivational factor that will trigger remediation activities in order to ensure timely compliance with the new safety and performance evaluation requirements set by IVDR.

More important than everything, manufacturers should not delay their preparation as effective from 27 May 2022, they may not be able to market their product portfolio in the European Union without conformity with IVDR requirements.

HOW CAN EVNIA HELP YOU WITH IVDR

Evnia used our own well-structured and **customizable templates** that undergo continuous improvements by incorporating new Guidances as soon as they are published!

From **methodological planning** and **execution** of search strategies to the **appraisal, analysis** and **narrative** of results, we have the **know-how** to draw credible conclusions after discussing evidence in a **critical manner**.

Evnia implements a thorough, validated **multi-step process** to develop a State-of-the-Art discussion fulfilling all requirements of the IVD Regulation.

We use various **customized tools** enabling our experts Medical Writers to develop a **tailored search strategy that will**

- Identify the intended field and similar devices
- Retrieve scientific evidence confirming your device's labelling statements or helping you to revise them

Evnia will ensure that you are submitting a **high-quality** Performance Evaluation that complies with IVDR requirements but will also to identify potential unknown and/or unmitigated risks associated with your in-vitro diagnostic medical device.

REFERENCES

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20170505.

ISO 13485 Medical Devices. International Standards Organization (ISO) website. https://www.iso.org/iso-13485-medical-devices.html

US FDA. Guidance for industry and food and drug administration staff. In Vitro Companion Diagnostic Devices. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

European Medicines Agency, Committee for Human Medicinal Products. Reflection paper on pharmacogenomics in oncology. 2008 April. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paperpharmacogenomics-oncology_en.pdf

Personalized medicine at FDA: a progress & outlook report; personalised medicine coalition. http://www.personalizedmedicinecoalition.org/Userfiles/PMCCorporate/file/PM_at_FDA_A_Progress_and_Outlook_Report.pdf

Available, Applicable Guidances

Global Harmonization Task Force (GHTF) Guideline 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. Study Group 1 of the Global Harmonization Task Force http://www.imdrf.org/docs/ghtf/archived/sg1/technical-docs/ghtf-sg1-n063-2011-summary-technical-documentation-ivd-safety-conformity-110317.pdf

International Medical Device Regulators Forum (IMDRF). Good Regulatory Review Practices Group (GRRP). Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (IMDRF/GRRP WG/N47 FINAL:2018). http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf

Global Harmonization Task Force (GHTF) Guideline SG5/N6:2012. Clinical Evidence for IVD medical devices – Key Definitions and Concepts. Study Group 5 Final Document. http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n6-2012-clinical-evidence-ivd-medical-devices-121102.pdf

Global Harmonization Task Force (GHTF) Guideline SG5/N7:2012. Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation. Study Group 5 Final Document. http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf

Global Harmonization Task Force (GHTF) Guideline SG5/N8:2012. Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices. Study Group 5 of the Global Harmonization Task Force. http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n8-2012-clinical-performance-studies-ivd-medical-devices-121102.pdf

International Medical Device Regulators Forum (IMDRF) MDCE WG/N56FINAL:2019 (formerly GHTF/SG5/N2R8:2007). Final document. Clinical Evaluation. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

ISO 20916:2019: In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practice. https://www.iso.org/standard/69455.html

Medical Device Coordination Group Document MDCG 2020-1. Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software (2020). https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020_1_guidance_clinic_eva_md_software_en.pdf