Scientific Validity Reports: a mandatory requirement for In Vitro Diagnostic Regulation (IVDR)

Guidance for Systematic Literature Reviews, essential to establish scientific validity and clinical performance, support compliance, and ensure patient safety as part of the new IVD regulatory framework.

Rito Bergemann, MD, PhD
VP WW Head HEOR,
Parexel

Julie Engel, PhD
Principal Consultant Regulatory Affairs,
Parexel

Sugandh Sharma, MSc
Senior Director, Evidence Evaluation,
Parexel

parexel®

Foreword

In vitro diagnostics (IVDs) play a critical role in diagnosis, proper treatment decisions, and monitoring patient outcomes. The European Union's new In Vitro Diagnostic Regulation (IVDR) introduces significant changes for IVD manufacturers, necessitating a comprehensive understanding of the regulatory approval requirements to market a product in Europe. The requirements now include clinical and scientific evidence to support the validity of the IVD, as has been standard for reviews of therapeutic products for many years.

This white paper examines the importance and implications of the new regulation for manufacturers, with a focus on the crucial role of the systematic literature review (SLR) and systematic evidence review (SER) within the regulatory framework. These reviews are essential for establishing scientific validity and clinical performance, supporting compliance, and ensuring patient safety. Additionally, the paper explores the newly introduced Scientific Validity Report (SVR), which now forms an integral part of the total documentation to be submitted under the regulation.

Similar to the biopharmaceutical industry, IVD manufacturers include seasoned multi-national leaders and exciting new entrants; regardless of size or history, these requirements apply to all and create new demands on organizations to enter or remain in the market to be compliant.

Manufacturers should familiarize themselves with the key regulatory changes and adhere to the transition timelines specified by the IVDR to ensure compliance and continued access to the European market for their IVDs. The benefit of these changes is both improved patient safety by ensuring that approved IVDs demonstrate high quality and performance.

Wyatt Gotbetter, SVP and Worldwide Head, Parexel Access Consulting
Mwango Kashoki, SVP and Global Head, Parexel Regulatory Strategy

Contents

1. Introduction

The field of in vitro diagnostics (IVDs) plays a critical role in healthcare by providing essential information for disease diagnosis, treatment decisions, and monitoring patient outcomes. To ensure the safety, effectiveness, and accuracy of IVDs, regulatory frameworks are in place to govern their development, manufacturing, and commercialization. The European Union's (EUs) new In Vitro Diagnostic Regulation (IVDR) framework represents a significant shift from the previous In Vitro Diagnostic Directive (IVDD), with resulting changes that impact manufacturers of IVDs and the analytes measured by these devices to enhance patient safety.

This white paper provides a comprehensive analysis of IVDR and its implications for manufacturers. We highlight the crucial role of the systematic literature review (SLR) and systematic evidence review (SER) within the regulatory framework; essential to establish scientific validity and clinical performance, support compliance, and ensure patient safety. We will also discuss the newly introduced Scientific Validity Report (SVR) as an integral part of the total documentation to be submitted under the regulation.

2. Key changes from IVDD to IVDR

The IVDR (EU/2017/746) introduces significant changes compared to its predecessor, the IVDD. These changes have far-reaching implications for manufacturers of IVDs and necessitate a comprehensive understanding of the new requirements to market a product in Europe. The introduction of the SVR is a novel and mandatory component within the regulatory framework.

2.1 Transition from IVDD to IVDR

The transition from the IVDD to the IVDR represents an important shift in the EU regulatory landscape for IVDs. While the IVDD provided a basic framework for ensuring safety and performance, the directive had limitations and did not adequately address evolving technological advancements and concerns related to patient safety. The IVDR addresses these limitations by introducing more stringent requirements and comprehensive regulations. Manufacturers should familiarize themselves with the key changes and adhere to the transition timelines specified by the IVDR to ensure compliance and continued European market access for their IVDs. The benefit for the patients is to ensure approved, marketed IVDs have demonstrable clinical benefits and safety.

The IVDR came into effect on 26 May 2022 with an original transition period ending 27 May 2024 whereby manufacturers were to submit total documentation to notified bodies (NBs) and obtain a conformity assessment. However, the final implementation date has been extended, due to the pandemic, to the following dates:

- 26 May 2025 for Class D devices
- 26 May 2026 for Class C devices
- 26 May 2027 for Class B and A devices

The transitional measures are not applicable to lower risk devices (class A not-sterile and class A with no measuring function), for which the due date to comply with IVDR was 26 May 2022. Under the IVDR, NBs have been designated by European Union member states to assess conformity of the IVDs. The timescales from submission of total documentation to approval have not currently been established and are subject to the number of NBs available to review.

The IVDR mandates the following process:

1: Classification of the IVDs based on intended purpose and risk profile

2: Identify the conformity assessment procedure based on the IVD classification

3: Gather evidence to support scientific validity, analytical performance and clinical performance of the analyte/IVD

4: Submit the evidence in the requisite format to NBs

2.2 Classification of IVDs and conformity assessment

Under the IVDR, biomarkers and analytes are subject to classification based on their intended purpose, risk level, and impact on patient management. Manufacturers must classify biomarkers and analytes in accordance with the IVDR classification rules to determine the applicable conformity assessment procedures.

This classification is intended to define the assessment process and the conformity procedure to be followed for each IVD. A highest-risk IVD is defined as having the greatest potential of impacting patient safety compared to high, moderate and low risk devices. Hence, the submission for the highest-risk IVD will be assessed more critically before it is approved to be placed in the market.

An overview of the classification of the IVDs into Class A, B, C or D:

Class D	Class C	Class B	Class A
Highest Risk	**High Risk**	**Moderate Risk**	**Low Risk**
Includes › analytes for life-threatening conditions › those transmissible in blood and biological matter meant for transfusion, transplantation, or cell administration › blood grouping markers of ABO, Rhesus, Kell, Kidd, and Duffy system	Includes › analytes for other blood grouping (not covered by Class D) such as for foeto-maternal blood group meant for transfusion, transplantation, or cell administration › analytes for sexual transmitted disease, infectious disease, congenital disorders › companion diagnostics › analytes for disease staging including cancer diagnosis and staging › human genetic testing › patient management by monitoring level of medicinal products › self-testing devices	Includes › self-testing devices for detection of pregnancy, fertility testing, level of cholesterol, glucose, erythrocytes, leucocytes, and bacteria in urine	Includes › products for general laboratory use such as instruments, buffer solutions, washing solutions, and general culture media and histological stains

2.3 Requirement of scientific evidence

The Conformity Assessment requirements of the IVDR specify that manufacturers must provide evidence of the scientific validity, analytical and clinical performance of the IVDs. In accordance with this regulation, a systematic literature review must be performed to gather comprehensive evidence for the device. This review needs to be updated periodically to ensure any newly published data are gathered, and presented to the NB. The Conformity Assessment process depends on the IVD classification. Under the IVDR, in vitro diagnostic devices in Class D, Class C, Class B, Class A sterile and Class A with measuring function, require the involvement of an NB for the CE certification. Only Class A not-sterile and Class A with no measuring function, do not require an NB and can be self-certified by the manufacturer.

Section 7.2 of the appendix provides the detailed procedure for identification of the evidence.

2.4 Introduction of the Scientific Validity Report (SVR)

The inclusion of the scientific validity report (SVR) as a mandatory component within the regulatory framework is designed to guarantee the scientific validity, and compliance of IVDs. Unlike other review processes, the SVR places particular emphasis on the importance of a systematic and evidence-based approach to evaluate and establish the validity of IVDs. Manufacturers are obligated to provide robust scientific evidence through comprehensive literature reviews, data analysis, and verification processes to substantiate the claims made for their IVDs, through systematic literature review.

2.5 SVR as an integral component of total documentation

The SVR is the first component to be completed when preparing the Technical Documentation for submission by the manufacturers to the NBs for regulatory approval. The SVR, in conjunction with the clinical evaluation and performance evaluation, offers a comprehensive perspective on the scientific validity and performance of the IVD. The SVR process involves collecting and analyzing data from various sources, including published literature, clinical studies, and post-market surveillance data. The regulation suggests that clinical and analytical performance can only be investigated once scientific validity is established. If there is insufficient evidence to establish scientific validity, the regulation recommends collecting and generating more data to support scientific validity. To comply with IVDR requirements and meet the expectations of the NBs, manufacturers are responsible for integrating the SVR seamlessly into their technical documentation.

2.6 Roles and responsibilities of manufacturers in SVR

It is the manufacturers' obligation to conduct and document the SVR in a thorough and systematic manner, ensuring the reliability and integrity of the collected data. Collaboration with experts, researchers, and external organizations is often essential to gather the necessary evidence and expertise required for the SVR. Manufacturers must maintain traceability, transparency, and accuracy of the SVR data and findings, facilitating the review and assessment by the NBs. By fulfilling their roles diligently, manufacturers can demonstrate the scientific validity, performance, and compliance of their IVDs, instilling confidence in regulators, healthcare professionals, and importantly, patients.

3. Conducting Systematic Literature Review (SLR)

3.1 Definition and purpose of SLR and SER

Systematic literature review (SLR) and systematic evidence review (SER) are rigorous methodologies employed to collect, analyze, and integrate existing scientific literature and evidence. SLR involves a comprehensive and systematic search of relevant literature across multiple sources (biomedical databases, clinical trial registries and grey literature sources), followed by a critical evaluation and synthesis of the findings. On the other hand, SER expands the scope to incorporate additional sources of evidence, such as unpublished data, expert opinions, and state-of-the-art reviews. The primary purpose of both SLR and SER is to ensure a robust evidence-based approach when assessing the scientific validity, performance, and clinical utility of analytes. The systematic approach to identify evidence was established in the 1990s and has been continuously refined since 1993 when Cochrane Collaboration was founded. The pharma industry has been using the SLR approach to identify robust evidence for regulatory approvals since the early 2000s.

3.2 Methodology and process of conducting SLR and SER

Conducting SLR and SER for analytes requires a systematic and standardized methodology to minimize bias and ensure reliability. The process typically involves defining the research question, formulating inclusion and exclusion criteria, conducting comprehensive literature searches, screening, and selecting relevant studies, extracting, and analyzing data, and synthesizing the findings. It is essential to follow established guidelines and frameworks, such as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Collaboration's Handbook for Systematic Reviews of Interventions, to ensure methodological rigor and transparency.

Figure 1: Methodology for developing SVR

3.3 Scientific validity plan and search protocol

To define the scope of the SLR and articulate the intended use of the IVR, a Scientific Validity Plan (SVP) is created. A SLR and SER begins with a well-defined search protocol documenting the detailed methodology including the inclusion criteria, searches, data sources, data to be extracted and reported. It serves as a roadmap to guide the search process, ensuring consistency, transparency, and reproducibility. A comprehensive SLR and SER should encompass a wide range of data sources to capture the breadth and depth of available evidence. These sources may include biomedical databases covering scientific and academic journals, conference proceedings, clinical trial registries, regulatory agency databases, and gray literature. In addition to published studies, it is crucial to consider independent SLRs conducted by reputable research organizations and state-of-the-art reviews that summarize the current knowledge and advancements in the field. The selection criteria should be carefully defined to ensure the inclusion of relevant and high-quality studies, while minimizing the risk of bias.

3.4 Analyzing and synthesizing literature findings

The analysis and synthesis of literature findings involves extracting pertinent information from selected studies, evaluating the quality and relevance of the evidence, and integrating the data to draw significant conclusions. This process may include statistical analysis, meta-analysis, or qualitative synthesis, depending on the nature of the available evidence. The synthesis should consider factors such as study design, sample size, patient characteristics, analytical methods, and clinical outcomes. The findings should be interpreted in the context of the specific analyte and its intended use within the IVD.

3.5 Integration of state-of-the-art reviews and independent SLRs

In addition to conducting a specific SLR and SER for the SVR, consider state-of-the-art reviews and existing SLRs performed independently. State-of-the-art reviews provide a comprehensive overview of the current knowledge and advancements in the field, encompassing a broader perspective that extends beyond individual studies. Independent SLRs conducted by reputable research organizations can offer additional insights and validation of scientific evidence. By integrating these existing reviews and SLRs into the SVR, manufacturers can ensure a comprehensive and up-to-date evidence base for their analytes used in the IVDs.

Conducting robust SLR and SER for analytes is crucial in meeting the requirements of the IVDR and demonstrating the scientific validity, performance, and clinical utility of IVDs.

4. Significance of SLR within the regulatory framework of IVDR

4.1 Complying with IVDR requirements

The IVDR mandates that manufacturers demonstrate the scientific validity and performance of their IVDs to ensure patient safety and enhance the overall quality of healthcare. Failure to comply with IVDR could result in legal consequences (such as fines and penalties), prohibition to sell IVDs in the EU or recall the marketed IVDs from the EU member states. SLR and SER play a crucial role in meeting these requirements.

Article 56(3) of the IVDR states that manufacturers shall perform a systematic review of the relevant scientific literature, including clinical data, before placing IVDs on the market. The systematic review is a fundamental component of the overall clinical performance evaluation process outlined in Annex XIII of the IVDR. The systematic review of scientific literature helps identify potential safety concerns, contraindications, and limitations associated with the biomarkers and analytes measured by the IVDs.

4.2 Supporting clinical performance evaluation

Annex XIII of the IVDR specifically addresses the requirements for clinical evidence and performance evaluation of IVDs. It outlines the steps, methodologies, and documentation necessary for conducting the clinical performance evaluation. It emphasizes the need for a comprehensive assessment of the clinical performance of IVDs. Annex XIII of the regulation sets forth the specific requirements for clinical performance evaluation, including the systematic review of scientific literature and other clinical evidence. SLR and SER provide manufacturers with a robust methodology to gather and evaluate the available evidence, ensuring the validity and reliability of the clinical performance data. By conducting SLR and SER, manufacturers can demonstrate the safety, accuracy, and clinical utility of their IVDs, thereby facilitating the clinical performance evaluation process required by the IVDR.

5. Conclusion

SLR and SER are essential components of the SVR, and regulatory framework outlined by the IVDR. The SLR and SVR facilitate compliance with the regulatory requirements, support the clinical performance evaluation process, ensure patient safety, and contribute to the overall quality of IVDs. By conducting rigorous SLR and SER and integrating the findings into the total documentation package, manufacturers demonstrate their commitment to meeting the high standards set forth by the IVDR and delivering safe and effective IVDs to healthcare professionals and patients.

Under the IVDR, around 80% of IVD medical devices will be under the control of NBs, the vast majority of them for the first time. Most of the IVDs on the market were self-certified by the manufacturer under the previous IVD directive.

However, the number of NBs causes a major bottleneck within the IVD industry. The limited number of NBs can lead to delays in the review and approval process, impacting market access and hindering timely compliance with the IVDR. It is crucial for manufacturers to proactively engage with the available NBs and consider potential strategies such as resource allocation, collaboration, and efficient project management to navigate these challenges.

As the industry adapts to the IVDR and overcomes the bottleneck, it is vital for manufacturers and stakeholders to be prepared and proactive in embracing the changes. Collaboration and knowledge-sharing among industry players, regulatory bodies, and NBs can help address any issues and facilitate a smoother transition for manufacturers seeking regulatory approval.

By understanding the implications of the IVDR, recognizing the importance of SVR, and acting appropriately to navigate the new process including the current issues, manufacturers can successfully adapt to the regulatory changes, deliver high-quality IVDs, and contribute to improved healthcare outcomes for patients worldwide.

6. Sources

EUR-Lex: 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: EUR-Lex - 32017R0746 - EN - EUR-Lex (europa.eu) (Accessed Sep 4, 2023)

European Commission - In Vitro Diagnostic Regulation (IVDR): Official text of the IVDR: https://ec.europa.eu/docsroom/documents/31221 (Accessed June 16, 2023)

European Commission - Notified Bodies under the IVDR: Information on the current list of notified bodies: EUROPA - European Commission - Growth - Regulatory policy - NANDO (Accessed June 16, 2023)

European Medicines Agency (EMA) - In Vitro Diagnostics: Overview of regulatory requirements and guidance on IVDs: Medical devices | European Medicines Agency (europa.eu) (Accessed June 16, 2023)

International Organization for Standardization (ISO): ISO 20916:2019 - In vitro diagnostic medical devices: Clinical performance studies using specimens from human subjects - good study practice: ISO 20916:2019 - In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice (Accessed June 16, 2023)

Guidance on classification rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746: https://health.ec.europa.eu/system/files/2023-02/md_mdcg_2020_guidance_classification_ivd-md_en.pdf (Accessed June 16, 2023)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement: Guidelines for conducting systematic reviews and meta-analyses: https://prisma-statement.org/ (Accessed June 16, 2023)

Cochrane Handbook for Systematic Reviews of Interventions: A comprehensive guide to conducting systematic reviews: https://training.cochrane.org/handbook (Accessed June 16, 2023)

7. Appendix

7.1 Rules and Examples for Analytes classified by IVDR

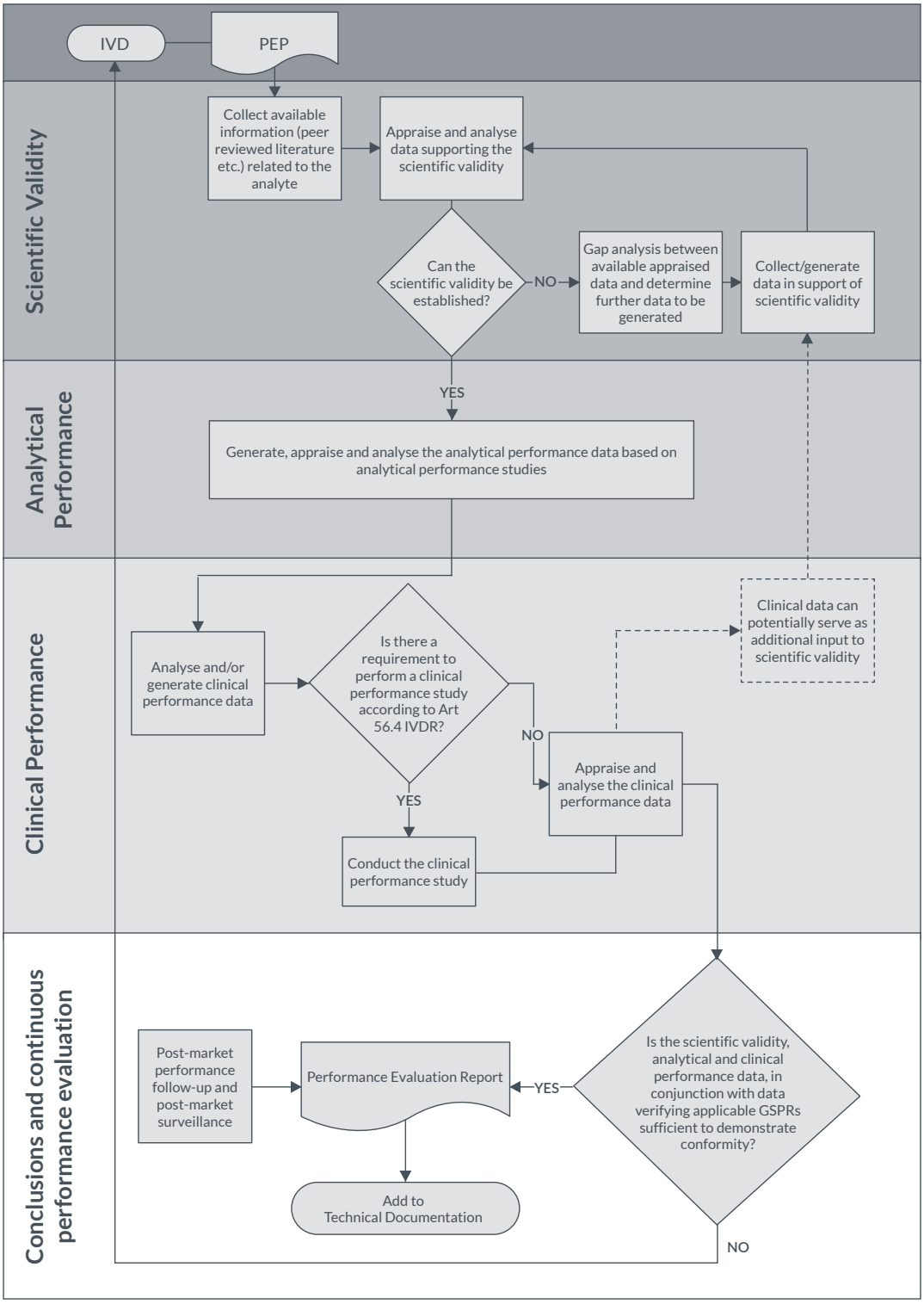
Classification	Class D (Highest Risk)	Class C (High Risk)	Class B (Moderate Risk)	Class A (Low Risk)
Rules	**Rule 1(a):** Devices intended to be used for the detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues, or organs, or in any of their derivatives, to assess their suitability for transfusion, transplantation, or cell administration **Rule 1(b):** Devices intended to be used for the 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 **Rule 1(c):** Devices intended to be used for determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management **Rule 2:** Devices intended to determine any of the following markers: ABO system, Rhesus system, Kell system, Kidd system, Duffy system	**Rule 2**: Devices intended to be used for blood grouping, or to determine foeto-maternal blood group incompatibility1, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue, or organs that are intended for transfusion or transplantation or cell administration **Rule 3(a):** Devices intended for detecting the presence of, or exposure to, a sexually transmitted agent **Rule 3(b):** Devices intended for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation **Rule 3(c):** Devices intended 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	**Rule 4(a):** Devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine **Rule 6:** Devices not covered by the other classification rules (Rules 1-5) **Rule 7:** Devices which are controls without a quantitative or qualitative assigned value	**Rule 5(a):** Products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination **Rule 5(b)**: Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures **Rule 5(c):** Specimen receptacles

Classification	Class D (Highest Risk)	Class C (High Risk)	Class B (Moderate Risk)	Class A (Low Risk)
Rules		**Rule 3(d):** Devices intended for pre-natal screening of women in order to determine their immune status towards transmissible agents **Rule 3(e):** Devices intended 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 **Rule 3(f):** Devices intended to be used as companion diagnostics **Rule 3(g):** Devices intended to be used for disease staging, 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 **Rule 3(h):** Devices intended to be used in screening, diagnosis, or staging of cancer **Rule 3(i):** Devices intended for human genetic testing **Rule 3(j):** Devices intended for monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring **Rule 3(k)**: Devices intended for management of patients suffering from a life-threatening disease or condition **Rule 3(l):** Devices intended for screening for congenital disorders in the embryo or foetus **Rule 3(m)**: Devices intended for screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities **Rule 4(a):** Devices intended for self-testing		

Classification	Class D (Highest Risk)	Class C (High Risk)	Class B (Moderate Risk)	Class A (Low Risk)
Examples	EGFR mutation (epidermal growth factor receptor mutation for cancer treatment) CFTR gene mutations (associated with cystic fibrosis) PD-L1 expression (predictive biomarker for immunotherapy response) Circulating tumor DNA (liquid biopsy marker for cancer detection and monitoring) HER2/neu gene amplification (breast cancer biomarker) JAK2 mutation (associated with myeloproliferative neoplasms) EGFRvIII mutation (glioblastoma multiforme biomarker) ALK rearrangement (non-small cell lung cancer biomarker)	BRAF gene mutation (associated with certain cancers) HLA typing for transplantation (e.g., HLA-A, HLA-B, HLA-DR) BRCA1 gene mutation (associated with hereditary breast and ovarian cancer) Hepatitis C viral load HIV viral load Antinuclear antibodies (ANA) Anti-dsDNA antibodies (associated with systemic lupus erythematosus) Beta-amyloid and tau proteins (Alzheimer's disease biomarkers) Alpha-synuclein (Parkinson's disease biomarker) CA19-9 (tumor marker for pancreatic cancer)	Troponin B-type natriuretic peptide (BNP) Prothrombin time (PT) Activated partial thromboplastin time (aPTT) Prostate-specific antigen (PSA) CA-125 (tumor marker for ovarian cancer)	Sodium (Na+) Potassium (K+) Chloride (Cl-) Total cholesterol HDL cholesterol LDL cholesterol

7.2 Methodology for generation of evidence for total submission to the Notified Body

Originally published in the Guidance on general principles of clinical evidence for in vitro diagnostic medical devices (MDCG 2022-2):



7.3 List of accredited Notified Bodies per IVDR

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 0459	GMED SAS	France
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 2962	QMD Services GmbH	Austria
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH	Germany

With Heart™

We're always available for a conversation

Parexel International Corporation
2520 Meridian Pkwy, Durham, NC 27713, USA
+1 919 544-3170

Offices across Europe, Asia, and the Americas
www.parexel.com

parexel®