IVDD (In Vitro Diagnostic Directive) -- IVDR (In Vitro Diagnostic Regulation)

IVDR (Regulation (EU) 2017/746) and IVDD (Directive 98/79/EC) –IVDR and IVDD across various critical aspects:

1. Legal Framework

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Legal Nature	**Directive** – Requires transposition into national laws of each EU Member State, leading to variations in implementation.	**Regulation** – Directly applicable in all EU Member States without national transposition, ensuring uniformity.
Legislative Complexity	Differences in national transpositions led to inconsistencies.	One single law for all Member States, ensuring consistency.
Enforcement Date	Effective from December 7, 1998, with mandatory compliance from December 7, 2003.	Adopted on April 5, 2017; became applicable from May 26, 2022 (with extended transition timelines for certain devices).

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2. Scope and Definitions

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Scope	Covered in vitro diagnostic devices but with vague definitions.	Expanded scope to include companion diagnostics, genetic testing, near-patient testing, and standalone software.
Definition of IVD	Any device used **outside the human body** for examining biological specimens.	Clarifies and expands on the **IVD definition**, including software and laboratory-developed tests (LDTs).
Companion Diagnostics	Not explicitly covered.	Companion diagnostics are explicitly defined and require **Notified Body (NB) assessment**.
Software as a Medical Device (SaMD)	Not clearly regulated.	Software that meets the definition of an IVD must comply with IVDR.

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3. Classification System

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Device Classification	Devices were classified into three categories: - List A (highest risk) - List B (moderate risk) - Self-test devices	**Risk-based classification into four classes:** - **Class A** (low risk) - **Class B** (moderate risk) - **Class C** (high risk) - **Class D** (highest risk)
Conformity Assessment Based on Risk	Risk assessment was limited.	A risk-based approach now **aligns with IMDRF/GHTF guidance**, improving patient safety.
Impact of New Classification	Only **20% of IVDs** required Notified Body involvement.	Under IVDR, **nearly 80-90% of IVDs** now require Notified Body involvement.

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4. Notified Body Involvement

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Notified Body (NB) Involvement	Required only for **(List A & B) and self-testing devices**.	**Mandatory for most devices** (except low-risk Class A non-sterile devices).
Notified Body Oversight	Limited involvement, leading to loopholes in device assessment.	Stricter oversight with **regular audits, technical file reviews, and unannounced inspections**.
Number of Notified Bodies	Over 20 Notified Bodies under IVDD.	As of 2024, only **10+ Notified Bodies** designated under IVDR, leading to backlog and delays.

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5. Conformity Assessment & CE Marking

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Conformity Assessment Routes	Self-certification allowed for most IVDs.	Majority of IVDs require **Notified Body conformity assessment**.
CE Marking Process	Simplified process for most manufacturers.	More stringent requirements, including **clinical performance data** and **risk management reports**.

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6. Performance Evaluation & Clinical Evidence

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Performance Evaluation	General requirements, **no structured performance evaluation**.	**Structured performance evaluation** including: - Scientific validity - Analytical performance - Clinical performance
Clinical Data Requirement	Limited to certain high-risk devices.	Required for **all IVDs**, proportionate to risk classification.

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7. Post-Market Surveillance (PMS) & Vigilance

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Post-Market Surveillance (PMS)	Minimal PMS requirements.	**Enhanced PMS requirements**, including: - Periodic Safety Update Reports (PSURs) - Trend reporting - Proactive risk management
Vigilance Reporting	No structured vigilance system.	**Mandatory reporting** of serious incidents and trend reporting.
Market Surveillance	Varying national market surveillance systems.	Strengthened and harmonized **EU-wide market surveillance**.

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8. Unique Device Identification (UDI) & Traceability

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Unique Device Identification (UDI)	Not required.	**Mandatory UDI system** for enhanced traceability and patient safety.
EUDAMED Database	Not available.	**Mandatory registration of devices & economic operators** in EUDAMED.

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9. Economic Operators' Responsibilities

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Manufacturers, Importers, Distributors	Responsibilities were not clearly defined.	**Clearly defined roles and responsibilities** for: - Manufacturers - Authorized Representatives - Importers - Distributors

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Authorized Representative (AR)	Minimal requirements.	AR must ensure regulatory compliance and **maintain a Person Responsible for Regulatory Compliance (PRRC)**.

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10. Transition Period & Implementation Challenges

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Transition Period	IVDD was in effect for over 15 years.	IVDR transition period **extended for certain devices** (Class D until May 2025, Class C until May 2026, Class B & A sterile until May 2027).
Implementation Challenges	National variations caused inconsistencies.	**Challenges** include Notified Body bottlenecks and manufacturers struggling to meet new requirements.

11. Post Market Surveillance

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
Post-Market Surveillance (PMS)	Basic PMS obligations with minimal proactive measures. PMS mainly relied on incident reporting.	**Enhanced PMS system**, requiring manufacturers to establish a **continuous PMS plan**, including **Periodic Safety Update Reports (PSURs)**, trend reporting, and proactive data collection.
General Safety and Performance Requirements (GSPR)	General safety and performance requirements **IVDD**, but with less stringent and detailed provisions.	**IVDR** replaces the **Essential Requirements (ER) with GSPR**, expanding and detailing requirements on safety, performance, risk management, and usability.
Correlation Table (IVDD to IVDR)	No direct correlation table available for IVDD to IVDR requirements.	IVDR requires manufacturers to provide a **Correlation Table**, mapping previous IVDD requirements to the new **IVDR General Safety and Performance Requirements (GSPR)**.
Certification Issued by Notified Body (NB)	Required for **(List A & B) and self-testing devices**. Many IVDs were self-certified.	Majority of IVDs now require **Notified Body certification** (except for low-risk Class A non-sterile devices). Certification includes a **Performance Evaluation Report (PER), Post-Market Performance Follow-up (PMPF), and continuous conformity assessment.**

Aspect	Directive 98/79/EC (IVDD)	Regulation (EU) 2017/746 (IVDR)
EU Declaration of Conformity (EU DoC)	Simple **EU DoC** stating compliance with IVDD requirements. Not all devices required Notified Body involvement.	**Stricter EU DoC requirements** under IVDR, requiring **clear reference to the GSPR, risk classification, Notified Body certificate details (if applicable), and UDI-DI (Unique Device Identification – Device Identifier).**

The transition from the In Vitro Diagnostic Directive (IVDD) to the In Vitro Diagnostic Regulation (IVDR) marks a significant shift in the European Union's regulatory framework for in vitro diagnostic devices (IVDs). While the IVDD, implemented in 1998, allowed for more flexibility and variation in national transposition, leading to inconsistencies across member states, the IVDR, which became fully applicable in 2022, ensures uniformity by directly applying to all EU member states without the need for national laws. The IVDR introduces a risk-based classification system, expanded scope to include new technologies like companion diagnostics and software as medical devices, and stricter requirements for performance evaluation, clinical data, and post-market surveillance. These changes aim to improve patient safety, enhance device efficacy, and address the rapid evolution of medical technology.

Under the IVDR, most IVDs now require mandatory Notified Body involvement for conformity assessment, a shift from the more lenient IVDD, which allowed self-certification for many devices. The new regulation also establishes clearer roles for economic operators, including manufacturers, importers, distributors, and Authorized Representatives, with stricter obligations for regulatory compliance. Additionally, the IVDR introduces mandatory systems for Unique Device Identification (UDI) and improved traceability, along with enhanced post-market surveillance requirements, ensuring ongoing monitoring of device performance. These changes not only harmonize the regulatory process across the EU but also establish a more robust framework for device safety, quality, and effectiveness throughout their lifecycle.

1. Legal Framework

The IVDD was a Directive, meaning that it required transposition into national laws by each EU Member State, leading to some inconsistencies in its application across the EU. Different member states could implement the directive in slightly different ways, causing variations in compliance and enforcement. The IVDR, on the other hand, is a Regulation, meaning it is directly applicable in all EU Member States without the need for national transposition. This change ensures a more uniform and consistent approach to the regulation of IVDs throughout the EU. While the IVDD was effective from December 7, 1998, with mandatory compliance by December 7, 2003, the IVDR was adopted on April 5, 2017, and became applicable from May 26, 2022, with extended transition timelines for certain devices.

2. Scope and Definitions

Under the IVDD, the scope was relatively limited and vaguely defined, primarily covering traditional IVDs used outside the human body for examining biological specimens. There was no explicit

mention of newer technologies, such as companion diagnostics, genetic testing, or standalone software. The IVDR significantly expands the scope to include these technologies and more. It defines IVDs more clearly, encompassing not only traditional devices but also software that meets the definition of an IVD. Additionally, the IVDR introduces a formal definition of companion diagnostics, which are devices used to select patients who will benefit from specific therapies, and these devices now require Notified Body (NB) assessment. Software used in diagnostics, which was not explicitly regulated under the IVDD, now falls within the IVDR if it meets the IVD definition, ensuring that technological advancements are adequately regulated.

3. Classification System

The IVDD had a relatively simple classification system with three main categories: List A (high-risk devices), List B (moderate-risk devices), and self-test devices. This classification was based on device type but lacked a comprehensive risk-based approach. The IVDR introduces a more detailed, risk-based classification system, categorizing devices into four classes: Class A (low-risk), Class B (moderate risk), Class C (high risk), and Class D (highest risk). This new system aligns more closely with international standards such as the IMDRF (International Medical Device Regulators Forum) and the GHTF (Global Harmonization Task Force). As a result of these changes, a significant shift in regulatory oversight occurs, with nearly 80-90% of IVDs now requiring Notified Body involvement, compared to only 20% under the IVDD.

4. Notified Body Involvement

Under the IVDD, Notified Body (NB) involvement was required primarily for List A and B devices, as well as self-testing devices. This meant that a significant portion of IVDs could be self-certified by manufacturers, leading to potential gaps in regulatory oversight. The IVDR significantly increases the Notified Body role, making their involvement mandatory for most devices, with the exception of Class A non-sterile devices. The IVDR also imposes more stringent Notified Body oversight, including regular audits, technical file reviews, and even unannounced inspections. This increased involvement helps ensure that IVDs meet safety and performance standards. However, as of 2024, there are fewer than 10 designated Notified Bodies under the IVDR, leading to a backlog and delays in device certification.

5. Conformity Assessment & CE Marking

The IVDD allowed many IVDs to undergo self-certification, with a simplified CE Marking process. Manufacturers could declare conformity with the directive's requirements without external scrutiny for many devices, which sometimes led to gaps in regulatory oversight. In contrast, the IVDR introduces a more stringent CE Marking process. Most IVDs now require Notified Body conformity assessment, and the requirements for clinical performance data, risk management reports, and other supporting documents are more comprehensive. This change ensures that the safety and efficacy of IVDs are more thoroughly evaluated before they can be marketed in the EU.

6. Performance Evaluation & Clinical Evidence

Under the IVDD, there were only general requirements for the performance evaluation of IVDs, with no structured framework. Clinical data was only required for certain high-risk devices. The IVDR requires a more structured and comprehensive approach to performance evaluation. Manufacturers must provide evidence of the scientific validity, analytical performance, and clinical performance of their devices. This includes providing clinical data for all IVDs, with the extent of the data required proportional to the risk classification of the device. This shift ensures that clinical evidence is gathered and evaluated systematically for all IVDs, enhancing the safety and effectiveness of these devices.

7. Post-Market Surveillance (PMS) & Vigilance

The IVDD had minimal requirements for Post-Market Surveillance (PMS) and relied mainly on incident reporting. There was no formalized system for ongoing monitoring of devices once they were on the market. Under the IVDR, PMS is significantly enhanced, with manufacturers now required to establish continuous PMS plans. These plans must include Periodic Safety Update Reports (PSURs), trend reporting, and proactive data collection to monitor device performance post-market. The IVDR also establishes a mandatory vigilance reporting system, requiring manufacturers to report serious incidents and trends in a timely manner. This shift strengthens the ability to identify and mitigate risks associated with IVDs after they enter the market.

8. Unique Device Identification (UDI) & Traceability

The IVDD did not require a system for Unique Device Identification (UDI) or traceability, which limited the ability to track and recall devices effectively. The IVDR introduces a mandatory UDI system, improving traceability and ensuring that devices can be tracked throughout their lifecycle. The EUDAMED database is also a key component of the IVDR, requiring the registration of devices and economic operators. This increases transparency and helps regulatory authorities and the public maintain a comprehensive record of all IVDs on the market.

9. Economic Operators' Responsibilities

Under the IVDD, the roles and responsibilities of economic operators, including manufacturers, importers, and distributors, were not clearly defined. The IVDR clearly delineates the roles and responsibilities of these operators, including Authorized Representatives (AR), importers, and distributors. For the first time, the AR is required to ensure regulatory compliance and maintain a Person Responsible for Regulatory Compliance (PRRC). This ensures that manufacturers, distributors, and importers all have a clearly defined role in ensuring compliance with regulatory requirements.

10. Transition Period & Implementation Challenges

The IVDD had been in effect for more than 15 years, with a relatively straightforward transition process for manufacturers. However, with the IVDR, the transition period has been extended for some devices, such as Class D devices until May 2025 and Class C devices until May 2026. Manufacturers face challenges in meeting the new, more stringent requirements, particularly with delays in Notified Body assessments, leading to potential market disruptions.

11. Post Market Surveillance

The IVDD had limited Post-Market Surveillance (PMS) requirements, primarily relying on incident reporting and passive surveillance. The IVDR mandates a more proactive approach to PMS, requiring manufacturers to establish a continuous plan for monitoring device safety and performance throughout the lifecycle. This includes the collection of post-market data, generation of PSURs, and trend reporting to identify potential issues before they become significant problems. The General Safety and Performance Requirements (GSPR) under the IVDR replace the earlier Essential Requirements (ER) of the IVDD, providing more detailed provisions for safety, performance, risk management, and usability.