ASCERTAIN

WHAT REGULATORY CHALLENGES DO DIAGNOSTICS BRING?

WHAT ARE DIAGNOSTICS?

They include a wide array of **medical devices**, from the simplest (e.g. a thermometer or home used pregnancy tests) to complex diagnostics that require specialised staff and infrastructure (e.g. Computer Tomographs, Magnetic Resonance Imaging). They are used to **measure the level of health indicators** (such as temperature, blood pressure, brain activity), the presence/absence of a disease or the characteristics of one if detected.

HOW ARE DIAGNOSTICS DIFFERENT FROM PHARMACEUTICALS?

Pharmaceuticals are used to **directly intervene in the course of a disease or to manage symptoms**, while **diagnostics** are used to **guide clinical decisions**. They help identify a disease, monitor its progression, and choose the best treatment. Furthermore, diagnostics are usually **devices**, while pharmaceuticals are substances (chemical or biological or both) that directly interact with the body.

HOW ARE DIAGNOSTICS REGULATED IN THE EU?

For regulatory purposes, it is important to establish that **not all diagnostics are the same** and thus **not regulated in the same way**. An important distinction is that some diagnostics are used directly on or inside the body, for example for biopsies and X-Rays, and are called "**in vivo**", while others are used on body samples such as blood, urine or tissue outside the body and are called "**in vitro**".

Regardless of their use, all diagnostics are medical devices and they must:

- **Meet general safety and performance requirements**, which are continuously monitored after the device has been placed on the market (post-market surveillance)
- **Have the CE** („Conformité Européene"-European Conformity) **mark** (more about this below at point 4)
- Meet **periodic reporting requirements** under the medical device vigilance system
- Have a **Unique Device Identifier** (UDI) number and be registered in the electronic system **EUDAMED**
- Fulfil **further requirements** depending on the type of device. For example, implantable devices must include an implant card and a patient information leaflet
- Ensure that the (electronic) **instructions for use are clear and understandable** for patients and healthcare professionals

In vitro diagnostics are regulated at the EU level under the **In Vitro Diagnostic Regulation** (IVDR) 2017/746, which took effect on May 26, 2022. This regulation **applies directly in all EU Member States and does not require adoption into national laws**. It classifies in vitro diagnostics by the **type of risk**, introduces **stricter rules for the performance of devices**, increases **transparency** and improves **information for patients** (by mandating the setting up of a European database on medical devices, EUDAMED, and requiring manufacturers to collect data about the device's performance after they are placed on the market).

WHAT IST THE CE MARK?

The CE marking mentioned above is a symbol that indicates that a product **meets the EU legal requirements to be sold in the EU**. It is an acronym meaning „Conformité Européene" (European Conformity). It is not just used for medical devices but for many other products including general electronics or toys.

It is important to note that it is not a quality mark but indicates that it **meets legal safety standards**. Furthermore, products bearing the mark can be **traded freely throughout the European Economic Area** (which includes the 27 EU Member States, Iceland, Liechtenstein, and Norway).

The path to the CE marking depends on the **risk classification of the device**. For low-risk devices, manufacturers can self-certify, but for **high-risk devices**, the product must undergo a **Quality Assurance process** including the product design and a post-market surveillance plan.

WHICH ARE THE NOTIFIED BODIES RESPONSIBLE FOR CE MARKING?

The organisations responsible for awarding the CE marking are called "**Notified Bodies**". They are independent organisations that are **designated by Member States** as being capable of **evaluating devices and deciding if they meet the legal safety requirements**. They are listed in a database called **NANDO** (New Approach Notified and Designated Organisations) Information System. Not all Notified Bodies can evaluate all kinds of products. Diagnostics, for example, can only be evaluated by Notified Bodies that are designated under the IVDR and have the specific scope for that type of diagnostic device.

WHAT ARE THE MAIN REGULATORY CHALLENGES?

a. Safety and validation requirements

Manufacturers have indicated that the **safety and validation requirements** (proof that a device consistently meets user needs and intended uses) are **complex and sometimes confusing**, leading to **higher costs**. Frequently mentioned issues include determining what constitutes **sufficient clinical evidence for approval, internal capacity and expertise for writing the clinical evaluation reports**, and **inconsistencies** in requirements for clinical data between different notified bodies.

For diagnostics that use Artificial Intelligence (AI), regulation can pose unique challenges. Technical issues like **reproducibility** of results or **algorithmic transparency** are mentioned, alongside **data privacy and security**.

b. Lack of health technology assessment guidelines specifically for diagnostics

Some diagnostics, especially high-risk, "new in class" or having a high impact on patients might need further evaluation to assess **eligibility for reimbursement** by national health insurance bodies. These evaluations are called **Health Technology Assessments (HTAs)** and are usually undertaken for new medicines. As there are many different types of diagnostics, HTAs can be complex and **standardised approaches and guidelines specifically designed for diagnostics are lacking**. So far, the only consensus of HTA guidelines is that they should **evaluate accuracy**. Some diagnostics could also be **evaluated together with the treatments** that the diagnostic has helped to choose.

It is worth keeping in mind that diagnostics include very different types and classes of devices, so a fully standardised framework for all diagnostics is impossible.

c. Post-market surveillance

Once diagnostics have been authorised and placed on the market, their safety, quality and performance still need to be **monitored as part of the post-market surveillance**. That means that users can also report any problems and manufacturers can act on this feedback to correct and improve the devices.

The process is **costly and labour-intensive**, and manufacturers can **struggle with data analysis** (data sources may not be connected and are difficult to identify), risk management (when issues reported are isolated incident vs trends), different regulatory requirements for post-market surveillance and adequate resource allocation.

d. Complex reimbursement

Pricing of diagnostics can be complex, and in some countries is done through **public procurement** (a process by which public bodies purchase goods and services). Reimbursement processes for diagnostics vary greatly across Europe and depend on the device type and on national or even regional rules (e.g., Sweden).

Examples include:

- Some countries (e.g. France) place certain devices on **lists eligible for public funding**.
- Some have **specific reimbursement framework or codes for laboratory services** provided outside of hospital (e.g. Norway).
- Others (e.g. the UK) **do not have a separate framework for diagnostics** and reimburse through block contracts with hospitals.

e. Lack of global harmonisation (different sometimes conflicting requirements) between for example EU and the USA

While differences between countries in Europe exist, there are enough similarities to sustain a European approach to diagnostics regulation overseen by EU regulations. But if we look outside of the region, the regulation for diagnostics is further complicated by the existence of bigger, conceptual differences. For example, **between US and the EU there are disagreements on the definition of diagnostics**, with "device" being used most in the EU and "service" in the US. Differences further continue on **scope** (specific regulation or not), **oversight** (optional at federal level in the US vs national authorities in the EU) and **documentation** required for regulatory purposes.

Please Remember: If you receive a diagnostic test result and are unsure what it means, you should always discuss it with a healthcare professional.

RESOURCES:

WHO. Health Topics. Diagnostics. **https://www.who.int/health-topics/diagnostics#tab=tab_1**

European Commission 2021. **https://ec.europa.eu/commission/presscorner/detail/en/ip_21_5209**

European Commission, Medical Devices In Vitro Diagnostics Overview. **https://health.ec.europa.eu/medical-devices-vitro-diagnostics/overview_en**

EUDAMED **https://webgate.ec.europa.eu/eudamed-help/en/welcome-to-the-eudamed-information-centre.html**

Medical Device Coordination Group, 2021. "MDCG 2021-24. Guidance on classification of medical devices" **https://health.ec.europa.eu/system/files/2021-10/mdcg_2021-24_en_0.pdf**

European Commission. CEE Marking **https://single-market-economy.ec.europa.eu/single-market/goods/ce-marking_en**

Kearney B, McDermott O. The Challenges for Manufacturers of the Increased Clinical Evaluation in the European Medical Device Regulations: A Quantitative Study. Ther Innov Regul Sci. 2023 Jul;57(4):783-796. doi: 10.1007/s43441-023-00527-z. Epub 2023 May 17. PMID: 37198369; PMCID: PMC10276779.

Pantanowitz, Liron, Matthew Hanna, Joshua Pantanowitz, Joe Lennerz, Walter H. Henricks, Peter Shen, Bruce Quinn, Shannon Bennet, and Hooman H. Rashidi. „Regulatory aspects of artificial intelligence and machine learning." Modern Pathology 37, no. 12 (2024): 100609.

WHO, Post-market surveillance of IVDs in non-laboratory settings. **https://www.who.int/tools/quality-management-system-for-non-laboratory-settings/pillar-6-post-market-surveillance-of-ivds-in-non-lab-settings**

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Vogler S, Windisch F. Assessing, Pricing and Funding Point-of-Care Diagnostic Tests for Community-Acquired Acute Respiratory Tract Infections-Overview of Policies Applied in 17 European Countries. Antibiotics (Basel). 2022 Jul 22;11(8):987. doi: 10.3390/antibiotics11080987. PMID: 35892377; PMCID: PMC9331460.

MTRC, In-Vitro Diagnostic Tests. **https://mtrconsult.com/general-market-access-landscape-vitro-diagnostic-tests-europe**

Find all publications on the ASCERTAIN website: **www.access2meds.eu/publications**

www.access2meds.eu/results/

www.linkedin.com/company/ascertain-eu

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