Biomedical Alliance in Europe

Implementation of the new EU Regulation for In Vitro Diagnostic Medical Devices: a ticking time bomb for the diagnostic sector.

Urgent actions are needed now to prevent a collapse of diagnostic testing

With only one year to go before its date of application, BioMed Alliance healthcare diagnostic providers are seriously concerned about the status of implementation of the In-Vitro Device Regulation (IVDR) and its potentially disastrous consequences for diagnostic practice in the EU. From 26 May 2022 onwards, in vitro diagnostic tests will need to comply with the IVDR, which aims to secure clinical effectiveness and safety of medical tests. This is highly welcomed, but it also requires a transformation of the entire diagnostic sector, including major changes in the conformity assessment process of IVDs. To date, many critical regulatory elements are not in place and important guidance is still lacking, making it extremely challenging for stakeholders to prepare fully for the new regulatory environment and thereby secure continuity of diagnostics after May 2022.

During the workshop on "The need for better EU Policies for health"[1], organised by the Panel for the Future of Science and Technology (STOA) of the European Parliament, representatives of the IVD working group of the BioMed Alliance stressed that without critical infrastructure, guidance documents and contingency plans, there will be disruption to the availability of essential diagnostic tests (CE-marked IVDs). Furthermore, clear and appropriate guidance is needed for in-house devices, also known as laboratory developed tests (LDTs), in order to help laboratories to prepare in time for the new legislation and to support the development of innovative solutions for niche applications, rare diseases and rapid responses to health crises.

The diagnostic sector will be transformed by the new regulation and it is up to policy makers and all stakeholders to avoid the risks of poor IVDR implementation. The state of play of the IVDR implementation (insufficient Notified Bodies, unavailability of the EUDAMED database, expert panels and/or reference labs not yet operational to evaluate the highest risk tests, lack of contingency plans, delayed guidance) is threatening to disturb the EU diagnostic sector and seriously affect patients' lives across Europe.

The main consequences will be:

- essential CE-marked tests will not be available on the European market and/or they will disappear
- specialty CE-marked tests (for genetics, virology, molecular diagnostics, cancer) will be particularly vulnerable
- specialty in-house IVD devices/LDTs that currently complement CE-marketed test will be embargoed if there is any equivalent CE-IVD alternative on the market, threatening access to innovative and specialized diagnostics.
- personalised diagnostics and tests for rare diseases will not be developed or used, and a tendency towards monopolies in CE-marked tests will limit their diagnostic range
- the development of new and creative solutions for rare diseases and health crises such as Covid-19 will be hampered

[1] https://www.europarl.europa.eu/stoa/en/events/details/the-need-for-better-eu-policies-for-heal/20210321WKS03401

Therefore, we call upon the European Commission and all Member States to address the following IVDR issues urgently:

1. Insufficient notified bodies. → The lack of notified body capacity will impact the availability of CE-marked IVD devices. Most medical decisions in hospitals are based on diagnostic test results, so this will seriously hamper patients' outcomes.

Current situation: Only 4 notified bodies have currently been designated under the IVDR. 90% of IVDs will need to undergo conformity assessment by a notified body, compared with 10% under the previous IVD Directive 98/79/EC[2]. The situation is alarming, considering that only 7 out of ca. 19,000 tests have been certified under the IVDR so far and only a further 249 tests are currently under review[3]. Processing of a notified body application for a certificate takes, on average, 10 months and 78% of IVD manufacturers have reported issues with the IVD certification process[4]. The hurdles to access a notified body along with the impossibility to anticipate long term is forcing manufacturers and particularly SMEs to stop the production of a range of CE-IVDs. This will create difficulties for health care diagnostic providers who rely on CE-marked tests to provide healthcare solutions to patients. It will not be possible for the diagnostic sector to replace missing tests with reactivated in-house tests, given the lack of preparation.

2. The IVDR threatens development and use of critical in-house devices/laboratory developed tests (LDTs) as article 5, section 5 (d) embargoes the use of LDTs if there is an apparently equivalent CE alternative on the market. The interpretation of the IVDR requirements for LDTs might restrict the use of these tests and impede the development of novel and specialized diagnostics and tests for rare diseases.

Current situation: Laboratory developed tests play an essential role in diagnostics throughout Europe. A recent case study[5] at a large university hospital laboratory in Belgium showed that 47% of tests implemented in the hospital laboratories are LDTs. In specialized laboratories, this number can increase to 80-90%[6]. These are often complex tests for rare diseases, specialised tests and/or tests that are performed rarely. LDTs fill a gap by providing quick to implement and personalised solutions and complement CE-marked kits in specialized diagnostics (the aforementioned case study found that there is currently no alternative available for 72% of LDTs). For instance, LDTs played an essential role in providing rapid solutions during the early stages of the COVID-19 pandemic. LDTs will be allowed under the IVDR if general safety and performance requirements are fulfilled and if there is no equivalent CE-IVD kit on the market. Setting high standards for laboratories' quality management systems and for the validation of LDTs is welcomed. However, prohibiting LDT use as soon as one equivalent CE-marked test is available threatens the ability of laboratories to continuously maintain complete and optimal

[2] Information provided by the European Commission during the STOA's workshop. https://www.europarl.europa.eu/cmsdata/232741/Tkachenko_210422%20%20IVDR%20STOA.pdf
[3] Information provided by the European Commission during the STOA's workshop. https://www.europarl.europa.eu/cmsdata/232741/Tkachenko_210422%20%20IVDR%20STOA.pdf
[4] European Commission Survey on IVDR preparedness coordinated by MedTech Europe
[5] Pieter Vermeersch*, Tobias Van Aelst and Elisabeth M.C. Dequeker: The new IVD Regulation 2017/746: a case study at a large university hospital laboratory in Belgium demonstrates the need for clarification on the degrees of freedom laboratories have to use lab developed tests to improve patient care. Clin Chem Lab Med. 2020;59(1):101-6.
[6] Bart R. Lubbers, Anke Schilhabel, Christa M. Cobbaert et al.: The new EU Regulation on in vitro diagnostic medical devices: implications and preparatory actions for diagnostic laboratories. Hemasphere. 2021;5(5):e568.

test portfolios for diagnostic patient care. Furthermore, this will encourage monopolies and the risk of failure to optimise diagnosis of variants, as for SARS-CoV-2 and drug-resistant cancerous variants. The European Commission together with national competent authorities must develop clear and appropriate guidance, especially on the definition of equivalence and valid justification for use of LDTs that facilitates harmonization of IVDR requirements at the EU level, taking into account input from relevant stakeholders. This will ensure optimal test quality but also that the regulatory burden for laboratories is no higher than strictly needed while maintaining availability of all relevant assays. This should happen as soon as possible, in order to help laboratories to continue their preparatory work and to warrant continuation of efficient, high-quality diagnostic healthcare based on LDTs after May 2022.

Key messages:

The European Commission and Member States must now:

- **prepare and publish contingency plans for implementing the IVDR that will not threaten the availability of any essential medical diagnostic laboratory tests**
- **speed up the preparation of appropriate guidance documents**
- **clarify the importance of in-house IVDs/LDTs by an appropriate interpretation of article 5, section 5 (d) in order to protect patient-centred care in specialized diagnostics and rare diseases**
- **work with all relevant stakeholders to avoid collapse of medical diagnostics.**

About BioMed Alliance:

The BioMed Alliance is an umbrella organisation representing 36 leading European medical professional societies focused on healthcare and biomedical research from bench to diagnosis and from clinical practice to bench. The BioMed Alliance IVD Working Group representatives have been in the frontline to develop the best diagnostic solutions to fight the COVID-19 outbreak, demonstrating the crucial role of LDTs. BioMed Alliance experts provide scientific input in the European Commission Medical Devices Coordination Group (MDCG) IVD Working Group. They produce policy papers and educational materials to raise awareness about the IVDR implementation. **This statement was produced in collaboration with the European Haematology Association (EHA) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM).**

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Key figures mismatch between EU regulatory provisions and clinical need for IVD medical devices	
Laboratory diagnostic tests essential for clinical practice and care: current situation	**Progress towards implementation of the new In Vitro Diagnostic Medical Device Regulation (EU) 2017/746 (IVDR)**
CE-MARKED IVDs	
• More than 27,000 laboratory diagnostic tests (IVDs) are used in medical practice • Under the EU In Vitro Diagnostic Medical Devices Directive 98/79/EC (IVDD), less than 10% of laboratory diagnostic tests need to be reviewed by a notified body • 18 notified bodies are approved to evaluate IVD tests under the IVDD [7] • The process of designating a notified body for the EU medical device regulations takes about 700 days • A notified body review of an application for a CE-certificate for an IVD test, submitted by a manufacturer, takes about 10 months	• IVDR date of application is 26 May 2022 • 90% of IVD tests (about 19,000) will need conformity assessment by a notified body for the first time, under the IVDR • Only 4 notified bodies have been designated so far for the IVDR • Only 1 more notified body is expected to be designated within the next 6 months • Only 7 IVD tests have been approved under the IVDR so far [8] • Another 249 tests are under review • 78% of IVD manufacturers have reported difficulties getting their IVD tests approved, due to lack of notified body capacity [9] • CE-marked tests which cannot undergo notified body evaluation will no longer be available for patients who need them
IN-HOUSE DEVICES/ LABORATORY DEVELOPED TESTS	
• A typical university hospital conducts 922 different laboratory diagnostic tests • 47% are in-house developed laboratory tests; for 72% of these, there is no commercially available alterative	• Regulatory oversight of laboratory-developed tests has been delegated to EU Member States, but guidance has not yet been published • The impact of the IVDR on the availability of laboratory-developed tests needs formal evaluation

[7] List of Bodies Notified under Directive: 98/79/EC In vitro diagnostic medical devices. (Accessed 7 May 2021) https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.pdf&refe_cd=98%2F79%2FEC&requesttimeout=900

[8] Information provided by the European Commission on 22 April 2021.

[9] European Commission Survey on IVDR preparedness, 27 Jan – 16 Feb 2021; courtesy of MedTech Europe.