Biomedical Alliance in Europe

16 January 2024

Statement: Urgent action needed to prevent widespread shortage of diagnostic tests

The medical community is increasingly concerned about approaching widespread issues with the availability of In Vitro Diagnostic Devices (IVDs) in Europe. Persisting problems with the implementation of the In Vitro Diagnostics Regulation (IVDR), insufficient certificates issued, the failure to deliver the EUDAMED database and general unpreparedness of the sector could lead to the disappearance from the market of a large number of essential IVDs in the near future and related loss of international competitivity compared to other jurisdictions.

The BioMed Alliance in Europe (BioMed Alliance), representing 36 European medical and research societies and more than 400.000 healthcare professionals, including laboratory professionals, is very concerned about the current situation. Healthcare professionals rely on both CE-marked and In-House IVDs to provide evidence-based diagnoses and surveillance to patients. The European Commission and member states must take action now to ensure that patient care is not severely disrupted in the near future.

Summary:

There are widespread issues with the implementation of the IVDR, the preparedness of the diagnostic sector, and the regulatory pathways to conformity assessment. This situation is likely to lead to substantial shortages of essential IVDs across Europe.

A variety of short-term measures and medium to long term reform is necessary to prevent a large-scale shortage of CE-Marked IVDs:

- An urgent extension of the transition periods for all IVD classes will provide much-needed breathing room to the sector
- EUDAMED must be fully implemented and widely used as soon as possible
- Special regulatory pathways to facilitate the conformity assessment of rare/niche/orphan IVDs should be created
- Additional efforts are required to raise awareness, and to provide support and guidance for IVD manufacturers, and particularly SMEs
- There is a need to simplify the re-certification of legacy devices, that have been successfully on the market without safety issues for a number of years
- There should be a legislative requirement for manufacturers to report to laboratory professionals and regulators when they intend to take an IVD or medical device off the market at least 6 months prior to withdrawal
- While, In-house IVDs (IH-IVDs) could fill the “CE gap”, Article 5.5, including the requirement of no equivalence to CE-IVDs, discourages their development due to the additional administrative burden and uncertainty of sustainability for IH-IVDs.

An increasingly problematic situation

The In Vitro Diagnostics Regulation (IVDR Regulation (EU) 2017/746) introduced fundamental changes in the regulatory system that have proved to be a big hurdle for manufacturers and the diverse Notified Bodies that are responsible for CE-certification. Under IVDR, more than 80% of IVDs are subject to Notified Body control, the vast majority for the first time. Implementation difficulties have already led to extended transition periods (see table), with many Class D IVDs still having to undergo a conformity assessment process which habitually takes 18 months. The total number of Class D IVDs available in Europe is estimated to be 1000+, representing around 1.5%-4% of the total number of IVDs available[1]. These are highly specialized diagnostic tests required in all areas of stratified/personalize health care. Despite an increase in the number of Notified Bodies (currently 12[2]), recent figures indicate that only a little over one hundred certificates[3] have been issued for Class D IVDs. The number of applications for certifications is also worryingly low, indicating that it will prove virtually impossible for all class D devices to be IVDR certified before the end of the transition period.

Proportions of approximately 40 000 IVDs overall and extended transition periods IVDR (established in REGULATION (EU) 2022/112)	
Class A (21%)	No extended transition period
Class A sterile and class B (49%)	26 May 2027
Class C (26%)	26 May 2026
Class D (4%)	26 May 2025
Sell off date	No longer applicable

Rising political pressure

The issues with the IVDR transition were discussed at the European Council meeting (EPSCO) on 30 November 2023, and several health ministers raised their concerns on the risk that essential IVDs might disappear from the EU market. France raised the point at AOB and also issued an information note ahead of the meeting, supported by 9 other national delegations. In addition to worries regarding the clear risk of supply disruptions for both IVDs and medical devices, the information note highlighted that small and medium sized companies /enterprises (SMEs) face particular issues with the transition.

[1] See: MedTech Europe (2021), *Results: Market composition of in vitro diagnostic medical devices (IVDs):* https://www.medtecheurope.org/wp-content/uploads/2021/09/medtech-europe-survey-report-detailed-results.pdf and RIVM (2018), *The impact of the new European IVD classification rules on the notified body involvement*: https://rivm.openrepository.com/bitstream/handle/10029/622381/2018-0082.pdf?sequence=1&isAllowed=y (p17)

[2] See European Commission, *NANDO Database* (consulted on 04-01-2024), https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies/notified-body-list?filter=legislationId:35,notificationStatusId:1

[3] 115 from MDCG on 20/12/23

A large number of diagnostic tests are affected

Unlike for medications, there is no obligation for manufacturers to give advance warning of IVD discontinuation, so anticipation of diagnostic shortages is based on estimates. The risks of disruption are not limited to Class D IVDs (essentially tests for blood typing and tissue compatibility, and tests to diagnose severe infections) but affect all risk classes including Class C IVDs (associated with high patient risk and/or moderate public health risk). The Class C category, which includes genetic tests for cancers and inherited disorders, represents around 25/30% of all IVDs[4]. While it is appropriate that tests which have been replaced by better alternatives are removed from the market during a process of "diagnostic pruning", loss of tests which are valuable to patient management due to difficulties with certification is unacceptable.

A large number of these tests are developed by SMEs[5], many of whom are facing Notified Body certification for the first time and struggle particularly with high costs and lengthy and complicated conformity assessment procedures. It has been estimated that approximately 17% of today's IVDs will be discontinued in Europe[6], for a variety of reasons. This is only a rough estimate, with many companies still having to start their conformity assessment procedure, so the number could increase. As Notified Body capacity rises, there is a clear need for optimisation of a standardised, predictable, manageable and affordable conformity assessment pathway. This pathway must be fit-for-use for SMEs, in order for patients not to lose their niche tests and Europe not to fall behind compared to other jurisdictions in providing a supporting environment for diagnostic innovation.

Impact on patient care

If a large number of IVDs disappear from the EU market, this would mean that essential information is no longer available for patient care. In particular, tests that are used for small patient groups, or in the context of rare metabolic, malignant or genetic diseases, may be affected and will have profound impact on clinical decision-making at the bedside.

The explosion of personalised medicine, and its dependence on genetic, proteomic, immune and/or metabolomic biomarkers, means that an ever-larger proportion of patients will require access to rare/orphan IVDs. Such IVDs offer manufacturers little return on investment considering the high costs of certification, which may lead to the decision not to pursue conformity assessment under IVDR. If even the orphan devices that are already on the market disappear, many patients overall,

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[4] See: MedTech Europe (2021), *Results: Market composition of in vitro diagnostic medical devices (IVDs):* https://www.medtecheurope.org/wp-content/uploads/2021/09/medtech-europe-survey-report-detailed-results.pdf and RIVM (2018), *The impact of the new European IVD classification rules on the notified body involvement*: https://rivm.openrepository.com/bitstream/handle/10029/622381/2018-0082.pdf?sequence=1&isAllowed=y (p17)

[5] See e.g. MedTech Europe (2023), *Transition to the IVD Regulation - MedTech Europe Survey Results for October 2022*, https://www.medtecheurope.org/wp-content/uploads/2023/02/mte_public-report-ivdr-survey_27-feb-2023.pdf and RIVM (2023), *Appeal to manufacturers: please take timely action to ensure that you meet the IVDR requirements*, https://english.igj.nl/binaries/igj-en/documenten/publication/2023/09/05/appeal-to-manufacturers-take-action-to-meet-ivdr-requirements/Manufacturers+please+take+timely+action+to+meet+IVDR+requirements.pdf

[6] Idem to footnote 5

each suffering from a rare acquired or inherited disorder, will lose access to essential diagnostics and care.

Increasing reliance on in-house IVDs

While laboratory-developed tests (in-house IVDs, IH-IVDs) could fill the "CE gap", several aspects of IVDR affect their development. In particular, Article 5.5, including its requirement of no equivalence to IVDR commercial tests, creates an additional administrative burden, with confusion regarding its respect relative to ISO 15189 conformity. This uncertainty of sustainability for IH-IVDs discourages their development for both administrative and economic reasons. These serious IVDR-related diagnostic issues were fully recognised by the participants of last year's conference organised by the Czech EU Council Presidency "Towards a New European Policy Framework: Building the Future Together for Rare Diseases"[7] (Prague, 25-26 October 2022). The "Call to Action"[8] that ensued from the conference was supported by 22 EU Member States, representing over 82% of the EU population. The option of transferring niche tests to the public diagnostic sector as IH-IVDs would put additional pressure on healthcare systems which are already struggling to face up to expanding demand for diagnostics in a highly controlled and ever more exacting regulatory environment[9].

Immediate action needed now

BioMed Alliance believes that urgent action is needed to prevent a major crisis in our health system due to a serious shortage of diagnostic tests. A variety of both short-term emergency solutions, and longer-term systemic reform is necessary.

Diagnostic laboratory professionals agree that the only way forward is to once again extend the transitional period for all IVD Classes, while maintaining staggered deadlines. This would give much needed breathing room for the sector to enhance preparedness, although this must be accompanied by measures to ensure acceleration of the preparatory process and transparency, with periodic updates to medical labs and lab professionals on the (dis)continuation and certification rate of tests in use.

Such measures should include acceleration of activation of the long-awaited EUDAMED system and encouragement of widespread uptake. Immediate use of the already completed modules would give a clearer view of the progression of test registration, help harmonisation between Notified Bodies, with consequent improved predictability for manufacturers, and favour concerted support of first-time users. We call on the Commission to ensure a swifter roll out, accompanied by measures to encourage widespread harmonised use and uptake of the system by manufacturers and notified bodies in order to facilitate the transition process.

We welcome the proposals made on these points by the European Commission (DG SANTE) at the Medical Device Coordination Group (MDCG) during a stakeholder consultation on 20 December

[7] https://www.mzcr.cz/towards-a-new-european-policy-framework-building-the-future-together-for-rare-diseases/

[8] https://www.mzcr.cz/wp-content/uploads/2022/12/CZPRES_Expert_Conference_on_Rare_Diseases_brochure.pdf

[9] See e.g. Vanstapel et al (2023), *ISO 15189 is a sufficient instrument to guarantee high-quality manufacture of laboratory developed tests for in-house-use conform requirements of the European In-Vitro-Diagnostics Regulation*

2023, but we consider that other actions must rapidly be envisaged if the IVDR is to achieve its objective to establish a robust, transparent, predictable and sustainable regulatory framework for medical diagnostic tests which ensures a high level of safety and health whilst supporting innovation.

Mid/long-term reform necessary to ensure continued availability

Next to the immediate, short-term, actions that are already being considered, policy makers must implement reforms to the system on the mid to longer term, to ensure continued availability of diagnostic and innovative tests in the years to come. Persisting structural issues must be addressed, leading up to the foreseen evaluation of the IVDR in 2027.

- There is a need for **special regulatory pathways to facilitate the certification of rare/niche/orphan IVDs and breakthrough innovation**, as exist in other (non-EU) regulatory systems[10]. The costs of recertification represent a particular hurdle for these IVDs, due to the small patient groups and limited return on investment for manufacturers.
    - They would benefit from a more centralised, affordable and transparent **pathway to (re)certification** which should be created within the EU regulatory framework.
    - Such a framework could also benefit **SMEs** and diagnostic laboratories, as these groups particularly struggle to navigate the regulatory system and cover the costs of (re)certification.
    - Pre/early certification access models should be developed, preferably in collaboration with **academic diagnostic experts,** the IVD Expert Panel, EU Reference Laboratories, the European Rare Disease networks (ERN), the European Commission, Competent Authorities and registered stakeholders in the Medical Devices Coordination Group (MDCG)
- **Additional efforts are required to raise awareness, and to provide support and guidance for IVD manufacturers** in general, to support them through the regulatory process and EUDAMED implementation and to ensure that they prepare their applications for (re)certification with sufficient quality and in a timely manner.
- **Notified bodies** need to limit **excessive bureaucratic load** by appropriate digitalisation and harmonisation, which will contribute to accelerated participation by manufacturers, particularly once EUDAMED is fully operational.
- There must be additional support and provisions to assist laboratories in using IH-IVDs and conforming with regulatory requirements. IH-IVDs already play an important role in the diagnostic sector and their role may further increase if CE marked devices disappear from the market. Article 5.5, particularly the requirement of no equivalence to CE-IVDs, discourages their development due to additional administrative burden and uncertainty of sustainability for IH-IVDs.

[10] See e.g. FDA (2023), *Breakthrough Devices Program*: https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program

- New and/or alternative regulatory pathways or provisions are needed for diagnostic tests that have been on the market under the previous IVD Directive without shortcomings or inadequacies for a number of years (**legacy devices**)
    - Explore possibilities of providing provisional certificates with conditions for legacy devices without full conformity assessment (grandfathering), again dependent on a functional EUDAMED
    - Consider differential management of class C and B IVDs since only the former are of high (individual risk) to patients and/or public health and the latter represent half of all IVDs. Reduction of regulatory complexity for the latter would allow concentration of resources for class C and D, with little/no significant risk to patients or society.
- **There should be a legislative requirement for manufacturers to report** to laboratory professionals and regulators when they intend to take an IVD or medical device off the market at least 6 months prior to withdrawal.
    - For pharmaceuticals, in accordance with Article 13(4) of Regulation (EC) No 726/2004, Marketing Authorisation Holders are required to inform EMA if their centrally-authorised product ceases to be placed on the market of a Member State, either temporarily or permanently. A similar system should be set up for IVDs and medical devices, to prevent future disruptions of supply.
- Creation of an **accountable single Governance structure** capable of overseeing the medical device regulatory system and coordinating and streamlining procedures, in concertation with national competent authorities.

Conclusion

The diagnostic sector is concerned about the current situation and the potential discontinuation of a significant number of CE marked IVDs. We call on the European Commission and Member States to continue the dialogue with stakeholders and to implement a variety of short-term emergency measures and long-term reforms to prevent loss of essential tests.

European diagnostic laboratories have undergone, and are still undergoing, significant upheavals during the transition period to international standardised certification, predominantly with ISO 15189. This has led to regrouping, on a geographic or functional basis, small diagnostic laboratories into larger units, with an undoubted gain in the transparency, traceability and safety of diagnostics, albeit with a significant shift in manpower allocation within the public diagnostic sector.

IVDR 2017/746/EU represents a similar process for the manufacturing sector and Notified Bodies, and for the end-users that will be faced with untimely notifications of discontinued tests. This process must achieve its objectives without loss of the diagnostic repertoire or our capacity to maintain and strengthen our contribution to individual patient management and diagnostic innovation. Urgent action must be taken now to ensure a continued high level of patient care and diagnostic capabilities and prevent a potential crisis in our healthcare system.