EFLM Paper

Christa Cobbaert*, Michael Neumaier, Ettore Capoluongo, Francois Mullier, Matthias Orth, Thomas Streichert, Harjit Pal Bhattoa, Patrick Bossuyt, Lucas Biaggini Barbosa, Mario Plebani and Tomáš Zima, on behalf of the European Federation of Laboratory Medicine (EFLM)

EFLM position statement on the proposed 2025/0404(COD) IVDR Amendment of Article 5.5

https://doi.org/10.1515/cclm-2026-0580
Received April 14, 2026; accepted April 14, 2026;
published online May 7, 2026

Abstract: Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR) was introduced to enhance patient safety and ensure the availability of safe and effective diagnostics across the European Union. However, its implementation has led to substantial unintended consequences, including certification bottlenecks, market withdrawals, diagnostic shortages, and delayed innovation, with disproportionate impact on small and medium enterprises and on healthcare institutions developing in-house *in vitro* diagnostic devices (IH-IVDs). As a result, thousands of diagnostic tests have been lost during the transition to IVDR. Restrictions imposed by Article 5.5 of the IVDR have proven particularly harmful for IH-IVDs addressing rare diseases, niche indications, and key developments such as precision oncology and precision coagulation, among others. In December 2025, the European Commission published a targeted legislative proposal (2025/0404(COD)) to amend the IVDR. This EFLM position statement critically evaluates the proposed reforms, with a specific focus on the revision of Article 5.5. The proposal introduces a more proportional, risk-based regulatory framework, reduces administrative burden, modernizes clinical evidence requirements, and strengthens predictability and regulatory capacity. Key improvements include removal of the equivalence justification requirement, recognition of existing laboratory quality management systems, increased flexibility in the use and transfer of in-house devices when justified by patient safety or public health, and extension of the in-house exemption to certain clinical trial laboratories. While the proposal represents a significant step forward, remaining challenges include the need for clearer definitions and harmonized guidance to avoid divergent interpretation across Member States. Overall, EFLM strongly supports the adoption of the revised Article 5.5 as proposed in 2025/0404(COD). The reform maintains essential safety and performance safeguards while enabling timely access to innovative, high-quality diagnostics. By reducing unnecessary regulatory barriers and better reflecting laboratory practice, the proposed revision is essential to prevent patient harm, support

Christa Cobbaert, Michael Neumaier, Ettore Capoluongo, Francois Mullier, Matthias Orth, Thomas Streichert, Harjit Pal Bhattoa, Patrick Bossuyt, Lucas Biaggini Barbosa: Members of the EFLM Committee on European Regulatory Affairs.

Mario Plebani: Past-President of EFLM and EFLM EB Member.

Tomáš Zima: President of EFLM and EFLM EB Chair.

***Corresponding author: Christa Cobbaert**, Department of Clinical Chemistry and Laboratory Medicine, Leiden, Netherlands, E-mail: c.m.cobbaert@lumc.nl. https://orcid.org/0000-0003-3565-1404
Michael Neumaier, Institute for Clinical Chemistry, Mannheim, Germany. https://orcid.org/0000-0003-0410-3931
Ettore Capoluongo, Department of Molecular Medicine and Medical Biotechnology, Federico II University, Naples, Italy; and Department of Laboratory Medicine, Rome, Italy
Francois Mullier, Université Catholique de Louvain, CHU UCL NAMUR, NTHC, Narilis, Yvoir, Belgium. https://orcid.org/0000-0001-6947-6099
Matthias Orth, Vinzenz von Paul Kliniken gGmbH, Institut für Laboratoriumsmedizin Stuttgart, Germany; and Medizinische Fakultät Mannheim, Ruprecht Karls Universität Heidelberg, Mannheim, Germany. https://orcid.org/0000-0003-2881-8384
Thomas Streichert, Institute for Clinical Chemistry, Cologne, Germany. https://orcid.org/0000-0002-6588-720X
Harjit Pal Bhattoa, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary. https://orcid.org/0000-0002-4909-0065
Patrick Bossuyt, Department of Epidemiology and Data Science, Amsterdam UMC, Netherlands. https://orcid.org/0000-0003-4427-0128
Lucas Biaggini Barbosa, Department of Clinical Pathology, Unidade Local de Saúde de Coimbra, Coimbra, Portugal. https://orcid.org/0009-0000-9700-4996
Mario Plebani, Department of Medicine-DIMED, University of Padova, Padova, Italy. https://orcid.org/0000-0002-0270-1711
Tomáš Zima, Institute of Medical Biochemistry and Laboratory Diagnostics, Prague, Czech Republic

innovation, and uphold the original objectives of the IVDR in European diagnostic medicine.

Keywords: IVDR reform; in-house tests; Art 5.5 flexibilization; personalized medicine; patient-centric strategy

1 Context: Why the 2025 IVDR reform matters

On 16 December 2025, the European Commission (EC) published a legislative proposal 2025/0404(COD) for a targeted revision of the EU2017/746 (IVDR) that has been plagued by major implementation challenges. For the marketing of commercial IVD tests (CE-IVD), the challenges comprise certification bottlenecks, device shortages, IVD withdrawals, delayed innovation affecting availability and competitiveness. Also, burdens disproportionately affect Small and Medium Enterprises (SMEs) in the diagnostic manufacturing field including providers of niche and orphan tests. For *in-house* tests (IH-IVD), hurdles are being experienced by the healthcare institutions providing them and are particularly related to harmful restrictions and disproportionate requirements as described in Art 5.5. of the IVDR. Although the EC aimed at bringing safe and effective medical tests to the EU-market, ~9,000 tests out of ~40,000 tests got lost in transition [1–7]. From our perspective as professionals in Laboratory Diagnostics, the unintended consequences are patient harm due to shortages and inaccessibility are more pronounced, thereby missing IVDR's key objectives of supporting safe and effective *in-vitro* medical tests on the EU-market in its current form.

At EFLM, the Committee for European Regulatory Affairs (CERA) has regularly pointed out IVDR-associated challenges in the past. Our position statement has patient safety and benefit at its centre. Here, we focus on pointing towards the strengths and weaknesses of the 2025/0404(COD) reform proposal as related to *in-house* tests described under Art 5.5. in the IVDR. We strongly advocate that EU Health Politics goes forward by adopting the amendments specified therein. To further the current practices already known to impede healthcare benefits, safety and timely diagnostic services with an enthusiastic "carry-on with the business" will continue not only to disadvantage a stakeholder group called "patients" that should have our central attention but will likely be detrimental for sustained leadership in innovation of diagnostic medicine in the European Union.

2 Key reforms proposed in IVDR 2025/0404 (COD)

The European Commission's IVDR reform includes the following categories that directly reshape IVDR practice:

- *Simplification and Reduction of Administrative Burden* related to lowering risk classification of certain IVD groups, especially software and reusable instruments; more flexible Person Responsible for Regulatory Compliance (PRRC) requirements, particularly for Small and Medium Enterprises (SMEs); and by replacement of the fixed 5-year certificate cycle by risk-based periodic reviews.
- *Evidence and Clinical Performance Modernization* introducing acceptance of broader evidence types, including *silico*, bench, computational, *ex vivo* data and more proportionate evaluation pathways are allowed. Yet, it remains crucial to generate clinical evidence and guarantee fitness-for-purpose of medical tests as reviewed by Sally Lord et al. [8].
- *Innovation and Availability of provisions* for breakthrough/orphan/special patient-group niche IVD devices and efforts to avoid device shortages and improve timely access and user notification.
- *Digitalization and Coordination* is given attention to by means of increased system digitalization and a stronger coordination between competent authorities.

3 Critical analysis of the proposed IVDR reforms

3.1 Strengths

- *Proportionality and Risk Alignment*
  The downgrading of classification for specific IVDs and introduction of risk-based certification brings the system closer to the principle of proportionality than the original IVDR intended – but failed – in practice. This reduces lowvalue regulatory work that will gain little for low-risk IVDs while freeing capacities in notified bodies.
- *Improved Regulatory Capacity and Predictability*
  Replacing the fixed 5-year recertification cycle with periodic reviews reduces recertification bottlenecks and supports continuous oversight rather than cyclical overload.
- *Enhanced Clinical Evidence Flexibility*
  Allowing non-clinical evidence broadens opportunities for rapid innovation and supports small-scale laboratories and niche diagnostic developers.
- *Alleviating Missing Specific Solutions for In-House Devices (Art. 5.5).*
  Being one of the most debated articles in practice, Article 5.5 – the *in-house* exemption for health-institution-manufactured IVDs – is currently addressed as follows:
  a. The conditions for the manufacture and use of *in-house* tests as a diagnostic service of the respective single health institutions are made more flexible,

e.g. allowing the transfer of *in-house* devices if this is in the interest of patient safety or public health (see 2025/0404(COD): pg.14; pg. 24 section (12); pg. 93 section (5/a/i/1)).

b. Under the new IVDR proposal, the condition that there is no equivalent device on the market is deleted (see 2025/0404(COD): pg.14; pg. 24 section (12); pg.93 section (5/a/i/3)).
c. Central laboratories manufacturing and using tests exclusively for clinical trials are added to the scope of the *in-house* device exemption (see 2025/0404(COD): pg.14; pg. 24 section (13); pg.93 section (5/a/iii)).

3.2 Weaknesses and remaining gaps

- *Lack of Clarity in Key Definitions*
  "Same or similar" clinical evidence criteria (Annex XIII in the IVDR) lack detail, which may cause inconsistent implementation across Member States – the exact problem IVDR was meant to fix.
- *Risk of Divergent Interpretation*
  Without harmonized MDCG guidance, and without coordinated governance between Notified Bodies, Competent Authorities and Expert Panels *ambiguity* on risk classification and clinical evidence will remain rather than solving existing challenges.

4 Comparison of Article 5.5 in IVDR 2017/746 vs. 2025/0404 (COD)

In the past years significant discussion arose around the provisions in Article 5.5 with its 9 subparagraphs (a–i). Next to rules for additional documentation, bureaucracy and justification efforts, Art. 5.5.a and Art. 5.5.d directly impact laboratory diagnostics at various operational levels specifically impeding the motivation to develop innovative medical diagnostic devices to meet patient needs unaccounted-for by the industrial diagnostic market [1–7].

Indeed, we need to emphasize that IH-IVD are most often manufactured and used by diagnostic laboratories with a strong scientific background and a particular interest to investigate small patient groups by measuring biomarkers, for which no commercial IVD is available or sufficient. These biomarkers represent different biomolecule classes including nucleic acids (DNA, DNA modifications and RNA species), proteins, lipids, carbohydrates and a multitude of metabolites. Consequently, IH-IVD testing comprises various technologies, methods and specimen types and is well-established in all *in-vitro* diagnostic disciplines investigating special patient groups. Indeed, IH-IVDs can account for up to 50 % or more of medical laboratories' biomarker portfolios in rare and niche IVD testing, for which the *in-vitro* diagnostic industry – for economic reasons – fails to take an interest [9, 10].

The proposed IVDR reform apparently aims at flexibilization and contextualization but must pass European Parliament and the European Council before it becomes law. To fully appreciate the impact of the IVDR proposal 2025/404(COD), a *side-by-side* comparison of the current and proposed IVDR Art 5.5 requirements are presented in Table 1.

4.1 Article 5.5 under the current IVDR (Regulation (EU) 2017/746)

- *Definition and Scope*
  Art 5.5 applies to *in-house* IVDs manufactured and used within a health institution if strict conditions are met. No CE-marking is required.
- *Core Provisions*
  - In Art. 5.5.a: The in-house IVD may not be transferred to another legal entity. This has major implications for availability of innovative diagnostics not covered by the usual CE-IVDs. It is unclear, how many thousand lives have been saved, because the IH-IVD SARS-COV2 tests were made available to various legal entities urgently needing them at the start of the COVID pandemic. Furthermore, Art. 5.5.a in its current form has major implications for biosafety, data safety, preanalytics, costs and diagnostic delays.
  - In Art. 5.5.d: Health institutions must have an appropriate quality management system (QMS) and must show that the *in-house* IVDs are developed and used under adequate quality control. Compliance with Annex I (General Safety and Performance Requirements) is needed and includes demonstrating scientific validity, analytical performance, clinical performance, doing risk management and meeting post-market surveillance obligations. Maintenance of IVD-specific technical documentation, proving compliance for each *in-house* test, and accepting audits by competent national authorities. Having justification for running *in-house* tests if an equivalent CE-marked test exists (a provision scheduled to apply from 2030), is considered an unfair requirement which is in contradiction with the professional Code of Conduct of academic Lab Professionals. This "equivalence justification requirement" is one of the

Table 1: *Side-by-side* comparison of the current Art 5.5 regulatory requirements in the IVDR 2017/746 and the Art 5.5. amendments proposed in 2025/0404 (COD).

	Original Art 5.5 as mentioned in the IVDR 2017/746	Revised Art 5.5 as proposed in 2025/0404 (COD)	Additional remarks in 2025/0404 (COD)
Art 5.5. a	The devices are **not transferred** to another legal entity;	The devices are **not transferred** to another legal entity, **except** to another health institution **in the duly justified interest of public health, patient safety or patient health, or to prepare or respond to a public health emergency.**	In the case of a transfer of the device to another health institution, the transferring and receiving health institutions **shall ensure traceability of the device**. The receiving health institution **shall report any incident** related to the device to the transferring health institution.
Art 5.5.c	The laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;	The laboratory of the health institution is compliant with standard EN ISO 15189 or, where applicable, national provisions for **quality and competence in medical laboratories**, including national provisions regarding accreditation.	This paragraph **shall also apply** to devices manufactured and used within a laboratory that is established in the Union and provides consistent, state of the art testing services for clinical research, provided those devices are intended exclusively for use in the framework of a **clinical trial subject to Regulation (EU) No 536/2014** of the European Parliament and of the Council*.
Art 5.5.d.	The health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an **equivalent device** available on the market;	**DELETED!**	
Art 5.5.e.	The health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;	Upon request by a **competent authority**, the health institution provides information on the use of such devices to its competent authority, which shall include the justification referred to in point (a).	
Art 5.5.f.(i.i.i)	A declaration that the devices meet the general safety and performance requirements set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification therefor;	A declaration either that the health institution is accredited to the standard referred to in point (c) or that the devices meet the relevant general safety and performance requirements set out in Annex I and, where applicable, information on which requirements are not fully met with a **reasoned justification** therefor.	
Art 5.5.g.	As regards class D devices in accordance with the rules set out in Annex VIII, the health institution draws up documentation that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to this Regulation are met. Member States may apply this provision also to class A, B or C devices in accordance with the rules set out in Annex VIII;	As regards class D devices in accordance with the rules set out in Annex VIII, where the health institution is not accredited to the standard referred to in point (c), the health institution draws up **documentation sufficiently detailed** to enable the competent authority to ascertain that the relevant general safety and performance requirements set out in Annex I are met.	
Art 5.5.h.	The health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g);	**DELETED!**	

most controversial elements and is strongly opposed by lab professionals in all diagnostic disciplines. It is considered an IVD-industry privilege.

– *Interpretation Challenges*
MDCG 2023-1 guidance exists but interpretation varies between Member States.

4.2 Article 5.5 in proposed 2025/0404 (COD)

In Table 1 relevant amendments and deletions are presented for current and proposed Art 5.5. in respectively the IVDR 2017/746 and the proposed 2025/0404(COD). Sources: EU 2017/746 [11] and 2025/0404 (COD) [12].

Key themes central in the current IVDR reform proposal are:

- *Equivalence-justification requirement is deleted* due to heavy criticism and impracticality.
- *Recognition that the current Article 5.5 imposes unnecessary administrative burden* on medical laboratories. The EC finally considers the QMS that medical labs have in place.
- *Expectation of greater national harmonization* due to the recognized variability in how Member States interpret Article 5.5.
- *Arguments in favor of the IVDR reform are the fact that the Commission acknowledges structural challenges* (administrative overload, misalignment with laboratory realities, regulatory friction) which negatively affect the use and accessibility of essential *in-house* tests.

4.3 Key takeaways

- Article 5.5 today is too strict, documentation-heavy, and hinders development, validation and use of essential and precision/personalized diagnostic tests in clinical care pathways with recognized unmet clinical needs. Some examples of essential IH-tests are listed in the attached Appendix.
- There is strong momentum toward modifying Article 5.5 because the Commission acknowledges administrative burden and structural challenges; stakeholders widely criticize the equivalence justification requirement as one of the most problematic challenges.

Anticipated changes revolve around removing the equivalence-justification requirement; reducing documentation obligations; harmonizing national interpretations, reducing burdens on medical laboratories and above all preventing patient harm.

4.4 Key benefits of a revised article 5.5 as proposed in 2025/0404 (COD)

- **Enhanced Patient Access to Diagnostics**
  By removing the obligation to prove lack of CE-marked equivalents, laboratories can rapidly deliver or adapt tests tailored to patient needs, especially where commercial options are inadequate.
- **Reduced Regulatory Burden Without Compromising Safety**
  Simplified documentation, reliance on ISO 15189 accreditation, and risk-based evidence maintain safety while reducing unnecessary bureaucracy.
- **Improved Harmonization Across the EU**
  Streamlined and clearer wording decreases variability in national interpretation, aligning with the Commission's objective of greater regulatory consistency.
- **Better Use of Healthcare Resources**
  Reduces duplication of documentation, administrative workload, and external consultancy dependence – especially important for SMEs and public hospitals, which the Commission highlighted as disproportionately affected by the current framework.
- **Safeguarding Patient Safety**
  The revised Art 5.5 maintains core safety and performance requirements; ensures validation through accredited quality systems; retains risk-based vigilance and competent authority oversight and enhances transparency through public notices. This achieves the original goals of the IVDR while eliminating unnecessary barriers.
  The proposed simplified Article 5.5 maintains high safety standards while enabling medical laboratories to provide essential *in-house* diagnostic tests efficiently and equitably. The revised Art 5.5 supports the Commission's core reform objectives on proportionality, simplification, predictability and improved availability- and ensures that EU patients continue to receive timely, innovative, and high-quality diagnostic care.

4.5 Strong EFLM support for legalizing Art 5.5 as proposed in 2025/0404 (COD)

The December 2025 targeted revision represents an acceptable and workable recalibration of the original EU regulatory approach in IVDR. *EFLM Executive Board and the EFLM Committee on European Regulatory Affairs strongly support the European Commission's goals* of simplification, proportionality, innovation support, and continued *in-house* test availability particularly regarding a revised Art 5.5 in 2025/0404(COD). This explicit simplification and flexibilization of Article 5.5 are key so that the reform will resolve the most critical challenges faced by hospital laboratories and the patients they serve. Patients depend on timely, accurate, and context-appropriate diagnostics, which critically must include availability of IH-IVD for unmet diagnostic needs. It is inconceivable that high-end

medical diagnostics could be sacrificed by making the "instrument of IH-IVD" unavailable to a well-regulated degree amongst special laboratories (see Art. 5.5.a) or permanently impeding diagnostic progress by unequal treatment of commercial and non-commercial providers of IVDs in *in-vitro* diagnostic healthcare. Medical laboratories are essential to delivering these. An improved, clear, and proportional Article 5.5, freed up from IVD-industry privileges that do not serve the patient and/or public health, is *thus not only a regulatory necessity – but a public- and patient-health imperative.*

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

Appendix to EFLM position statement on the proposed 2025/0404(COD) IVDR Amendment of Article 5.5

The purpose of this SUPPLEMENT/ANNEX is to feature very few examples of *in-house developed IVD* (IH-IVD) in order to demonstrate – deliberately in generic form rather than scientific specialty detail – their clinical importance and grave impact on patient health. The currently active IVDR prohibits availability of IH-IVD tests beyond the respective local use, while at the same time regulatory hurdles targeting the non-commercial IVD arena effectively demotivate specialty laboratories to invent and further develop the high-quality *in-vitro* diagnostic testing to meet the urgent diagnostic needs of specific patient groups in precision medicine.

The *examples* below comprise IH-IVDs as defined by modification and off-label use of CE-IVD, classical IVD designs and the use of Research-Use-Only components for diagnostic purposes.

Biomarker background of S100β as a CE-IVD

S100β is a *protein* historically known to be useful as a tumor marker in the diagnosis of relapsing malignant melanoma. There is but one CE-IVD test (marketed by a single diagnostics manufacturer) to be run on a fully automated clinical analyzer. The patient material, in which to measure S100β is mandatory serum (the watery phase of coagulated whole blood obtained after centrifugation in the laboratory). The use of other biomaterials is explicitly forbidden by the manufacturer.

More recently, S100β has been recognized as a marker of glia cells in the white matter of the brain indicating traumatic brain damage e.g. in accidents involving a head injury.

Measuring S100β as an IH-IVD

To harvest serum from blood, an appropriate timespan for coagulation must be allowed in order to avoid spurious coagulation activity to occur during the analysis within the analyzer that may result in clogging up and incapacitating the instrument. As an average, a coagulation time of 45 min is usually allowed for serum specimens. In a tumor-diagnostic scenario, this time span is not critical, and appropriate coagulation can be awaited with no unfavorable effects on further procedures.

In contrast, suspected brain injuries require diagnosis without delay. Considering that in clinical situations, imaging procedures by CT scan are carried out within 20 min, the time to clinical decision-making is very limited. As a powerful biomarker, the results of S100β analysis should be available together with the brain image results, a task that cannot be accomplished with serum turn-around-times. Hence, we explicitly violated the manufacturer´s "specific instructions of use" and have established S100β measurement in human blood plasma. Thereby we avoided the wait for complete coagulation to occur prior to analysis and can report the laboratory diagnostic result in a timely manner as part of an integrative diagnostic approach.

In our hospital, there is clinical data on the impact this IH-IVD adaptation of the S100β CE-IVD has had on clinical management to the benefit of patients suffering from head traumata. We also carried out an analytical performance study to compare serum S100β and plasma S100β determinations (1). While the results of our study have been communicated in a peer-reviewed scientific journal as an original paper in 2021 and elsewhere, these data – after 5 years – have not prompted inquiries/reactions/consequences from the side of the industrial vendor of the S100β CE-IVD.

Conclusion

Against the backdrop of the provisions in Art. 5 (5), this example shows the design of an IH-IVD based on an CE-IVD and the use outside the "intended use" of the commercial

variant. The S100β IH-IVD solves the unmet diagnostic need of patients in a life-threatening emergency room setting. It also calls for improved communication between stakeholders in *in-vitro* diagnostic medicine to get IH-IVD to the market.

References

1: Haselmann V, Schamberger C, Trifonova F, Ast V, Froelich MF, Strauß M, et al. Emergency setting. Pract Lab Med 2021;26:e00236. DOI: 10.1016/j.plabm.2021.e00236.

Biomarker background of IVD for heparin-induced thrombocytopenia

Heparin-induced **t**hrombocytopenia (HIT) is the most frequent drug-induced thrombocytopenia that potentially results in adverse drug reactions with a life-threatening complete thrombotic obstruction of arteries in limbs and organs.

Among hospitalized patients, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the most widely used anticoagulants in the world. Depending on the type of heparin (UFH vs. LMWH), the duration of heparin exposure, and the patient population (e.g. surgical vs. medical), 0.1% to 5 % of patients develop an immunological reaction mediated by platelet-activating antibodies targeting complexes of platelet factor 4 (PF4) and heparin. These patients are at a markedly increased risk of thromboembolism caused by an extensive platelet activation. Conversely, this "platelet consumption" results in paradoxically low thrombocyte counts in the peripheral blood (thrombocytopenia).

Diagnosis of heparin-induced thrombocytopenia

When HIT is suspected, clinical assessment tools (4Ts score) are being used to guide the initial decision-making according to different risk categories for a HIT. Based on an Intermediate/high pre-test probability (4Ts score ≥4), an immunoassay should be performed. In case of a positive immunoassay, several international guidelines (1–3) recommend functional testing in order to avoid overdiagnosis and thus overtreatment (i.e. recommendation 1A in British Guidelines).

Different immunoassays (all CE-IVDs) and functional assays (mostly IH-IVD) are available. One functional assay is available as CE-IVD but there are discussions about its clinical validation and performance (4) as well as specificity to distinguish true HIT from cases without HIT (5).

Functional HIT assays as IH-IVDs

Functional HIT tests are of various designs to detect pathogenic antibodies and differ in 1) the platelet activation biomarkers analyzed (serotonin release, heparin-induced platelet activation (HIMEA)), 2) the technical detection read-outs (light transmission aggregometry, flow cytometry, multi electrode aggregometry), and 3) the type of donor platelet preparations used (e.g. platelet-rich plasma (PRP), washed platelets (WP), or whole blood (WB)). Donor platelets need to be confirmed being responsive to the presence of patient serum or plasma containing anti-PF4 antibodies in addition to heparin. All functional assays are dependent on the detection of platelet activation in the presence of blood (serum or plasma) from HIT patients and a low concentration of heparin. While the serotonin release assay (SRA) is considered the gold standard, it is complex to perform, requires the use of radioactive materials and has a turn-around time of more than 72 h. HIMEA appears to be highly sensitive and specific for diagnosing HIT with a turn-around-time of less than 24 h (6). Confirmation of a positive functional test is done by inhibition of platelet activation in the presence of excess heparin concentrations.

In essence, this listing aptly demonstrates the diversity and complexity of diagnostic testing for HIT as covered by IH-IVDs. The complexity of the HIT functional assays described above means that they need to be performed in experienced centres. Considering the clinical importance of HIT and its accurate diagnosis, it is generally agreed upon that IH-IVDs are indispensable in this area of specialty hemostasis testing.

Conclusion

Given the provisions in Art. 5 (5), this example shows the large variety of different IH-IVD to test to confirm or exclude a frequently occurring suspicion of HIT to react to a potentially life-threatening situation as well as to avoid unnecessary treatment with alternative anticoagulants (like argatroban, danaparoid, bivalirudin and fondaparinux) that by

themselves increase the risk of major bleeding complications and require IH-IVD for monitoring in some situations.

References

1. Arachchillage DJ, Thachil J, Anderson JAM, Baker P, Poles A, Kitchen S, et al. BSH committee diagnosis and management of heparin-induced thrombocytopenia: third edition. Br J Haematol 2024;204:459–75. doi: 10.1111/bjh.19180.
2. Yves G, Emmanuel DM, Claire P, François M, Sophie S, Stéphanie R, et al. Diagnosis and management of heparin-induced thrombocytopenia. Anaesth Crit Care Pain Med 2020;39:291–310. doi: 10.1016/j.accpm.2020.03.012.
3. Adam C, Gowthami MA, Beng HC, Douglas BC, Andreas G, Yves G, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv 2018;2:3360–92. doi: 10.1182/bloodadvances.2018024489.
4. Solano C, Mutsando H, Self M, Morel-Kopp MC, Mollee P. Using HitAlert flow cytometry to detect heparin-induced thrombocytopenia antibodies in a tertiary care 513 hospital. Blood Coagul Fibrinolysis 2013;24:365–70. doi: 514 10.1097/MBC.0b013e32835cc17e.
5. Skornova I, Simurda T, Stanciakova L, Lauko V, Holly P, Samos M, et al. A functional assay for the determination of heparin-induced 518 thrombocytopenia via flow cytometry. Diagnostics 2023;13. DOI: 519 10.3390/diagnostics13183019
6. M-Morel-Kopp M-C, Mullier F, Gkalea V, Bakchoul T, Minet V, Elalamy I, ET AL. Subcommittee on platelet immunology. Heparin-induced multi-electrode aggregometry method for heparin-induced thrombocytopenia testing: communication from the SSC of the ISTH. J Thromb Haemost 2016;14:2548–52. doi: 10.1111/jth.13516. Epub 2016 Nov 19.

Biomarker background of IVD for bleeding disorder of unknown cause (BDUC)

Bleeding **d**isorder of **u**nknown **c**ause (BDUC) is a diagnosis by exclusion characterized by normal hemostatic investigations despite a clinically significant bleeding tendency. BDUC is frequent because only 30–40 % of patients referred to a hematologist for diagnosis of mild to moderate bleeding disorder (MBD), will be diagnosed with a recognized MBD such as von Willebrand disease (vWD), mild hemophilia (Factor VIII, IX or XI deficiency) or inherited platelet function defect (1).

Diagnosis of bleeding disorder of unknown cause (BDUC)

According to recent recommendations of the International Society of Thrombosis and Hemostasis (ISTH) (1), Initial hemostatic testing for a patient with a bleeding tendency include prothrombin time (PT), activated partial thromboplastin time (aPTT), Clauss fibrinogen, thrombin time (TT), vW Antigen and function, FVIII, FIX, FXI, light transmission aggregometry. Abnormal results should be repeated to confirm the diagnosis of specific MBD. In case of normal first line tests, further hemostasis testing may be performed depending on local availability and expertise. These second- or third-line tests are often IH-IVDs and include platelet function assays and fibrinolysis assays (1).

IH-IVDs used to exclude a BDUC

Platelet function tests need to be performed on fresh while blood, so patients need to travel for phlebotomy to minimize preanalytical variables (1). Among platelet function tests, IH-IVDs include different platelet secretion assays and whole-mount transmission platelet electron microscopy to exclude platelet dense granule deficiency before BDUC is diagnosed. Platelet flow cytometry for platelet glycoprotein deficiency and study of platelet procoagulant activity may also be performed (2–4). Euglobulin clot lysis time, turbidity-based plasma clot lysis, and fluorogenic plasmin generation are examples of IH-IVD that may identify abnormalities in the fibrinolysis pathway in some BDUC patients (5).

Conclusion

Better diagnosis using specialized IH-IVDs and treatment is required for patients with BDUC as these patients (and especially women) suffer, throughout their lives, from comparable bleeding symptoms to other types of MBDs, including mucocutaneous bleeding, excessive hemorrhage with surgery, heavy menstrual bleeding and postpartum hemorrhage, leading to iron deficiency and anemia.

References

1. Baker RI, Choi P, Curry N, Gebhart J, Gomez K, Henskens Y, et al. ISTH SSC standardization of definition and management for bleeding disorder of unknown cause: communication from the SSC of the ISTH.

Von Willebrand factor, platelet physiology, and women's health issues in thrombosis and haemostasis. J Thromb Haemost.2024;22:2059–70. doi: 10.1016/j.jtha.2024.03.005.
2. Mezzano D, Harrison P, Frelinger AL 3rd, Mumford AD, Noris P, Lordkipanidzé M, et al. Expert opinion on the use of platelet secretion assay for the diagnosis of inherited platelet function disorders: communication from the ISTH SSC subcommittee on platelet physiology. Thromb Haemost 2022;20:2127–35. doi: 10.1111/jth.15781.
3. Jourdi G, Ramström S, Sharma R, Bakchoul T, Lordkipanidzé M. FC-PFT in TP study group. Consensus report on flow cytometry for platelet function testing in thrombocytopenic patients: communication from the SSC of the ISTH. J Thromb Haemost 2023;21:2941–52. doi: 10.1016/j.jtha.2023.07.006.
4. Poncelet P, Lecompte T, Bauters A, Mullier F. Quantitative flow cytometry-medical applications with a focus on blood platelets. Int J Mol Sci 2026;27:1976. doi: 10.3390/ijms27041976.
5. Mehic D, Pabinger I, Gebhart J. Accelerated fibrinolysis: a tendency to bleed? Hamostaseologie 2025;45:312–9. doi: 10.1055/a-2561-6786.

Background of next generation flow/fluorescence (NGF) as biomarker platform

NGF (next generation flow/fluorescence) (1–3) is a highly standardized and a very high sensitivity (up to 10^{-5}–10^{-6}) technology behind advanced multiparametric flow cytometric diagnostic testing. NGF is the generic platform for high-precision identification and characterization of cell populations. Currently, the main applications are to detect the circulating malignant cells with very high sensitivity (minimal residual disease; MRD) in hematologic oncology, multiple myeloma, myelodysplastic syndromes and both acute and chronic leukemia's.

Using NGF as diagnostic IVD

NGF is a demanding technique with the capability to perform multiparametric analysis on millions of cells. This requires dedicated specialty laboratories to design and run IH-IVDs composed by adapting certified reagent components depending on the diagnostic question at hand. In addition to the inherent analytical complexity, the commutability of test results between laboratories is limited due to unstandardized procedures in the preanalytical phase, the technical lab equipment, the operator skills in interpretation and protocol standardization. Finally, no certified software can provide definitive MRD assessments obtained by NGF without expert review (4–5). The read-outs from the Instrument serve as preliminary filters to be interpreted and validated by the operator before the final report is issued. Result interpretation remains a critical step, which is dependent on the expertise and practices of each laboratory.

The consequence of this complexity can also be appreciated from the fact that there are international collaborations between NGF labs (e.g. EuroFlow Consortium, www.euroflow.org) exchanging protocols and methods to seek improved commutability of lab results/findings and warrant the quality of diagnostic NGF.

Conclusion

Given the provisions in Art. 5 (5) and the fact that there are no CE-IVD available, it appears that without sufficient flexibility in this specific diagnostic field only warranted by IH-IVD, thousands of patients with hematologic malignancies would face losing accurate assessment of their disease status and MRD assessments, which in turn will influence the right/wrong decision-making on the side of therapeutic medicine. Furthermore, international non-commercial collaborative (multi-legal-entity) networks like EuroFlow can only function based on their exchange of data, protocols and reagents and thus, by definition may violate the rule of non-distribution beyond single health care providers. Yet, without them quality and sustainability of meeting patients' needs for economic reasons would highly compromise key IVDR objectives.

References

1. Flores-Montero J, Sanoja-Flores L, Paiva B. Next generation flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. Leukemia 2017;31:2094–103.
2. Kumar S, Paiva B, Anderson KC. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328–46.
3. Oliva S, Genuardi E, Paris L. Prospective evaluation of minimal residual disease in the phase II FORTE trial: a head-to-head comparison between multiparameter flow cytometry and next-generation sequencing. eClinicalMedicine 2023; 60:102016.

4. Yoroidaka T, Takamatsu H, Urushihara R, Itagaki M, Yoshihara S, Sato K, et al. Prognostic value of minimal residual disease detected by EuroFlow next-generation flow cytometry and next-generation sequencing in patients with multiple myeloma achieving complete response and receiving lenalidomide maintenance after autotransplant: a prospective comparison study. Haematologica 2025;110:2160–70.
5. Flores-Montero J, Sanoja-Flores L, Paiva B, Puig N, García-Sánchez O, Böttcher S, et al. Next generation flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. Leukemia 2017;31:2094–103. doi: 10.1038/leu.2017.29.

Background of next generation sequencing (NGS) as biomarker platform

NGS (next generation sequencing) is a generic platform technology being used by various *in-vitro* disciplines in diagnostic medicine for very different tasks. These tasks range from detection of inherited rare diseases to molecular alterations of genes important for tumour development, malignant growth and metastasis. NGS procedures comprise lengthy preparatory and analytical steps before mixtures of reagents and patient samples can be run on sequencing analysers. Finally, the data analysis requires complex bioinformatic pipelines for which no standards exist, and which are also often developed in a non-commercial environment of specialty laboratories.

IH-IVD offer flexibility in performing the NGS in oncology setting

Genomic profiling is a crucial part of the cancer disease characterization for personalized treatment (1) and can provide relevant diagnostic evidence to significantly improve outcomes for patients with diverse actionable genomic alterations (1). Different panels of genes (from targeted customized panel to untargeted whole genome or exome pipelines) are present on the market. CE-IVD kits are available for various sources but can be used in both diagnostic and research-use-only settings without restrictions. The lengthy process of NGS and the various diagnostic applications the technology is being used for generates significant preanalytical, analytical and post-analytical issues in the workflow (see also above for NGF). This includes the lack of standardized DNA/RNA extraction methods allowing each laboratory to adopt different protocols for nucleic acid isolation, lack/difference in standardization of DNA quantification affecting assay performance when detecting copy number alterations or low-frequency genetic tumour variants (2). At the post-analytical level, licensed software used for the analysis of BAM/VCF files is not always provided as CE-IVD.

Another important example is the liquid biopsy testing in bodily fluids of cancer patients. Presently, there are no CE-IVD kits covering the entire testing pipeline. Current commercial kits only indicate the amount of input DNA to be pipetted into the reaction mix meaning that every laboratory is required to adapt the methods – even the commercial ones – for their specific in-house use.

Conclusion

The above examples relate to the lack of complete standardization in NGS pipelines (3–7). Every step and process in molecular diagnostics in oncology must be considered as dynamic in the absence of fully automated processes covering all steps from sample preparation through to result reporting (4–7). Until commercial kits become available that will provide CE-certification for the complete workflow, regulation like Art. 5 (5) must allow for flexibility of IH-IVD usage in compliance with regional and national certification requirements. It should be emphasized at this point that IH-IVD in molecular diagnostics in general participate in independent quality assessment schemes (EQA) or benchmark their performance against other qualified centres conducting the same tests. Additionally, compliance with ISO15189 rules do support the ongoing efforts to standardize IH-IVD (8).

References

1. Marchetti P, Curigliano G, Biffoni M, Lonardi S, Scagnoli S, Fornaro L, et al. ROME trial investigators. ConsortiaGenomically matched therapy in advanced solid tumors: the randomized phase 2 ROME trial. Nat Med 2025;31:3514–23.
2. Arreaza G, Qiu P, Pang L, Albright A, Hong LZ, Marton MJ, et al. Pre-analytical considerations for successful next-generation sequencing (NGS): challenges and opportunities for formalin-fixed and paraffin-embedded tumor tissue (FFPE) samples. Int J Mol Sci 2016;17:1579.
3. Roy S, Coldren C, Karunamurthy A, Kip NS, Klee EW, Lincoln SE, et al. Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: a

joint recommendation of the association for molecular pathology and the college of American pathologists. 2018;20:4–27.
4. Roy S, Coldren C, Karunamurthy A, Kip NS, Klee EW, Lincoln SE, et al. Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: a joint recommendation of the association for molecular pathology and the college of American pathologists. J Mol Diagn 2018;20:4–27.
5. Horgan D, Pesapane F, Van der Buckle M, de Maria R, Dube F, Singh J, et al. From theory to practice: Implementing next-generation sequencing and public health genomics in healthcare systems. Crit Rev Oncol Hematol 2024;201:104433.
6. Horgan D, Van den Bulcke M, Malapelle U, Troncone G, Normanno N, Capoluongo ED, et al. Tackling the implementation gap for the uptake of NGS and advanced molecular diagnostics into healthcare systems. Heliyon 2023;10:e23914.
7. Horgan D, Plebani M, Orth M, Macintyre E, Jackson S, Lal JA, et al. The gaps between the new EU legislation on *in vitro* diagnostics and the on-the-ground reality. Clin Chem Lab Med 2022;61:224–33
8. Gristina V, Malapelle U, Daniele G, Iannantuono GM, Bazan Russo TD, Berardi R, et al. Liquid biopsy in oncology: results of a delphi consensus study endorsed by the AIOM-SIAPEC/IAP-SIBioC-SIF Italian scientific societies. J Liq Biopsy 2025;11:100453.
9. Vanstapel FJLA, Orth M, Streichert T, Capoluongo ED, Oosterhuis WP, Çubukçu HC, et al. 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. Clin Chem Lab Med 2023;61:608–26

The exception is the rule: rivaroxaban transition into human breast milk

Background: Anticoagulant background of rivaroxaban in lactation

Rivaroxaban is a direct oral anti-coagulant (DOAC) working as a factor Xa inhibitor and has been established for management of thromboembolic disorders, including postpartum venous thromboembolism and pulmonary embolism. However, manufacturers recommend against using rivaroxaban during the lactation period due to insufficient safety data regarding infant exposure, as breastfeeding women were excluded from clinical trials. Traditional anticoagulants like unfractionated heparin, low-molecular-weight heparins, and vitamin K antagonists remain the recommended options for nursing mothers. But in this case the mother declined oral antithrombotic treatment with vitamin K and regular monitoring. The 40-year-old postpartum woman with peripartum cardiomyopathy and submassive bilateral pulmonary embolism received 15 mg rivaroxaban twice daily after initial enoxaparin treatment. Both commercial IVD and IH-IVD tests for rivaroxaban in plasma or serum are available, but the question was whether relevant amounts pass into human breast milk, posing a risk to the infant (1).

Measuring rivaroxaban passage into breast milk

The commercial tests are not intended for breast milk as a biomaterial to be tested, thus prohibiting their use to characterize the infant's exposure. Therefore, whole breast milk outputs were collected before and after oral rivaroxaban dosing of the mother, with simultaneous plasma sampling, using an IH-IVD liquid chromatography tandem-mass spectrometry analysis. The milk-to-plasma (M/P) ratio was found to be 0.4. The calculated relative infant dose (RID) was quantified at 1.3 % and thus being substantially below the 10 % safety threshold.

Conclusion

This case demonstrates that rivaroxaban passes into breast milk in minimal quantities (1). While it would be considered to be insufficient to cause anti-coagulation in the infant's hemostasis, the IH-IVD delivers quantifiable amounts. The knowledge of drug disposition in lactating women is important to enable adequate and safe treatment decisions for both mothers and their breastfeeding children.

While being a special diagnostic scenario and an isolated case, it is an example that defines what we designated precision medicine (1). Without an IH-IVD and an understanding of the analytical process, such diagnostic service is not possible to provide guidance to the breastfeeding mother.

References

1. Martin HJW, Cornelia B, Carsten M, Thomas S, Roman P, Guido M. The direct factor Xa inhibitor rivaroxaban passes into human breast milk. Chest 2016;150:e1–4.

References

1. Cobbaert C, Schweiger C, Buchta C, Streichert T, Vanstapel FJLA, Mullier F, et al. Urgent call to the European Commission to simplify and contextualize IVDR article 5.5 for tailored and precision diagnostics. Clin Chem Lab Med 2025;63:2366–70.
2. Vanstapel FJLA, Orth M, Streichert T, Capoluongo ED, Oosterhuis WP, Çubukçu HC, et al. 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. Clin Chem Lab Med 2023;61:608–26.
3. Vanstapel FJLA, Guilaine BG, Cobbaert C. In-house diagnostic devices under the EU IVDR and unwanted side-effects of intentional transparency. Clin Chem Lab Med 2023;62:e1–3.
4. Dombrink I, Lubbers BR, Simulescu L, Doeswijk R, Tkachenko O, Dequeker E, et al. Critical implications of IVDR for innovation in diagnostics: input from the BioMed alliance diagnostics task force. HemaSphere 2022;6:e724.
5. Buchta C, van Hellemond JJ, Hellbert K, Neumaier M, Cobbaert C. The disparaging requirements of article 5.5 of the IVDR for laboratories Lancet Microbe 2026:101334. https://doi.org/10.1016/j.lanmic.2025.101334.
6. Mullier F, Meijer P, Cobbaert C, Lasne D. Attempts to align research in thrombosis and hemostasis with the in vitro diagnostic medical device regulation (IVDR, European Union) requirements. J Thromb Haemost 2025;23:2107–11.
7. Fahie-Wilson MN, Cobbaert CM, Horvath AR, Smith TP. Interference by macroprolactin in assays for prolactin: will the in vitro diagnostics regulation lead to a solution at last? Clin Chem Lab Med 2022;60:1350–5.
8. Lord SJ, Horvath AR, Sandberg S, Monaghan PJ, Cobbaert CM, Reim M, et al. Crit Rev Clin Lab Sci 2025;62:182–97.
9. Vermeersch P, Van Aelst T, Dequeker EMC. 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;59:101–6.
10. Lubbers BR, Schilhabel A, Cobbaert CM, Gonzalez D, Dombrink I, Brüggemann M, et al. The new EU regulation on in vitro diagnostic medical devices: implications and preparatory actions for diagnostic laboratories. HemaSphere 2021;5. https://doi.org/10.1097/HS9.0000000000000568.
11. 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 (text with EEA relevance). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746.
12. Document 52025SC1051. COMMISSION STAFF WORKING DOCUMENT EVALUATION on the Targeted evaluation of regulation (EU)2017/745 on medical devices and regulation (EU)2017/746 on in vitro diagnostic medical devices accompanying the document proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending regulations (EU) 2017/745 and (EU) 2017/746 as regards simplifying and reducing the burden of the rules on medical devices and in vitro diagnostic medical devices, and amending regulation (EU) 2022/123 as regards the support of the European Medicines Agency for the expert panels on medical devices and regulation (EU) 2024/1689 as regards the list of Union harmonisation legislation referred to in its Annex I. SWD/2025/1051 final. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52025SC1051&qid=1776088231313.