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REVIEW

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Implementation of the new EUR IVD regulation and relation with ISO15189 accreditation: Guidance is urgently required for haemostasis testing

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Abstract

On May 26th 2017 the European Parliament and the Council of The European Union adopted the new regulation on in vitro diagnostic medical devices (IVDR)-Regulation EU 2017/746-planned to be applied from May 26th 2022 in substitution to the previous IVD directives (IVDD 98/79 EC). After several health and legal causes due to medical device malfunctions, the European Union (EU) extensively reviewed the previous regulatory, which had remained unchanged since 1998. Aim of the work is to analyse the effects of the new IVDR on the field of haemostasis and thrombosis testing with particular attention to specific clinical conditions. Clinical laboratories will mainly deal with three different situations: (1) Diagnostic test performed with IVDR products used according with clinical indication certified by manufacturers. (2) Diagnostic test performed with certified IVDR products without clinical validation. (3) Diagnostic test performed with reagents classified as Research Use Only (RUO). At present, only few clinical laboratories through different European countries have been prepared to the new IVDR, while many laboratories are not yet aware about crucial aspects of the new process that deeply involves laboratory medicine. In conclusion, each laboratory should be aware of the IVDR certification of the reagents/instruments used in its laboratory. There are several urgent needs regarding IVDR certification: studies about the clinical performance of haemostasis tests, guidelines for LDTs (definition and documentation), internal and external quality controls for the tests recommended/suggested in the guidance/guidelines and finally implementation and/or update of clinical and laboratory guidelines.

KEYWORDS
CE-IVD, fibrinolysis, haemophilia, haemostasis, ISO15189, IVDR, lab developed test, lupus anticoagulant, platelet function testing, research-use-only

1 | INTRODUCTION

In vitro diagnostic medical devices (IVD) are tests used on biological samples to detect or monitor diseases and for diagnosis and prognosis in the clinical pathway. The implementation of precision medicine, also involving the evaluation of genetic and acquired biological factors, highly increases the use of IVD in different clinical settings.[1]

On May 26th 2017 the European Parliament and the Council of The European Union adopted the new regulation on in vitro diagnostic medical devices (IVDR)-Regulation EU 2017/746-planned to be applied from May 26th 2022 in substitution to the previous IVD directives (IVDD 98/79 EC).[2,3]

After health and legal causes due to medical device malfunctions (i.e., poly Implant Prostheses (PIP) breast implants, Transcatheter

Aortic Valve Implantation (TAVI) heart valves, and Essure contraceptive implant),[4–6] the European Union (EU) extensively reviewed the previous regulatory, which had remained unchanged since 1998.[7] From a legal point of view the main difference between the previous IVDD and the current IVDR is that IVDD should have been implemented by the different EU state members, while the new IVDR must be considered as EU law and, consequently, have the same legal validity as national laws.

IVDR was mainly defined to improve manufacturing process of diagnostic medical devices, whose quality should be certified by notified authority.

The Regulation mentions that '*the smooth functioning of the internal market as regards in vitro diagnostic medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for in vitro diagnostic medical devices in order to meet common safety concerns as regards such products. Both objectives are being pursued simultaneously and are inseparably linked whilst one not being secondary to the other*'.[2]

Due to COVID-19 pandemic and difficulties on applying the new IVDR together with the acquisition of knowledge by users (medical doctors, laboratories, and health authorities), EU Commission has proposed on October 2021 a progressive roll-out of the new IVDR to avoid a shortage of supply of in vitro medical devices.[8]

The aim of the present work is to analyse the effects of the new IVDR on the field of haemostasis and thrombosis testing with particular attention to specific clinical situations.

2 | IMPACT OF IVDR EU 2017/746 ON DIAGNOSTIC INDUSTRIES

IVDR EU 2017/746 describe the new rules which are less open to interpretation compared with previous regulation because they not only detail the entire cycle of medical test production but also specify clinical indication of test or medical device in relation to scientific and clinical data. In fact, IVDR define that manufacturers must demonstrate for each test clinical evidences, analytical performances (i.e., linearity and precision) and sensitivity and specificity (Table 1), and the relevance and appropriateness in relation to clinical use.

Clinical performance, as defined in EU directive, is a continuous process by which data are assessed and analysed to demonstrate scientific validity and analytical performance of that device for its intended purpose, as stated by manufacturer.

Guidance from MedTech Europe sets out ways in which the manufacturer can state the intended purpose of an IVD in the instructions for use. According to IVDR Annex I 20.4.1c, seven elements must be taken into account to certify an IVD: (1) What is detected and/or measured, (2) Its function, (3) The specific information that is intended to be provided, (4) Whether it is automated or not, (5) Type of measurement (qualitative, semiquantitative or quantitative), (6) The type of specimen(s) required, (7) Where applicable, the testing population. All details in relation to performance evaluation plan and clinical performance studies are detailed in EU document Annex XIII.[2]

TABLE 1 Methods suggested to establish performance characteristics

Performances characteristics	Method
Specimen type, specimen handling, and collection	CLSI Document H21-A5
Accuracy and precision of measurement: repeatability and within-laboratory precision study	CLSI Document EP05-A3
Analytical sensitivity: Limit of blank, limit of detection	CLSI Document EP17-A2
Analytical specificity: interferences study	CLSI Document EP07-A2
Measuring range: Limit of quantitation, linearity study	CLSI Document EP17-A2, CLSI Document EP06-A, EP34-Ed1E
Lot-to lot variability	CLSI Document EP26-A
Assay cut-off: Reference interval	CLSI Document EP28-A3c
Analyser comparison study	CLSI Document EP09-A3 and CLSI Document EP24-A2

In general, more evidences are demanded with the new IVDR, which classifies IVDs in relation to risks according to the Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746.[2,9–12] The aim of the new regulation is to ensure not only safety of IVD but also their effectiveness taking into consideration the state of the art.

The new IVDR details information required also for:

- Tests providing information about the predisposition of a medical condition or disease, for example, genetic tests,
- Tests providing information to predict treatment response to medicines, for example, companion diagnostics (particularly for oncology treatments),
- Medical softwares which are explicitly mentioned in the definition of IVDs,
- Lab Developed tests (LDTs) used within health institutions, which are also requested to meet safety and performance requirements.

In summary, IVDR specifies that all products used for laboratory diagnostic are considered as IVD, including materials, softwares, and are classified into four classes according to the Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746. Besides, IVDR highlight that all tests on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are in vitro diagnostic medical devices.[2–13]

IVDR change from a list-based approach to a risk-based approach (following the Global Harmonization Task Force rules for classification). Even if there are still ambiguities about the exact classification of some tests, IVDR defines the following four classes:

Class D covers general life-threatening conditions and more specifically transmissible agents in blood and biological materials intended to be transplanted or re-administered into the body. Such transmissible agents may also present a high risk to the wider population. It also specifically covers blood grouping or tissue typing when this involves markers of the following systems: ABO, Rhesus, Kell, Kidd, and Duffy.

Class C covers a diverse mix of high-risk IVD devices which present a lesser risk to the wider population. It tends to include situations where the failure of a diagnosis could be life-threatening, including testing for infectious diseases and cancer. It also covers fields such as companion diagnostics and genetic screening. In addition, Class C covers self-testing IVD devices in general (see exceptions below).

Class B is the default class that takes in all IVD devices that are not covered specifically in other classification rules. This is a departure from the system applied to other medical devices for which the default class is Class I, that is, the lowest risk class. It tends to cover devices that present lower risks to the patient and the population at large than IVD devices in Classes D and C. Class B also covers self-testing IVD devices for pregnancy and fertility testing as well as detection of cholesterol levels and detection of glucose, erythrocytes, leucocytes and bacteria in urine. Internal quality controls without a quantitative or qualitative assigned value are also in Class B.

Class A covers broadly speaking laboratory devices (e.g., wash buffers), instruments and specimen receptacles.[2,14]

As a consequence, in contrast with the previous system, with the new IVDR medical devices will be subject to verification and certification by notified bodies with increase cost for regulatory compliance, while only Class A devices will be allowed on the market based on self-certification.[15–19]

3 | IMPACT OF IVDR ON LABORATORY MEDICINE

Altogether, clinical laboratories will have to manage three different situations:

1. Perform diagnostic test with IVDR products used according with clinical indication certified by manufacturers (i.e., prothrombin time for monitoring vitamin K antagonists or coagulation factor measurements).
2. Perform diagnostic test with certified IVDR products without clinical validation (i.e., coagulation factor inhibitor measurements).
3. Perform diagnostic test using reagents without EU certification but classified as Research Use Only (RUO) (i.e., reptilase time useful in the diagnosis of dysfibrinogenemia, with reagents provided by manufacturers which have not undergone the IVDR certification process).[20,21]

With the new IVDR it is possible that clinical and analytical evidences will not be available in some cases, even for crucial test. As a consequence, it could happen that essential tests for diagnosis and monitoring diseases may not be longer available or classified as laboratory developed tests (LDT) or RUO. Practical consequences of using IVD registered as RUO will depend on national laws but, already now, some European countries may not allow reporting results of RUO tests that will be used for patient management.

There are several variations in the approaches to accreditation of medical laboratories in the European countries, but harmonization according to ISO 15189 and ISO 22870 (for POCT) is ongoing.[22]

Based on IVDR art 5, laboratory developed tests (LDT) can be considered as: in house test, test performed with RUO reagents, IVD certified test in which adjustments are made that change the intended use, IVD certified test in which adjustments to the protocol are made without changing the intended use. The requirements of this regulation '*shall not apply to devices manufactured and used only within health institutions established in the Union*'. Concerns rise about the use of LDT in the different clinical laboratories of EU. In particular, how the different European countries will identify reference laboratories, how LDT analytical and clinical performances will be evaluated considering the specific combination reagents/instrument used, which guidelines will be considered if available, how samples will be managed from hospitals where there are no IVDR commercial assay available.

There is missing information in the new EU regulation about LDT definition and documentation required for LDTs causing problems for both laboratories and health authorities.[12]

The new system based on risk classification of IVD medical devices is certainly an important change. In particular, the application of the classification rules shall be governed by the intended purpose of the devices. If the device is intended to be used in combination with another device, the classification rules shall apply separately. Accessories for an '*in vitro* diagnostic' medical devices shall be classified in their own right separately from the device with which they are used. A software which drives a device or influences the use of a device, shall fall within the same class as the device. If the software is independent of any other device, it shall be classified in its own right.

Clinical laboratories are committed to the use of IVDs marketed by manufacturers which have received CE-IVD certification and there is an urgent need for acceptable test classification and clinical indication according their use in specific settings such as healthy or sick population.

4 | IMPACT OF IVDR ON HAEMOSTASIS LABORATORY

No specific references have been made for haemostasis testing which are automatically included in class B except for D-Dimers, PT and drug measurements that are classified as C.

Diagnostic Laboratory on haemorrhagic and thrombotic diseases and drug monitoring includes several tests classified into screening or confirmation tests, which show different level of difficulties other than frequency in relation to clinical settings (i.e., rare diseases as haemophilia, in patients with or without factor inhibitors) or level of specialization acquired by the clinical laboratory.

There are missing data to assess the clinical performance (diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations) as requested by IVDR for numerous tests in haemostasis laboratory. For example, Hayward and Moffat showed that diagnostic sensitivity and specificity are reported only for a fraction of the tests used for the diagnosis of bleeding disorders.[20] Since 2013, only data for electron microscopy and lumiaggregometry were reported.[23,24] Another condition is represented by factor VIII and factor IX inhibitor measurement for which commercial reagents are not certified yet, or the use of coagulative/chromogenic tests in monitoring new therapeutic haemophilia products (i.e., extended half life-EHL products).

It must be highlighted that, according to the new IVDR, methodologies and protocols should be adopted depending on the intended use (e.g., thrombin generation). At present, nobody knows what will happen when using an IVDR reagent from one company on an IVDR certified instrument from another company, since obviously manufacturers will not validate each new batch on competing instruments. This should be probably seen as an LDT situation and therefore be the responsibility of the user to validate/verify, except when the manufacturer demonstrates the validity of use. This could be an important issue for manufacturers that only/mainly commercialize reagents. Altogether, this lack of data regarding clinical performances will have an impact on the intended used submitted by the manufacturers. We can anticipate that except for some D-dimers reagents, there will be a gap between the intended use proposed by the manufacturer and clinical guidance and guidelines (see Table 2).

In addition, for some of the tests used in the haemostasis laboratory (i.e., platelet function testing, FVIII/FIX levels for monitoring specific haemophilia product, methods assessing fibrinolytic potential in plasma), there are no yet external quality controls (EQA) available

TABLE 2 Clinical use of several haemostasis tests

Test	Clinical use	Reference of guidance or guidelines	Dependence of reagents/ instruments	External quality control available
D-dimers	Exclusion of VTE	FDA: NPV ≥ 97% (with lower limit of CI 95%). CSLI: 98% (with lower limit of CI 95%)[25]	Yes[26,27]	Yes
	Diagnosis of DIC	[28]	Yes[29]	Yes
Measuring direct oral of anticoagulants	Bleeding	[30]	Yes[31]	Yes[31]
	Reversal	[32]		
	Perioperative	[33]		
	Recurrence of thrombosis	[34]		
	Stroke	[35]		
Monitoring of $P2Y_{12}$ inhibitors	To assess risk of bleeding or thrombosis during prolonged DAPT	[36–38]	Yes[36–38]	PFA-100, PFA-200: Yes[39]
	For early de-escalation from prasugrel to clopidogrel inpatients			
	To shorten the time window to surgery following P2Y12 inhibitor discontinuation			
Anti PF4-heparin tests	Screening for HIT diagnosis	[40]	Yes[41]	Yes[42]
	Screening for VITT diagnosis	[43]	Yes[44]	Yes[45]
Functional tests for HIT	Confirmation of HIT diagnosis	[40]	Yes[46]	No (first attempt[46])
Antithrombin, protein C, protein S, acquired protein C resistance, factor V Leiden, G20210 A prothrombin mutations,	Thrombophilia testing	[47]	Yes[48–50]	Yes[51]
Lupus anticoagulant, b2GPI-dependent anticardiolipin antibodies, b2GPI-antibodies (ab2GPI)	Thrombophilia testing (antiphospholipid syndrome)	[52,53]	Yes[52,54]	Yes[54]
Thrombin generation	Investigation of hypo and hypercoagulability	[55]	Yes[56]	Yes

(Table 2). This will not prevent manufacturers to get IVDR certification but will depend on the obligation or not to have ISO15189 accreditation for medical testing.

As we can expect that ISO15189 accreditation will become mandatory for all tests performed in medical laboratory in the European Union, there is an urgent need to develop EQA. For platelet function testing, EQA is difficult because of preanalytical variables which affect significantly platelet function. In addition, in contrast to other haemostasis parameters, freezing or freezed-dried samples are not possible. The requirement for fresh samples also restricts availability of abnormal internal quality controls (IQC) and is not always compatible with the regulations concerning the collection of blood from healthy subjects. Where no appropriate proficiency is available, ISO 15189 states '*the laboratory shall develop other approaches and provide objective evidence for determining the acceptability of examination results*'. The Haemostasis and Thrombosis Task Force of the British Society for Haematology (BSH) and UK NEQAS for Blood Coagulation therefore defined an approach that could be generally adopted to ensure confidence in the results obtained in platelet function testing. Among the suggestions, for IQC: '*laboratories should run a fresh sample from a donor expected to give a normal aggregation pattern for each new lot of reagents and whenever an abnormal aggregation pattern is seen in a patient. Each set of investigations should include at least one normal aggregation trace for each agonist*'. For EQA, splitting a sample from a donor between two sites (using same reagents and aggregometers) should be employed to allow comparability geographically close enough for samples to be tested within the required timescale.[57] Of course, it will be not possible for all laboratories. Other options will be required. For example, for confirmation of heparin-induced thrombocytopenia by functional assays, a 5B9 monoclonal anti-PF4/heparin IgG mimicking human HIT antibodies, could be used as an internal and external quality control.[46] Another option proposed by RCPA in Australia and ECAT in the Netherlands for PFA-100/PFA-200 is the wet-challenge. They sent to the laboratory a 'wet-challenge' tube, with this containing a platelet function antagonist, and the EQA participating laboratory then tested normal whole blood collected fresh on site on their PFA-100, either without any manipulation (to generate a normal PFA-100 EQA test sample result) and also repeating the test(s) after addition of this normal whole blood to the 'wet-challenge' tube (to generate a 'pathological' PFA-100 EQA test sample result).[39]

Although the most frequent tests, such as PT and activated Partial Thromboplastin Time (aPTT) will be available on the market without particularly problems, major problems will be faced by medical laboratories, in particular those with high degree of specialization in relation to clinical requirements.

Wide variation exists in specific reagents, methods, and equipment used (combination of instruments and software), making interpretation and comparison of results difficult. All IVD in clinical laboratories should be used in respect of package leaflet information for users while other use is considered as in-house testing.

Another point is that normal pooled plasmas (NPPs) are frequently used in haemostasis laboratory such as in lupus anticoagulant testing. The implementation of normalized ratios and mixing studies with NPPs reduces laboratory variability and increase lupus anticoagulant diagnosis specificity.[58] However, the problematic around NPPs is substantial. Most of laboratories use commercial lyophilized or frozen plasmas while in-house production of NPPs is recommended as stated in the latest updated ISTH guidelines. Indeed, the use of commercial plasmas is not encouraged because of the lack of specifications in manufacturer's product inserts and alterations due to the preparation process and additives. Nevertheless, the use of commercial lyophilized or frozen plasmas is still allowed according to ISTH guidelines if they meet the specifications for clotting factors and number of residual platelets.[59] There are still some uncertainty regarding the position of NPPs in the new IVDR regulation. As NPP is used as a 'reagent' or calibrator, it should fulfil the requirements of the new IVDR regulation. Because every mixing test done in the laboratory is not a commercial test but an in-house developed test it should fulfil the criteria for a LDT. Others argue that normal pool plasmas (NPPs) are considered as 'unassayed controls' meaning that they are exempted from IVDR. This point should be clarified in a near future.

According IVDR, measurement of factor inhibitors in congenital disorders using commercial reagents available on the market only for measuring factor levels without formal indication for factor inhibitor measurement, will be considered as 'in-house test' or 'laboratory developed tests' (LDT). Currently, no international consensus for essential requirements for quality, safety and performance of LDTs is available.[12]

In summary, in the haemostasis field, clinical laboratories will find on the market products certified as IVDR to be used strictly for the certified clinical indications. If used in other clinical conditions the same products will be considered as LDT. On the other hand some reagents could not be certified and available only for research use (RUO).

As for other specialties (clinical chemistry, haematology, immunology, and microbiology) also haemostasis laboratories will have to address the need for more efforts in terms of validation, implementation of standards, quality controls, clinical relevance and documentations.

Formal relationships should be available among manufacturers, scientific societies, clinicians and clinical/laboratory staff to ensure the most suitable assay for a particular clinical situation, the assay results are correctly interpreted and that each patient receives the optimal diagnosis and treatment regimen. In case of lack of sufficient scientific evidence health authorities should support new clinical trials as recommended by IVDR.

5 | CONCLUSIONS

The new IVDR could be considered as an opportunity to both increase quality of testing and improve patient safety and favour IVD harmonization through different countries. At present several commercial tests still not have IVDR requirements with the risk that they will no longer be available after the period of transition defined by EU.[13]

Clinical laboratories should be able to reassess their in-house IVD investing human and financial resources and this is a crucial point. In fact, specialized reference laboratories could be discouraged from using adapted LDT's, particularly if the bureaucracy involved in justification of use is prohibitive.[19] Besides, the development of new diagnostic tests could face difficulties in relation to the large investments needed to conduct both analytical and clinical validation studies, as reported by the new IVDR. Possibilities for LDT use in the haemostasis field, according to Scientific Societies and developed guidelines, should be protected during this transition phase.

As Biomedical Alliance in Europe conducted through a survey last year, scientific and professional societies should map the degree of knowledge of medical laboratories and issues in relation to LDT's.[19] At present, few clinical laboratories through different European countries have been prepared to the new IVDR and, consequently, many laboratories are not even aware about crucial aspects of the new process that deeply involve laboratory medicine.

Once new IVDR is acknowledged, each lab should list the reagents/instruments/softwares used in its laboratory and contact the manufacturers to find out if they will get IVDR certification, in which class risk and for which intended use and highlight which test or reagents are classified as LDT or RUO. To support clinical laboratories guidelines for LDTs (definition and documentation) should be available, in particular for the tests recommended/suggested in clinical practice through scientific society guidelines. Furthermore there is an urgent need for IQC and EQC for the tests recommended/suggested in the guidances/guidelines.

To conclude we think that scientific societies should favour the implementation and update of clinical and laboratory guidelines especially on rare diseases, keeping into consideration the new IVDR. New studies are needed on clinical performance of haemostasis tests also to ensure that the intended use put in the instructions is in line with the use of the tests in clinical practice.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Jameson JL, Longo DL. Precision medicine-personalized, problematic, and promising. *N Engl J Med*. 2015;372:2229-2234.
2. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices. https://eur-lex.europa.eu/legal-content
3. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. http://data.europa.eu/eli/dir/1998/79/oj
4. McCulloch P. The EU's system for regulating medical devices. *BMJ*. 2012;345:e7126.
5. Lewi H, Frame JD. The scandal of device regulation in the UK. *Lancet*. 2012;379:1790.
6. Parvizi N, Woods K. Regulation of medicines and medical devices: contrasts and similarities. *Clin Med*. 2014;14(1):6-12.
7. Principles of In Vitro Diagnostic (IVD) Medical Device Classification, Global Harmonization Task Force, 19 February 2008. http://www.imdrf.org/docs/ghtf/final/sg1/procedural-docs/ghtf-sg1-n045-2008-principles-ivd-medical-devices-classification-080219.pdf#search=%22ivd%22
8. REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and deferred application of requirements for in-house devices. Brussels, 14.10.2021 COM(2021) 627 final 2021/0323 (COD).
9. MDCG 2021-4 Application of transitional provisions for certification of class D in vitro diagnostic medical devices according to regulation (EU) 2017/746 April 2021.
10. MDCG 2021-22 Clarification on "first certification for that type of device" and corresponding procedures to be followed by notified bodies, in context of the consultation of the expert panel referred to in Article 48(6) of Regulation (EU) 2017/746 Medical Device Coordination Group Document MDCG 2021-22.
11. MDCG 2022-2 Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs) January 2022.
12. Spitzenberger F, Patel J, Gebuhr I, Kruttwig K, Safi A, Meisel C. Laboratory-developed tests: design of a Regulatory Strategy in compliance with the international state-of-the-art and the regulation (EU) 2017/746 (EU IVDR [in vitro diagnostic medical device regulation]). *Ther Innov Regul Sci*. 2022;56(1):47-64.
13. Bank PCD, Jacobs LHJ, van den Berg SAA, et al. The end of the laboratory developed test as we know it? Recommendations from a national multidisciplinary taskforce of laboratory specialists on the interpretation of the IVDR and its complications. *Clin Chem Lab Med*. 2020;59:491-497.
14. https://ec.europa.eu/health/system/files/202201/md_mdcg_2020_guidance_classification_ivd-md_en.pdf
15. Lubbers BR, Schilhabel A, Cobbaert CM, et al. The new EU regulation on in vitro diagnostic medical devices: implications and preparatory actions for diagnostic laboratories. *Hema*. 2021;5(5):e568.
16. Van Drangelen A, de Brujin A, Pennings J, van der Maaden T. *The Impact of the New European IVD-Classification Rules on the Notified Body Involvement: A Study on the IVDs Registered in The Netherlands*. National Institute for Public Health and the Environment; 2018.
17. Heinzelmann E. The new, stringent MDR and IVDR regulations: viewing this change as an opportunity. *Chimia*. 2018;72(6):430-431.
18. Hoffmüller P, Brüggemann M, Eggermann T, et al. Advisory opinion of the AWMF Ad hoc Commission in-vitro Diagnostic Medical Devices regarding in-vitro diagnostic medical devices manufactured and used only within health institutions established in the union according to regulation (EU) 2017/746 (IVDR). *Ger Med Sci*. 2021;19:Doc08. doi:10.3205/000295
19. Cobbaert C, Capoluongo ED, Vanstapel FJLA, et al. Implementation of the new EU IVD regulation – urgent initiatives are needed to avert impending crisis. *Clin Chem Lab Med*. 2021. doi:10.1515/cclm-2021-0975
20. Hayward CP, Moffat KA, Liu Y. Laboratory investigations for bleeding disorders. *Semin Thromb Hemost*. 2012;38(7):742-752.
21. Casini A, de Moerloose P. How I treat dysfibrinogenemia. *Blood*. 2021;138(21):2021-2030.
22. Boursier G, Vukasovic I, Brguljan PM, et al. Accreditation process in European countries – an EFLM survey. *Clin Chem Lab Med*. 2016;54(4):545-551.

23. Brunet JG, Iyer JK, Badin MS, et al. Electron microscopy examination of platelet whole mount preparations to quantitate platelet dense granule numbers: implications for diagnosing suspected platelet function disorders due to dense granule deficiency. *Int J Lab Hematol*. 2018;40(4):400-407.
24. Badin MS, Graf L, Iyer JK, Moffat KA, Seecharan JL, Hayward CP. Variability in platelet dense granule adenosine triphosphate release findings amongst patients tested multiple times as part of an assessment for a bleeding disorder. *Int J Lab Hematol*. 2016;38(6):648-657. doi:10.1111/ijlh.12553
25. CLSI. *Document H59-A*. Clinical and Laboratory Standard Institute; 2011.
26. Olson JD, Cunningham MT, Higgins RA, Eby CS, Brandt JT. D-dimer: simple test, tough problems. *Arch Pathol Lab Med*. 2013;137(8):1030-1038.
27. Pernod G, Wu H, de Maistre E, et al. Validation of STA-Liatest D-Di assay for exclusion of pulmonary embolism according to the latest Clinical and Laboratory Standard Institute/Food and Drug Administration guideline. Results of a multicenter management study. *Blood Coagul Fibrinol*. 2017;28(3):254-260.
28. Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013. [Epub ahead of print]. doi:10.1111/jth.12155
29. Suzuki K, Wada H, Imai H, Iba T, Thachil J, Toh CH. A re-evaluation of the D-dimer cut-off value for making a diagnosis according to the ISTH overt-DIC diagnostic criteria: communication from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(7):1442-1444.
30. Testa S, Legnani C, Antonucci E, et al. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost*. 2019;17(7):1064-1072.
31. Hollestelle MJ, Meijer P. International external quality assessment for measurements of direct oral anticoagulants: results and recommendations. *Br J Haematol*. 2020;188(3):460-464. doi:10.1111/bjh.16179
32. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemost*. 2018;16(2):209-219. doi:10.1111/jth.13912
33. Squizzato A, Poli D, Barcellona D, et al. Management of DOAC in patients undergoing planned surgery or invasive procedure: Italian Federation of Centers for the diagnosis of thrombotic disorders and the surveillance of the antithrombotic therapies (FCSA) position paper. *Thromb Haemost*. 2022;122(3):329-335.
34. Testa S, Paoletti O, Legnani C, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost*. 2018;16(5):842-848.
35. Siedler G, Macha K, Stoll S, et al. Monitoring of direct oral anticoagulants plasma levels for secondary stroke prevention. *J Thromb Haemost*. 2022;20:1138-1145. doi:10.1111/jth.15677
36. Frelinger AL 3rd, Gachet C, Mumford AD, et al. Laboratory monitoring of $P2Y_{12}$ inhibitors: communication from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(11):2341-2346.
37. Godier A, Garrigue D, Lasne D, et al. Management of antiplatelet therapy for non-elective invasive procedures or bleeding complications: proposals from the French Working Group on perioperative Haemostasis (GIHP) and the French Study Group on Thrombosis and Haemostasis (GFHT), in collaboration with the French Society for Anaesthesia and Intensive Care (SFAR). *Arch Cardiovasc Dis*. 2019;112(3):199-216.
38. Godier A, Garrigue D, Lasne D, et al. Management of antiplatelet therapy for non elective invasive procedures of bleeding complications: proposals from the French working group on perioperative haemostasis (GIHP), in collaboration with the French Society of Anaesthesia and Intensive Care Medicine (SFAR). *Anaesth Crit Care Pain Med*. 2019;38(3):289-302.
39. Favaloro EJ. Novel approaches to quality control and external quality assessment for platelet function testing with a focus on the platelet function analyser (PFA-100 and PFA-200). *Ann Blood*. 2019;4:3.
40. Gruel Y, De Maistre E, Pouplard C, et al. Diagnosis and management of heparin-induced thrombocytopenia. *Anaesth Crit Care Pain Med*. 2020;39(2):291-310.
41. Nagler M, Bachmann LM, ten Cate H, ten Cate-Hoek A. Diagnostic value of immunoassays for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood*. 2016;127(5):546-557.
42. Eekels JJM, Althaus K, Bakchoul T, et al. An international external quality assessment for laboratory diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost*. 2019;17(3):525-531.
43. Nazy I, Sachs UJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC subcommittee on platelet immunology. *J Thromb Haemost*. 2021;19(6):1585-1588.
44. Vayne C, Rollin J, Gruel Y, et al. PF4 immunoassays in vaccine-induced thrombotic thrombocytopenia. *N Engl J Med*. 2021;385(4):376-378.
45. Reilly-Stitt C, Kitchen S, Jennings I, et al. Anti-PF4 testing for vaccine-induced immune thrombocytopenia and thrombosis and heparin induced thrombocytopenia: results from a UK National External Quality Assessment Scheme exercise April 2021. *J Thromb Haemost*. 2021;19(9):2263-2267.
46. Pouplard C, Rollin J, Vayne C, et al. Multicentre evaluation of 5B9, a monoclonal anti-PF4/heparin IgG mimicking human HIT antibodies, as an internal quality control in HIT functional assays: communication from the ISTH SSC subcommittee on platelet immunology. *J Thromb Haemost*. 2022;20(1):252-259. doi:10.1111/jth.15560
47. Connors JM. Thrombophilia testing and venous thrombosis. *N Engl J Med*. 2017;377(12):1177-1187.
48. Van Cott EM, Orlando C, Moore GW, Cooper PC, Meijer P, Marlar R. Recommendations for clinical laboratory testing for antithrombin deficiency; communication from the SSC of the ISTH. *J Thromb Haemost*. 2020;18(1):17-22.
49. Moore GW, Van Cott EM, Cutler JA, Mitchell MJ, Adcock DM, Subcommittee on plasma coagulation inhibitors. Recommendations for clinical laboratory testing of activated proteinC resistance; communication from the SSC of the ISTH. *J Thromb Haemost*. 2019;17(9):1555-1561.
50. Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, Brinkman HJM. Recommendations for clinical laboratory testing for protein S deficiency: communication from the SSC committee plasma coagulation inhibitors of the ISTH. *J Thromb Haemost*. 2021;19(1):68-74.
51. Mackie I, Cooper P, Kitchen S. Quality assurance issues and interpretation of assays. *Semin Hematol*. 2007;44(2):114-125.
52. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis*. 2019;78(10):1296-1304.
53. Devreese KMJ, Ortel TL, Pengo V, de Laat B, Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(4):809-813.
54. Tripodi A. Diagnostic challenges on the laboratory detection of lupus anticoagulant. *Biomedicine*. 2021;9(7):844.
55. Tripodi A. Thrombin generation: a global coagulation procedure to investigate hypo- and hyper-coagulability. *Haematologica*. 2020;105(9):2196-2199.
56. Ninivaggi M, de Laat-Kremers R, Tripodi A, et al. Recommendations for the measurement of thrombin generation: communication from the ISTH SSC subcommittee on lupus anticoagulant/antiphospholipid antibodies. *J Thromb Haemost*. 2021;19(5):1372-1378.
57. Jennings I, Perry D, Watson H, et al. Quality assurance and tests of platelet function. *Br J Haematol*. 2018;181(4):560-561. doi:10.1111/bjh.14668

58. Devreese KMJ, de Laat B. Mixing studies in lupus anticoagulant testing are required at least in some type of samples. *J Thromb Haemost*. 2015;13(8):1475-1478.
59. Devreese KMJ, Groot PG, de Laat B, et al. Guidance from the scientific and standardization committee for lupus anticoagulant/antiphospholipid antibodies of the international society on thrombosis and haemostasis: update of the guidelines for lupus anticoagulant detection and interpretation. *J Thromb Haemost*. 2020;18(11):2828-2839.

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