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JTH COMMENTARY

Attempts to align research in thrombosis and hemostasis with the In Vitro Diagnostic Medical Device Regulation (IVDR, European Union) requirements

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In the current issue of *Journal of Thrombosis and Hemostasis*, Joly et al. [1] reported an important study for clinicians and laboratories managing patients with thrombotic thrombocytopenic purpura. Using a cohort of 500 plasma samples from 362 patients, they showed excellent analytical (detection limit: 0.1 IU/dL; repeatability coefficient of variation (CV) <11%; reproducibility CV at 40 IU/dL: 7.5%) and clinical performance at diagnosis (threshold: 10 IU/dL; sensitivity and positive predictive value: 100%) and during the follow-up (threshold: 20 IU/dL; specificity: 100% [95% CI: 99%-100%]; positive predictive value: 96% [90%-100%]; negative predictive value: 98% [97%-100%]) of the ADAMTS13 activity measurement on the Ceveron s100 automated system.

Beyond the LiverPRO study [2], this is the second study providing performance characteristics of a biomarker or *in vitro* diagnostic medical device (IVD) in accordance with the new In Vitro Diagnostic Medical Device Regulation (IVDR) by the European Union (EU) [3].

Therefore, we take the opportunity to summarize some key elements of this new European Regulation:

i) Classification: Medical devices are classified into classes A, B, C, and D, taking into account the intended purpose of the devices and their inherent risks.

ii) Deadline compliance: The majority of the hemostasis tests are class C and class B devices that should be fully compliant before 2028 and 2029, respectively, according to the 2024/1860 regulation [4].

iii) Intended use and laboratory developed tests (LDTs): The intended use of a test should be clearly expressed in the intended use section in the instructions for use (IFU) provided by the manufacturer [5]. An extension of the intended use is, according to the Medical Device Coordination Group Document (MDCG) 2022-6 [6], a significant change (eg, additions regarding what is detected and/or measured; additional test purposes such as screening, monitoring, and diagnosis; for companion diagnostics: extension of the target population[s] or of the tissue type or associated medicinal products; and addition of specimen type[s]) [6–8]. In the field of thrombosis and hemostasis, laboratory tests are frequently used outside the indicated intended use reported in the IFU. In this situation, the IVD becomes a LDT under the IVDR [8–11]. In addition, some European countries (ie, Belgium) require clinical laboratories to declare their LDTs since May 26, 2024, to the Federal Agency for Medicines and Health Products. We have recently reviewed the IFU of the most frequently used reagents

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in Europe and showed that the information given is very heterogeneous (publication submitted). We observed disagreement for each of the assays assessed with some intended uses not supported by guidance or guidelines (ie, thrombin time and antithrombin). Some indications in use by clinical laboratories (ie, D-dimers for the diagnosis of disseminated intravascular coagulation) are not provided by the manufacturers. We only found information on clinical performance for a limited number of assays (D-dimers, dilute Russell viper venom time, heparin-induced thrombocytopenia antibodies, anticardiolipin immunoglobulin [Ig] G/IgM, anti-β2 glycoprotein-I [antiβ2GPI] IgG/IgM), and ADAMTS13 activity (only for 1 manufacturer). For some assays, data are available in the literature but are not reported in the IFU. Studies like those of Joly et al. [1] are of major importance and the data should be transferred into the IFU for the Ceveron ADAMTS13 assay.

iv) Analytical and clinical performances:
   a. One of the key changes in this new IVDR are the clinical evidence requirements [1,5–7]. The results of analytical and clinical performance evaluation studies of sufficient quantity and quality are necessary to demonstrate that the device provides the expected clinical benefit and safety when used as intended by the manufacturer.
   b. Analytical performance refers to the ability of a biomarker to measure an analyte accurately and reliably in clinical samples. It focuses on parameters such as linearity, precision, sensitivity, specificity, and reproducibility.
   c. Clinical performance evaluates the ability of the same biomarker to yield results that correlate with a specific clinical condition. It assesses clinical sensitivity, specificity, and positive and negative predictive values.
   d. Indicators of clinical performance vary and depend strongly on the intended purpose and risk class (IVDR, Article 56) [12]:
      i. When the intended use mentions "diagnosis," "screening," or "disease monitoring": Diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, and AUC should be reported (with 95% CI); for example, the use of D-dimer for the exclusion of venous thrombosis.
      ii. When the intended use mentions "aid to diagnosis" (without clear medical decision points [cut-offs]), a method comparison with a reference method on a significant number of samples should be provided: for example, the intended use of dilute Russell viper venom time, anticardiolipin IgG and IgM, and anti-β2 glycoprotein-I IgG and IgM is aiding the diagnosis of an antiphospholipid syndrome, and the intended use of ADAMTS13 activity is aiding diagnosis and follow-up of thrombotic thrombocytopenic purpura (Table) as illustrated by Joly et al. [1].
      iii. For the other assays like activated partial thromboplastin time, expected values in normal and affected populations should be available according to IVDR.

With the study of Joly et al. [1], the Technofluor ADAMTS13 activity assay on the Ceveron s100 can be categorized as intended use for diagnosis and disease monitoring in addition to the currently intended use "quantitative determination of ADAMTS13 activity in citrated human plasma on the Ceveron s100" (IFU Rev. 003 09/10/2023; Table).

We are still in a transition period until at least 2030, meaning that most of IFUs will be adapted following IVDR implementation. IVD manufacturers prioritize IVDR compliance of the highest risk classes of tests first, which likely means that we still have to wait for class B updates some years. Clinical performance data are sometimes available for some laboratory assays, but these data are not always available to the clinical laboratories. Hemostasis laboratories should prepare for IVDR by drawing up a register of all their LDTs, but it is currently difficult because the information is not publicly available.

Hopefully, the performance data will be more broadly available in the future European Database on Medical Devices, which should provide a living picture of the lifecycle of medical devices that are made available in the European Union.

The first study providing performance characteristics according to IVDR was about the development and validation of the LiverPRO score to detect hepatic fibrosis (with slightly better performances than the current standard [Fib-4]) [2]. Following this study, LiverPRO score was the first CE-certified medical device software product (IVDR class B) using routine laboratory tests, integrating into laboratory information systems for immediate clinical use [2].

The selected input variables were age (years), aspartate aminotransferase (AST; U/L), alkaline phosphatase (ALP; U/L), gamma-glutamyl transferase (U/L), international normalized ratio (INR), albumin (g/L), sodium (mmol/L), bilirubin (mg/dL), platelet count (10^9/L), and cholesterol (mmol/L). Most tests in this score are rather well standardized in Western Europe with the exception of albumin and PT/INR.

The model was validated in several cohorts involving several countries, many laboratories, and different methodologies for the laboratory tests.

However, surprisingly, the authors did not provide any comment about the assays, their variability (and their analytical performances), or any remark in the manuscript stating, "take care of nonexchangeability of test results in case data from different labs were grouped" [2].

If LiverPRO score shows slightly better clinical performance in comparison to the Fib-4 (with a mix of laboratory assays), this means that in the real life, clinical performances will be better or worse, depending on the combination of the assays used locally. Notably, INR is still inappropriate to assess the severity of chronic liver disease [13].

The impact of the methodology on clinical decisions has already been illustrated in many clinical scenarios (eg, anti-Xa [14], platelet count [15], and D-dimers [16]).

In conclusion, although the IVDR introduces more guarantees regarding safety and effectiveness of medical tests, it also has disadvantages for IVD manufacturers because of unpredictable time paths, increased costs, and brakes on innovation [17–19]. The protracted role out of the IVDR makes IVD manufacturers postpone necessary changes in the IFU, because changes bring along yearly costs and a

TABLE Information on intended use and clinical performance provided by manufacturers in the instructions for use of ADAMTS13 assays.

			Intended use					
Company	**Brand mark**	**Reference/version number**	**Quantitative determination of ADAMTS13 activity**	**Aid in the diagnosis of TTP**	**Aid in the follow-up of TTP**	**Screening tool for estimating ADAMTS13 activity**	**Clinical performance**	**Additional information related to intended use**
Werfen	HemosIL Acustar ADAMTS13 activity	0009802048 IVDR 2020/04	X	X	X		No	Should be used in conjunction with other clinical and laboratory findings (a method comparison with FRET [*n* = 100] is given).
Technoclone	Technozyme ADAMTS13 Activity	5450701 IVD	X	X			Yes	Reference of clinical performance not mentioned. Contact of Technoclone's local distributor required.
	Technofluor ADAMTS13 Activity	5800100 IVD 2021/02	X				Yes	Only quantitative measurement of ADAMTS13 activity Reference of clinical performance not mentioned. Contact of Technoclone's local distributor required.
	TECHNOSCREEN ADAMTS-13 activity	5700100 IVD 2020/07				X	Yes	Deficiency of ADAMTS13 needs to be confirmed by a quantitative system. Reference of clinical performance not mentioned. Contact of Technoclone's local distributor required.

IVD, in vitro medical device; IVDR, In Vitro Diagnostic Medical Device Regulation; TTP, thrombotic thrombocytopenic purpura.

heavy burden when adapted technical dossiers are required by the notified bodies. We foresee, based on the ongoing targeted evaluations of the European Commission, that a future, debureaucratized version of the IVDR (with lighter regimes and lower costs) could have the desired beneficial effects: risk-based classification of tests and clinical evidence documentation, adequate description of the intended use of tests in clinical care pathways, increased quality, and reduced inappropriate prescribing (over and underuse) [20].

In the meantime, we encourage

- IVD manufacturers to report scientific validity and analytical and clinical performance data in their IFUs.
- Thrombosis and hemostasis researchers to report these data in the scientific literature, following IVDR terminology and other requirements.
- Encourage hospital-industry collaboration (eg, access to samples).
- Encourage multidisciplinary collaboration in and with clinical societies like the International Society of Thrombosis and Hemostasis in case of development of a medical device software product.

In conclusion, studies such as one reported by Joly et al. [1] are of extreme importance to provide both analytical and clinical evidence needed to bring IFUs of IVD in accordance with the new In Vitro Diagnostic Medical Device Regulation (IVDR), a European Union (EU) regulation.

AUTHOR CONTRIBUTIONS

F.M. drafted the manuscript. All authors performed critical revision, reviewed the manuscript, and approved the submitted version.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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