Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 1074–1075

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

How the European in vitro diagnostic regulation could negatively impact the European response to the next pandemic: an urgent call for action before May 2022

Pieter Vermeersch [1, 2, *], Emmanuel André [1, 3]

[1)] Clinical Department of Laboratory Medicine and National Reference Centre for Respiratory Pathogens, University Hospitals Leuven, Leuven, Belgium
[2)] Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium
[3)] Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium

ARTICLE INFO

Article history:
Received 1 March 2021
Received in revised form
20 April 2021
Accepted 1 May 2021
Available online 9 May 2021

Editor: L. Leibovici

Keywords:
COVID-19 testing
Diagnostic test approval
Europe
In vitro diagnostic regulation
IVD
IVDR
Lab-developed test
Medical device legislation

The revised European Union (EU) regulatory framework with regard to medical devices was published in 2017. The new European regulation 2017/745 on medical devices and European regulation 2017/746 on *in vitro* diagnostic (IVD) medical devices came into force on 25th May 2017 and will replace the three existing medical device directives (93/42/EEC, 98/79/EC and 90/385/EEC) [1]. The new regulations will become applicable in May 2021 for medical devices and in May 2022 for IVD medical devices. A regulation is a legal act of the EU which comes into force as law in all member states simultaneously.

The impact of the new IVD regulation cannot be underestimated since this regulation "lays down rules concerning the placing on the market, making available on the market or putting into service of *in vitro* diagnostic medical devices for human use and accessories for such devices in the Union" [1]. A Dutch study on the registered devices in the Netherlands estimated that 84% of the IVD tests will need to be certified by a notified body under the new IVD regulation, compared to only 7% under the old IVD directive [2]. Another major change is that the general safety and performance requirements in annex I of the IVD regulation will also apply to lab-developed tests (LDTs), also called in-house tests, which are not put on the market.

While laboratories almost exclusively use commercial CE-IVD tests for their core laboratory routine tests, LDTs are of the utmost importance in tertiary-care settings and play an essential role in technology development and maturation and for the measurement of analytes and microorganisms which are not covered by commercial CE-IVD assays [3].

The coronavirus disease 2019 (COVID-19) pandemic has demonstrated that the ability of laboratories to set up and implement LDTs quickly is essential to respond to an emerging health crisis. Within 2 weeks after the first report of a cluster of cases of pneumonia in Wuhan, China, on 31st December 2019, the Institute of Virology of Charité Universitätsmedizin, Berlin, Germany, set up a lab-developed test for the detection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 [4]. This test, or alternative LDTs, were subsequently implemented in 46 expert laboratories in 30 European countries, including our own laboratory by 29th January 2020, before the pandemic reached Europe [5]. A recent perspective in The New England Journal of Medicine, which looked at the shortcomings in the United States' response to COVID-19, noted how a distributed network of German laboratories had the expertise and capacity needed to rapidly develop and implement PCR tests, facilitated by their centralized national healthcare system [6]. The IVD regulation could, however, profoundly impact our ability to respond to a future pandemic since this regulation will significantly restrict the use of LDTs. Article 5.5 of the IVD regulation lists all the conditions that have to be met before an LDT can be used, including (a) the devices are not transferred to another legal entity, (b) the target patient group's specific needs cannot be met—or cannot be

* Corresponding author: Pieter Vermeersch, Clinical Department of Laboratory Medicine, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.
E-mail address: pieter.vermeersch@uzleuven.be (P. Vermeersch).

https://doi.org/10.1016/j.cmi.2021.05.009

met at the appropriate performance level—by an equivalent device available on the market, and (c) the devices are not manufactured on an industrial scale.

First, the IVD regulation will prohibit *de facto* the transfer of an LDT (reagents, calibrator, control material, etc.) to other legal entities, profoundly restricting the possibility for laboratories to implement an LDT developed by another laboratory, as was the case with the RT-PCR test developed by the Charité group in laboratories throughout Europe. Second, the IVD regulation also prohibits the use of LDTs on an industrial scale. While the term 'industrial scale' is not defined in the IVD regulation, the fact that by the end of March 2020 more than 500 000 LDT RT-PCR tests had been performed in Germany would almost certainly run afoul of the IVD regulation as this scale by far outpaces the scale of many commercial IVD tests currently used in Europe. A possible solution could be to provide an exemption from these requirements in the case of an emerging global health threat such as a pandemic.

Third, as per the IVD regulation, an LDT cannot be used if there is an equivalent device on the market. This would have meant that the use of LDTs would have been prohibited from 12th March 2020, the day the first commercial PCR test (Roche Cobas SARS-CoV-2 test) received CE-IVD approval and became available worldwide, although the production by this manufacturer and the subsequent commercial players could not meet even part of the global demand for months. Illustratively, the company Roche, the largest IVD company in the world, were already experiencing supply problems before the end of March. This was hardly surprising as the Roche projected to produce 400 000 tests/week by the end of March, hardly enough to cover the >360 000 tests performed in Germany alone in the last week of March, according to the daily situation reports of the German Robert Koch Institute.

This situation illustrates a profound weakness of the IVD regulation in the context of an emerging global health threat. While laboratories are forbidden to use LDTs when an equivalent commercial CE-IVD assay is on the market, manufacturers are under no obligation to make sure that there is adequate supply to fulfil the needs of patients. It would therefore be required that the regulatory framework is adapted to allow laboratories to develop an LDT in case of inadequate supply at the international level, and to use the LDT during a predefined time period irrespective of the later availability of commercial CE-IVD assays. If laboratories will be forced to replace their LDT as soon as a CE-IVD assay becomes available on the market, they will most likely never develop an LDT. Availability during a pandemic should be assessed at the global level to avoid recurrent shortages worldwide, particularly in countries with lower resources.

Finally, it would have been unwise for Charité to make the protocol of their LDT publicly available since the IVD regulation does not provide any protection for the inventor or inventions which are in the public domain. Any commercial company will be allowed to register a test and force the inventing institution to buy its own test. The direct consequence could therefore be that publicly funded clinical and research laboratories might limit the sharing of their findings and protocols, which would be in opposition to current demands of EU funding agencies and would negatively impact the overall capacity of European laboratories to respond rapidly to emerging diseases. Finally, increased regulatory oversight of LDTs could also result in a slower response to a future pandemic [7].

These problems all stem from the fact that the IVD regulation was pushed by manufacturers of *in vitro* diagnostics and approved by the European parliament without careful assessment of the impact on the overall knowhow and responsiveness of our European healthcare systems. As part of the ongoing plans aiming to consolidate our preparedness for the ongoing and future pandemics, the European Commission should urgently address the aforementioned problems, as they could profoundly impact our ability to respond to a future pandemic. The IVD regulation will also profoundly impact the incentives for publicly funded laboratories to maintain and increase their current level of expertise in the design and validation of LDTs as a complement to IVD diagnostic tests.

The recent experience has shown that it is an illusion to think that commercial manufacturers would be able to respond to a future pandemic as fast as European laboratories did to the COVID-19 pandemic, given the inherently slower decision process at commercial companies and regulatory requirements. Laboratories and commercial companies should be seen and supported as complementary actors to improve the diagnostic tests offered to European citizens and beyond.

The ultimate goal of the IVD regulation should be to guarantee the safety, clinical effectiveness, and availability of medical laboratory tests to European citizens. Decisions regarding the use of LDTs should take into account the downstream consequences for patient care, such as the essential role of LDTs in adapting technologies to better respond to emerging or neglected health problems such as pandemics and rare diseases. The IVD regulation currently considers laboratory tests as simple commodities in a free market where market mechanisms will correct any imbalances, a concept that cannot be applied in the context of a global health emergency. The COVID-19 pandemic has illustrated that market mechanisms and commercial tests cannot cover all patient needs under any given circumstance, and that sufficient degrees of freedom for laboratories to develop and implement LDTs will ultimately benefit European citizens.

Author contributions

PV and EA drafted and critically reviewed the manuscript.

Transparency declaration

PV is a senior clinical investigator of the FWO-Vlaanderen. PV reports speaker fees from Roche and Becton Dickinson. PV is principal investigator for a study for Roche and EA is principal investigator for studies for Biomérieux and Imec. This commentary did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

[1] 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. Available from: https://eur-lex.europa.eu/eli/reg/2017/746/oj.

[2] van Drongelen A, de Bruijn 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. RIVM Letter Report 2018-0082; 2018.

[3] Vermeersch P, van Aelst T, Dequeker EM. 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.

[4] Corman V, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020;25:2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045.

[5] Reusken BEM, Broberg EK, Haagmans B, Meijer A, Corman VM, Papa A, et al. Laboratory readiness and response for novel coronavirus (2019-nCoV) in expert laboratories in 30 EU/EEA countries, January 2020. Euro Surveill 2020;25:2000082. https://doi.org/10.2807/1560-7917.ES.2020.25.6.2000082.

[6] Botti-Lodovico Y, Rosenberg E, Sabeti PC. Testing in a pandemic—improving access, coordination, and prioritization. N Engl J Med 2021;384:197–9.

[7] Vermeersch P, Cotton F, De Smet D, Martens G, Oyaert M, Cavalier E. Lessons from the Belgian experience with regulatory control during the COVID-19 pandemic for the implementation of the European IVD regulation 2017/746. Acta Clin Belg 2021. https://doi.org/10.1080/17843286.2020.1787659 (online ahead of print).