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LESSONS FROM THE BELGIAN EXPERIENCE WITH REGULATORY CONTROL DURING THE COVID-19 PANDEMIC FOR THE IMPLEMENTATION OF THE EUROPEAN IVD REGULATION 2017/746

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To the editor

The Coronavirus SARS-CoV-2 is the cause of coronavirus disease 19 (COVID-19), an acute respiratory syndrome with the potential of progressing to respiratory failure and death. After this coronavirus was first identified at the end of 2019 in Wuhan China, the outbreak evolved into a pandemic, putting an unprecedented burden on hospitals and health care workers worldwide. The first confirmed case of a SARS-CoV-2 infection in Belgium, a salesman returning from China, was identified on 4 February and successfully quarantined in the following weeks [1]. The second positive case was documented on 29 February, followed by a series of new positive cases and confirmed local transmission in early March 2020. A lockdown started 18 March and the peak of new infections occurred on 6 April. During the

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next 2 months, there were almost 10.000 reported COVID-19 related deaths, making Belgium one of the most hard-hit countries in Europe [2]. To address the challenges posed by the COVID-19 pandemic, the Belgian federal parliament granted the minority federal government special powers on 26 March to take any measures it deems necessary to deal with the COVID-19 crisis.

The Belgian Federal Agency for Medicines and Health Products (FAMHP) is the Belgian competent authority for the quality, safety and efficacy of medicines and health products including in vitro diagnostic (IVD) tests [3]. When the new European IVD Regulation 2017/746 will come into full application on 25 May 2022 (unless delayed due to the COVID-19 pandemic), the FAMHP will also oversee all lab-developed tests which are not within the scope of the current IVD directive [4]. The FAMHP describes its field of competence as 'research and development (R&D), registration and marketing authorization, production and distribution (inspection and control activities), vigilance, proper use of medicines and health products', encompassing the entire process from development of laboratory tests over registration, authorization and post-marketing surveillance including 'proper use' [5]. Of important note, the FAMHP does to our knowledge not have any laboratory medicine professionals among its own staff.

The activities of the FAMHP are officially divided into three Directorates general: pre-authorization, post-authorization, and inspection. The borders between these different activities have, however, blurred during the COVID-19 crisis. The FAMHP general director post-authorization, who is also a member of the Belgian COVID-19 taskforce for medical supplies, formally announced during a conference call on Friday 24 April a new policy for serologic tests for the detection of antibodies against SARS-CoV-2. He would henceforth organize the validation of all tests for anti-SARS-CoV-2 antibodies (deciding where the validation is performed, how the validation is performed, and whether the results are acceptable or not) and sign contracts with the companies to buy tests for the whole country. While the FAMPH cannot prevent the use of CE-marked kits (e.g. kits that were validated in Germany or in the Netherlands), the FAMHP convinced the national healthcare system (RIZIV-INAMI) to only reimburse tests that were approved by the FAMHP. The rationale for this strategy was twofold. First, to prevent that kits with an unacceptable performance are used in Belgium (CE-marking during the COVID-19 pandemic is self-declared by the manufacturer). Second, to allow the routine implementation of a serological test in all Belgian laboratories by 'rationalizing its use for clinical purposes and sparing heavy validation steps consuming time, samples and reagents' [6]. This process bypasses the normal role of laboratory professionals for the validation of laboratory tests and their role in deciding whether the performance of a laboratory test is acceptable.

While the intentions of this new policy may have been noble, we believe as laboratory medicine professionals that this new policy did not have a beneficial effect, was unnecessary and is open for undisclosed potential conflicts of interest. The Belgian magazines Le Vif and Knack reported on 16 June 2020 on the controversies surrounding the national validation of the LIAISON® SARS-CoV-2 IgG from Diasorin, the first assay validated according to the new procedure [7,8]. The evaluation was performed in April 2020 in a laboratory designated by the FAMHP and resulted in a government contract for 7 million euros that was announced during the conference call of Friday 24 April. All Belgian laboratories who had a Diasorin Liason XL platform received kits during the last week of April without any

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information about the test performances and costs. The only data that were communicated during the conference call to the clinical laboratories were a sensitivity of 100% and a specificity of 100%.

Despite repeated requests by laboratories, no additional information was made public during the next weeks regarding the validation plan, the number of samples tested or the results until a publication on 25 May in Clinical Chemistry and Laboratory Medicine [6]. The same team also published a Letter to the Editor in Journal of Infection, with the unexpected co-authorship of the FAMPH general director post-authorization about the validation [9]. In both publications, the authors suggested to use new cut-off values, different from the values in the product insert of the CE-marked kit, in order to improve the test performance. This was surprising as sensibility and specificity of 100% had previously been claimed.

We find the fact that the results of the national validation were only available 1 month after kits were shipped to laboratories unacceptable. The new national policy in fact hampered implementation of serologic assays in laboratories as companies were not allowed to provide kits to other laboratories for validation despite the fact that Belgian clinical laboratories operate under ISO15189:2012-based Belgian national regulations (Praktijkrichtlijn/Directive Pratique 2017). The use of different cut-offs as suggested in the above-mentioned publications implies the modified test is no longer CE-marked, but rather an in-house test which requires in-house validation in each laboratory. The FAMHP as a competent authority should be aware of this. There has also been some discussion regarding the national selection of Diasorin as the sensitivity of this assay in asymptomatic and paucisymptomatic people might be lower than some other assays currently on the market [10]. The Dutch serology task force recently concluded that the Diasorin assay did not meet their criteria for sensitivity [11]. Finally, the negotiation with the company Diasorin also did not have the intended effect as Belgium signed a confidential contract for 7€/test compared to only 4 €/test in Italy [7,8].

The Belgian approach was unique as laboratory medicine professionals were at no point involved in determining how tests should be validated, defining acceptance criteria, determining which tests are acceptable, or defining the need for serologic testing in Belgium. In France and in the Netherlands, for example, these tasks were not performed by the competent authority, but rather by laboratory medicine professionals in collaboration with the Institute of Public Health and/or the National Reference Center. The Belgian approach was also unique in combining the roles of test evaluation, selection, and registration, signing national contracts and post-authorization surveillance. Complaints about test performance were handled by the same people within the FAMHP who decided on the validation plan, approved the performance, and signed the contract with the company. This is contrary to any form of good governance as these people within the FAMHP are at the same time judge (competent authority) and party (signs contracts with the companies they are supervising). Of note, after May 2022 the FAMPH will also oversee lab-developed tests, further increasing the risk of potential conflicts of interest.

The Royal Belgian Society of Laboratory Medicine (RBSLM) asks that the FAMHP formally recognizes the competence of laboratory medicine professionals to select tests with an adequate performance. Given the possible conflicts of competences, we also ask that site visits of laboratories performing lab-developed tests will be performed by Sciensano, the Belgian Scientific Institute for Public Health, which

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is responsible for the certification of clinical laboratories in Belgium [12]. This will avoid that the FAMPH which directly interacts with large commercial companies would also judge whether there are patient needs that are not met by a commercial assay on the market which justify the use of a lab-developed test under the European IVD regulation 2017/746.

In conclusion, we are convinced that Belgian laboratories today have excellent and performant quality control systems in accordance with ISO15189:2012 and Belgian national regulations, and are qualified to select laboratory tests. The RBSLM believes that additional national validations cause delays and are simply outside the scope of a competent authority. This approach should be abandoned and validation and selection of laboratory tests can be entrusted to laboratory medicine professionals to preserve the current high quality of IVD testing during this SARS- CoV-2 pandemic and beyond.

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