HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Aileen Fallon
Clerk to the Committee (Work Programme)
Special Committee on Covid-19 Response
Leinster House
Dublin 2
D02 XR20

16th June 2020

Re: Written submission from the Health Products Regulatory Authority (HPRA) on the topic of Covid-19 (SARS-CoV-2) testing and contact tracing

Your Ref: SCC19R-I-0150

Dear Ms. Fallon
Please find attached the written submission from the Health Products Regulatory Authority (HPRA) on the topic of Covid-19 (SARS-CoV-2) testing and contact tracing. This submission is being provided in response to your letter dated 5th June 2020.

In the attached, we address the topics detailed in your request which are within our remit as the Competent Authority for medical devices. These topics include provision of regulatory support to testing at national level, market surveillance on the regulatory compliance of tests and contribution to relevant expert groups. The HPRA does not have a role in the procurement or supply of test, laboratories or testing capacity or the implementation of contact tracing.

Our submission outlines the emergence of diagnostics tests for COVID-19 testing, the applicable EU regulations and some specific challenges.

The HPRA are happy to provide further information on this submission to the Committee if needed.

Yours sincerely,

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Dr. Lorraine Nolan
Chief Executive
Health Products Regulatory Authority

1. Introduction

The Health Products Regulatory Authority (HPRA) is the Competent Authority (CA) for medical devices and *in vitro* diagnostic medical devices (IVDs) in Ireland. Our role primarily relates to the monitoring of the safety of medical devices and IVDs after they have been placed on the market.

Tests for the diagnosis of SARS-CoV-2 (COVID-19) are classified as IVDs and must be CE-marked in accordance with the IVD Directive (IVDD; 98/79/EC), as amended, before being placed on the market in Europe. Further information on the regulatory system for IVDs is provided in Annex I.

In general, the HPRA does not authorise IVDs to be placed on the market. Through the operation of vigilance and market surveillance systems for IVDs, the HPRA ensures that all IVDs sold into the Irish market comply with the relevant legislation. IVDs must achieve the performance criteria specified by the manufacturer and in doing so must not compromise the health and safety of patients, service providers and any other persons. We also provide advice to relevant stakeholders on the regulatory aspects of IVDs.

The HPRA does not have a role in procurement, supply, laboratories, testing capacity or planning of contact tracing.

In response to the request from the Oireachtas Special Committee on Covid-19 Response, dated 5 June 2020, our submission provides detail of the HPRA's involvement in the COVID-19 testing programme. It is accompanied by annexes I to III, which provide additional background information on various aspects of the legal framework for IVDs and, as appropriate, medical devices.

2. Testing for SARS-CoV-2 (COVID-19)

In accordance with the national testing strategy implemented by the National Public Health Emergency Team (NPHET), all IVD testing for diagnosis of COVID-19 in Ireland is currently conducted in the National Virus Reference Laboratory (NVRL), in a number of hospital diagnostic laboratories and other designated laboratories. Samples are taken by healthcare professionals in healthcare settings, community test centres or in the patient's home.

A national testing strategy has been implemented under NPHET to ensure that;

- test results are reported to the relevant stakeholders (for monitoring and surveillance purposes as COVID-19 is a notifiable disease);
- contact tracing activities are initiated (where appropriate);
- an incorrect test result does not lead to false reassurance resulting in an individual failing to seek the necessary medical help. During this time, the individual may also unknowingly spread the virus.

The current testing strategy in Ireland, based on expert advice, involves laboratory-based pathogen detection using nucleic acid technology (NAT) methods.

3. HPRA activities to support testing for SARS-CoV-2 (COVID-19) at national level

At the outset of the pandemic, in the absence of an available CE marked test for this novel virus, the NVRL developed an RT-PCR[1] assay based on the WHO protocol for testing for SARS-CoV-2. This

[1] RT –PCR is Reverse Transcriptase Real Time Polymerase Chain Reaction, this method works by generating many copies of the specific SARS-CoV-2 genetic material to levels that are measurable

Laboratory Developed Test (LDT) was the first test introduced in Ireland to detect COVID-19 infection and the first diagnosis of COVID-19 infection in Ireland was based upon this assay. The test was manufactured 'in-house' by the NVRL under a "Health Institution Exemption" which exists under the IVD Directive. Further information on the Health Institution Exemption can be found in Annex II.

Due to the urgent need to increase testing capacity in Ireland, the HPRA, following requests from health services, authorised a number of national derogations via the HPRA's COVID-19 national derogations process. Such derogations facilitate the urgent assessment of non-CE marked medical devices, where access to such devices in Ireland is in the interest of the protection of public health. Derogations take the form of a desk based review of technical documentation relating to the product in question. The introduction of the product into service would usually be supported by the performance of validation or other testing by the laboratory it is intended to be used in.

Under this process, the HPRA permitted the use of two non-CE marked tests for SARS-CoV-2 and the use of the NVRL's lab developed test in a commercial laboratory. The HPRA also authorised a national derogation to permit the use of a non-CE marked sample collection kit (including a swab) due to a critical shortage of these products for sampling of suspected COVID-19 patients.

Prior to their introduction to clinical use, the NVRL and a number of hospital laboratories in Ireland conducted a validation of the non-CE marked tests and the sample collection kit subject to derogation to confirm their appropriateness for the healthcare system in Ireland. The two commercial tests have since been CE marked. Further information on the regulatory derogation process for COVID-19 is provided in Annex III.

In order to further increase the testing capacity for COVID-19 in Ireland at a time when CE marked test kits were in short supply, a number of hospital laboratories established test methods for COVID-19 under the Health Institution Exemption (Annex II). Similar to the medical devices subject to national derogation, the tests used under the in-house exemption were independently validated by the laboratories in question and confirmed fit for purpose prior to being put into clinical use.

4. HPRA Market surveillance activities

Under EU legislation, a manufacturer may place a general category IVD, for example a COVID-19 test, on the market without any explicit permission from national Competent Authorities by self-declaring the compliance of the product with the legislation and registering the test in the Member State in which they are based. This allows them to affix a CE mark and access all EU markets.

Existing shortcomings in the current European regulatory system for IVDs (these are described in further detail under Annex I), have meant the absence of specific criteria and a pre-market regulatory check for COVID-19 tests under the IVD Directive. As such, some tests currently on the market may not perform as well as others. To mitigate this risk, all diagnostic testing conducted under the national testing strategy involves tests which are validated in the NVRL, in hospital diagnostic laboratories and other designated laboratories. As outlined below, the HPRA also conducts reviews of registered COVID-19 tests to assess the performance evaluations and claims made by the manufacturer. The HPRA is also working closely with EU and international counterparts to share information on tests for COVID-19.

Note: In relation to shortcomings within the current legislation, the system is currently in a process of transition. The incoming IVD Regulation (IVDR), which is applicable from May 2022, will strengthen the regulatory system for IVDs due to the increased requirements for these tests and the greater oversight by independent certification organisations, called notified bodies. The changes coming on stream under the IVDR are outlined in further detail in Annex I.

As part of the HPRA's market surveillance activities, a number of other activities are also ongoing including: -

4.1 Communication on risks and raising awareness of key elements of testing

The HPRA continues to raise awareness of the national testing strategy as implemented by NPHET through its market surveillance activities. These activities include regular updates to its website, direct correspondence with manufacturers, suppliers and distributors to deter placement of tests on the market of tests which are not in line with the national testing strategy, and proactive communications.

Our monitoring of product entering the market in Ireland has also prohibited the entry of a number of non CE marked/falsified COVID-19 tests.

An important communication issued by the HPRA during the pandemic involved the dissemination of an information notice to outline the risk of falsified tests for COVID-19. This communication was widely circulated to key stakeholders including the Pharmaceutical Society of Ireland (PSI) and the Irish College of General Practitioners (ICGP). The information notice was also highlighted through online and social media.

4.2 Review of general category IVDs registered with the HPRA

Tests for COVID-19 under current legislation are classified as general category IVDs, requiring that manufacturers self-declare that their test meets the requirements of the IVD Directive. The manufacturer must register the test with the Competent Authority in the country where they are legally based. As part of our market surveillance activities, the HPRA is undertaking a review of the performance evaluations and product claims for tests registered in Ireland. Any deficiencies in the technical documentation reviewed will be communicated to the manufacturer and a plan agreed in relation to appropriate follow-up.

4.3 Monitoring of the marketplace for developments in testing practices

Through our market surveillance activities, the HPRA is aware of the emergence of a number of test offerings which are outside of the national testing strategy which have the potential to impact the public health response to COVID-19.

4.3.a Low technology (lateral flow) antibody tests

Low technology (lateral flow) antibody tests have been supplied to healthcare and other settings in Ireland. Despite communicating through various means (via the HPRA website, information notice and directly to many suppliers) that the current testing strategy in Ireland is based on molecular testing, the HPRA is aware that lateral flow tests are available and used in Ireland. There are considerations in relation to their use and the implications in the context of the national testing strategy. The limitations of such tests are well documented in communications such as the WHO recommendation and the statement from the Royal College of Pathologists of Australasia. There is also a risk that the results of tests undertaken outside the established pathways will not be followed up appropriately and may not be captured in epidemiology data. These concerns were discussed with the NPHET Subgroup on Diagnostic Testing Approaches and their strategic framework document submitted to and accepted by NPHET recommended the restriction of these tests to research use only due to the risk that they may undermine the public health response to COVID-19. The HPRA will continue to monitor the situation and will discuss any further concerns regarding these tests and their potential to undermine the public health response to COVID-19 with the Department of Health.

4.3.b Private (commercial) entities offering SARS-CoV-2 (COVID-19) testing using laboratory based tests

The HPRA has also recently identified a number of private (commercial) entities offering SARS-CoV-2 (COVID-19) testing using laboratory based tests. Some of these offerings involve direct sample taking by members of the public in the home [using a nasal / oropharyngeal swab (for subsequent RT-PCR testing) or via finger-prick (for subsequent antibody testing)].

Under the national testing strategy, samples for diagnosis of COVID-19 are taken by trained healthcare professionals and testing is performed using molecular tests. The HPRA is concerned by the potential for inaccurate results posed by members of the public self-sampling, in particular self-swabbing as this can be quite a difficult task. We are anxious to ensure there is appropriate follow-up of any results obtained (appropriate clinical follow up, contact tracing etc.). Given the considerable debate regarding COVID-19 and immunity, and the lack of data in this area, we believe that any test results from antibody testing should be carefully interpreted.

While the HPRA does not have any role in relation to the provision of testing services or the oversight of these services, we will, as the Competent Authority for medical devices, continue to investigate these test offerings. Any concerns regarding these products, and their impacts on the public health response to COVID-19 in Ireland, will be raised with the Department of Health.

5. HPRA Contribution to Expert Groups

5.1 Medical Devices Criticality Assessment Subgroup

The HPRA is a member of the COVID-19 Medical Devices Criticality Assessment Subgroup which is chaired by the Department of Health. Our role as part of this group is to provide regulatory advice to the group in the context of the procurement of medical devices and IVDs. The HPRA worked with the Department of Health and HSE to assist in the review of offers of supply and to provide regulatory input regarding same. We also assisted with the onward communication of offers of supply from manufacturers and suppliers to relevant channels (HSE and NVRL). The HPRA worked with members of the medical devices criticality group to ensure there was no regulatory impediment to the scaling up of the testing capacity in Ireland.

5.2 HIQA's Rapid Health Technology Assessment (HTA)

The HPRA provided regulatory advice to HIQA during the drafting of its Rapid health technology assessment of alternative diagnostic testing approaches for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The HPRA also keeps the group informed of progress at EU level in relation to the development of performance criteria for COVID-19 tests.

5.3 NPHET Subgroup on Diagnostic Testing Approaches

Following completion of the HIQA Rapid HTA, the COVID-19 National Public Health Emergency Team (NPHET) recommended the establishment of a NPHET subgroup on diagnostic testing approaches. The role of the subgroup was to report to NPHET with a strategic framework for implementation within the existing HSE COVID-19 Testing Programme. The HPRA participated in this subgroup and provided advice to the group in the context of the regulatory framework for IVDs. The HPRA also provided information on emerging testing practices and any concerns identified through our market surveillance activities. The strategic framework was published on 2 June 2020.

5.4 European IVD Working group

The HPRA is a member of the IVD Working Group at EU level which is chaired by the EU Commission. Regular meetings of the IVD Working group are held to support the work of Member States during the pandemic and the HPRA participates in these meetings. The HPRA contributed to the development of a working document of Commission services on SARS-CoV-2 / COVID-19 tests. The HPRA is also contributing to the next stage of this work which involves consideration to amend the regulatory pathway for COVID-19 tests to increase the level of regulatory oversight prior to their placement on the market. The shortcomings in the current regulatory system for IVDs are described in further detail under Annex I. The incoming IVD Regulation (IVDR), which is applicable from May 2022, will strengthen the

regulatory system for IVDs due to the more stringent requirements for these tests and the greater oversight by notified bodies. The changes coming on stream under the IVDR are outlined in further detail in Annex I.

5.5 International Group on COVID-19

The HPRA is also involved at international level in discussions with a range of EU and other regulators globally. The aim of the group is to share information on regulatory guidance, device safety and performance, and also developments in the area of medical devices and IVDs used in the context of the pandemic. In the area of IVDs, the focus has been on sharing information on evaluations of various tests by independent bodies and on advancements and availability of tests.

ANNEX I:

Regulation of tests for SARS-CoV-2 (COVID-19)

In Europe, tests for SARS-CoV-2 (COVID-19) are classified as *in-vitro* diagnostic medical devices (IVDs) and must be CE-marked in accordance with the *In Vitro* Diagnostic Medical Devices Directive IVDD; 98/79/EC, as amended, before being placed on the market in Europe. The IVD Directive is transposed into Irish law by way of S.I. No. 304 of 2001, European Communities (*In-vitro* Diagnostic Medical Devices) Regulations, 2001, as amended.

Classification of tests for SARS-CoV-2 (COVID-19)

Laboratory-based tests for SARS-CoV-2 (COVID-19) and point of care/near-patient tests (professional use tests) are classified as general category IVDs. For general category IVDs, manufacturers **self-declare** that their test meets the requirements of the IVD Directive and the manufacturer must register the test with the CA in the country where they are legally based. There is no independent oversight of these tests prior to their placement on the market and there are no specific performance criteria defined (for example for sensitivity and specificity). This is a shortcoming of the current legislation and can lead to the placement on the market of tests which do not display acceptable performance.

Note: A test for COVID-19 (SARS-CoV-2) used by an individual to generate a result for that individual is considered to be a self-test under the IVD Directive. Self-tests require certification by an independent third party called a notified body for the self-testing elements. To date there are no CE marked self-tests for SARS-CoV-2 (COVID-19).

The IVD Regulation (2017/746/EU)

The regulatory system for IVDs has recently undergone substantial revision at European level. A new European regulation on IVDs was published in May 2017 (the IVD Regulation; IVDR). This regulation will replace the existing IVD Directive and national SI and will be fully applicable five years after entry into force (May 2022). This will bring about a number of important changes to ensure safe access to new and innovative IVDs for patients. Some key changes include new classification rules for IVDs, revised conformity assessment routes to be applied to demonstrate safety and performance and more detailed requirements for performance studies. The IVDR represents a significant development and strengthening of the existing regulatory system for IVDs in Europe and will replace the IVD Directive which has been in place for over 20 years.

One of the key changes under the IVDR relates to the conformity assessment procedures required of manufacturers prior to an IVD being placed on the market. Requirements vary based on the risk classification of the device, that is, for low risk (Class A) up to high risk (Class D). Assessment and certification by a notified body will be required for those IVDs in Classes B, C and D. This provides for the independent pre-market certification of a product prior to it becoming available for use in health services and corrects this shortcoming of the existing legislation. Class A devices placed on the market in a sterile condition will also require notified body review, limited to the sterile aspects of the product.

Depending on the intended purpose specified by the manufacturer, tests for SARS-CoV-2 (COVID-19) will likely be in Class D. This represents a significant change to the existing regulatory system, where the majority of IVDs are self-declared by the manufacturer rather than being assessed by a notified body.

In the interim, due to the lack of common technical specifications (performance specifications which must be met by a test) for tests for SARS-CoV-2 (COVID-19) and the placement on the market of some poorly performing tests, discussions are ongoing at the European IVD Working group to develop performance criteria for these tests and to consider amending the regulatory pathway for these tests to increase the level of regulatory oversight prior to their placement on the market.

ANNEX II:

Health Institution Exemption (Article 1(5) of the IVD Directive)

In general hospital laboratories purchase *in-vitro* diagnostic medical devices (IVDs) from commercial suppliers; however, in certain situations suitable commercial IVDs may not be available (as in the current pandemic where there is a worldwide demand for the same products). In such scenarios hospital laboratories may develop their own tests. These IVDs are regarded as 'in-house' or 'lab developed tests' (LDTs). These tests are not considered to be placed on the market or put into service and are exempt from the requirements of Directive 98/79/EC as amended.

Under the in-house exemption: -

- IVDs that are manufactured 'in-house' and used to test patient samples from the same health institution are **excluded** from the legislation.
- IVDs that are manufactured 'in-house' and used to test samples from external patients i.e. from a GP practice or another hospital are **excluded** from the legislation.
- Non CE marked tests may be used by health institutions and under these circumstances the hospital validates the test for use in their institution

If, however, the IVDs that are manufactured 'in-house' are then transferred to another laboratory for use in that laboratory, and if the laboratory is outside the health institution's own legal entity, such tests are considered to fall **within** the scope of the IVD Directive and must be CE marked in accordance with the IVD Directive. In such scenarios the health institution becomes the legal manufacturer of the IVD and the test is within the scope of the IVD legislation.

ANNEX III:

National Regulatory Derogation Process

The HPRA developed a regulatory derogation process for the urgent assessment of applications to facilitate the use of critical non-CE marked medical devices and IVDs in the context of the COVID-19 emergency in Ireland. The HPRA derogation procedure is only applicable to supply to Ireland and was introduced to provide an urgent assessment of applications for the short-term use of non-CE marked medical devices in Ireland when required in response to the COVID-19 emergency. The HPRA assesses these applications to determine whether the provision of non-CE marked devices is in the interest of the protection of health. The regulatory derogation process consists of two application forms, one which is completed by the manufacturer and the second which is completed by the consultant or clinical lead in the health institution where it is intended to use the device. The HPRA also conducts a desk based review of the technical and clinical documentation supporting the product subject to derogation

As the demand for non-CE marked IVDs in the context of COVID-19 is stabilising the HPRA is now encouraging all manufacturers to follow the conformity assessment procedures and regulatory requirements set out in the IVD Directive to ensure that devices placed on Irish market and made available to Irish patients are CE marked in accordance with the legislation.