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Guidance on state of the art of COVID-19 rapid antibody tests

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Introduction

The COVID-19 pandemic is evolving rapidly, and so is the market of *in vitro* diagnostic medical devices for COVID-19. In particular, many rapid tests[1] for the detection of antibodies against SARS-CoV-2 virus are becoming available. Determining what would be adequate performance for those tests is challenging. Directive 98/79/EC on *in vitro* diagnostic medical devices[2] establishes that devices must be designed and manufactured[3] in such a way that they are suitable for the intended purpose[4] specified by the manufacturer, taking into account the generally acknowledged state of the art. The manufacturer should therefore justify why the device is suitable for the intended purpose claimed, in light of the state of the art. To facilitate the fulfilment of this legal requirement, the considerations presented in this guidance are intended to establish particular elements on the current state of the art for COVID-19 rapid antibody tests. It will also assist with understanding what the current state of the art is.

For the purpose of this guidance, state of the art is the developed stage of current technical capability and/or accepted clinical practice with regard to products, processes and patient management, based on the relevant consolidated findings of science, technology and experience.

Note: The state of the art embodies what is currently and generally accepted as good practice in technology and medicine. The state of the art does not necessarily imply the most technologically advanced solution. The state of the art described here is sometimes referred to as the "generally acknowledged state of the art".[5]

Therefore, state of the art does not refer to the best in class but rather to what is achievable by a majority of devices, and is therefore expected to be achieved by the devices on the market.[6]

Naturally, the state of the art will improve over time. Therefore, the guidance presented here may be seen as the minimum expected from devices being placed on the market at the time of publication of this document. It may be revised or replaced by other documents as scientific knowledge and technology evolves.

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1 Rapid tests are defined as qualitative or semi-quantitative IVDs, used singly or in a small series, which involve non-automated procedures and have been designed to give a fast result (Commission Decision 2002/364/EC on common specifications for *in vitro* diagnostic devices, OJ L 131, 16.5.2002, p. 17)

2 OJ L 331, 7.12.1998, p.1.

3 Note: this guidance is not exhaustive in its nature and should be read in conjunction with Directive 98/79/EC and other available documents and guidance. Aspects which are common to most IVDs and are not particularly specific to SARS-CoV-2 or COVID-19 rapid antibody tests have been left out of this document.

4 It is important to note that additional requirements for self-testing exist and should be followed in addition to the indications provided here.

5 Source: Modified from IMDRF/GRRP WG/N47 FINAL:2018 as adopted by the MDCG New Technologies and CIE working group

6 For reference see Commission Decision 2008/932/EC of 2.12.2008, C(2008)7378, OJ L 333/5 of 11.12.2008 on a certain HIV test of the manufacturer M.B.S. In the case in question, the combined data of various national institutes showed a picture according to which all HIV tests could be grouped into three tiers, grossly corresponding to three generations of tests. In that case, the HIV test in question was deemed not to correspond to the "state of the art" because it fell in the lowest performing tier.

Therefore, it is crucial that the manufacturer clearly specifies the device's intended purpose, considering what levels of performance are needed and what aspects of the state of the art are relevant in light of that particular intended purpose. In addition, the manufacturer is expected to continuously take into account the state of the art as relevant new information becomes available and where necessary, update the device's performance data, adjust the intended purpose, or, if this cannot be done, carefully reassess whether the device actually can be considered in conformity with the requirements of the Directive.

Legal requirements of Directive 98/79/EC on device performance

Directive 98/79/EC establishes that devices must achieve the relevant performance, in particular in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.[7]

The intended purpose must be specified in the instructions for use and/or on the label, unless it is obvious to the user.[8] For COVID-19 devices, it is always necessary to define the intended purpose. This should be complete and precise, including aspects such as :

- the intended user,
- the target population,
- window between infection and antibody detection,
- result interpretation (including limitations of interpretation),
- assay design (target antigen(s), antibody types)[9],
- limitations of the assay,
- whether the assay is intended, for example, to detect the antibody response in individual patients' recovery, to assess if the patient has been previously infected, to assess response to vaccination,
- the exclusion of antibody test use as first line test for diagnosis.

The instructions for use must also describe the performance of the device with regard to the non-exhaustive parameters listed above.[10] The technical documentation of the device must contain adequate performance evaluation data showing the performances claimed by the manufacturer. The data should originate from studies conducted in an environment targeted by the assay (e.g. clinical settings) or result from relevant references.[11] The information on the establishment of performance should be complete to allow an assessment of its quality.

For biological analytes such as virus specific antibodies there is no reference procedure of higher order. Therefore, the performance evaluation should be done in direct comparison to diagnostic device(s) measuring the same analyte which are estimated as reflecting the "state

7 Directive 98/79/EC Annex I A(3)
8 Directive 98/79/EC Annex I B 8.5
9 Include information on target antigen to antibodies to be measured, including information on variant protein (wild type or other variants).
10 Directive 98/79/EC Annex I B 8.7 (d)
11 Directive 98/79/EC Annex III (3)

of the art" at the time of the performance study (reference devices). Samples with discrepant test results obtained for the device under evaluation and reference (comparator) device should undergo further investigation (e.g. further assays, patient history) to clarify the probable "true" status, as far as possible.

State of the art

In the course of development of this guidance, 102 instructions for use of COVID-19 rapid antibody tests placed on the European market before September 2020 were examined in order to assess the state of the art from the perspective of real market performance. Performance criteria/considerations for devices used for the detection of antibodies against SARS-CoV-2 published by different sources, including the WHO, were also reviewed. The outcome of this analysis was used as a basis for the following findings:

1) Performance evaluation modalities

The performance should be ideally evaluated for each claimed clinical specimen type unless equivalence between the relevant biological matrices has been demonstrated.

- **Interference studies:** Standard interference studies should be performed and should take into account the typical potential sources of interference in the sample matrix in question. Please refer to pages 25-26 of the following document 'Current performance of COVID-19 test methods and devices and proposed performance criteria - Working document of Commission services' for more information.[12]
- **Cross reactivity studies:** samples from patients with infection history of related viruses, e.g. SARS-CoV-1, MERS-CoV, human common cold coronaviruses, or other respiratory infections (including influenza). Please refer to pages 25-26 of the following document 'Current performance of COVID-19 test methods and devices and proposed performance criteria - Working document of Commission services' for more information.[12]

Note: Antibodies for other respiratory infection agents are considered as potentially pertinent cross reacting agents to be systematically tested in addition to other more usual cross reactants. As part of post market surveillance, it remains the responsibility of the manufacturer to continuously monitor the performance of their devices, including for new potentially cross-reacting agents and update their relevant documentation, where necessary.

- **Diagnostic sensitivity evaluation:**

The positive sample panel should include at least 200 samples from individuals with a confirmed diagnosis of a SARS-CoV-2 infection with details on timing between sampling and potential onset of symptoms.

Considering that diagnostic sensitivity depends highly on the time interval between the contact with the virus and sample taking, diagnostic sensitivity studies should use samples at

[12] https://ec.europa.eu/docsroom/documents/40805

various stage and severity of disease and from putative infections. Samples could be longitudinal, drawn at different times from the same individuals. The positive sample panel should include early and later samples homogenously distributed in terms of the time interval between contact with the virus and sample taking.

Depending on the intended purpose of the device, it may be difficult to get access to well-defined panels reflecting the full diversity of potential antibody responses, representing e.g. different time points after infection, different follow-up courses of infection, asymptomatic / symptomatic infection, etc. Therefore, an option may be to use the device in parallel with an established device[13] to investigate a representative set of samples, without preselection or exclusion of specimens, from a high incidence situation such as from a local or regional outbreak or from hospitals.

- **Diagnostic specificity evaluation:**

The negative panel should include at least 200 samples.

The negative panel should consist of samples derived either from patients tested for antibodies for SARS-CoV-2 and confirmed as negative, or samples collected prior to November 2019.

The negative samples should broadly represent the different factors present in the target population according to the intended purpose of the device. Age, gender, demographics and additional factors such as previous disease history (e.g. non-SARS-CoV-2 respiratory tract infections) or long-term medication of the patient should be considered.

2) Diagnostic performance of the device

Diagnostic sensitivities mentioned in the studied IFUs were heterogeneously determined, making it difficult to conclude on a minimum value reflecting the state of the art for this performance. It should nevertheless be noted that performance criteria/considerations published by different sources, including the WHO, for devices used for the detection of antibodies against SARS-CoV-2 generally require at least 90% diagnostic sensitivity for each antibody type (IgM, IgG or total Ig).

In the case of diagnostic performance established by comparison with a device used as reference, the diagnostic sensitivity should be at least equivalent to reference device(s), see Section "Legal requirements of Directive 98/79/EC on device performance".

Diagnostic specificity should be at least 98%.

Confidence intervals should be provided for the estimates of both the diagnostic sensitivity and diagnostic specificity, 95 % confidence intervals are recommended.

[13] Whereby an established device is understood as a device that meets the minimum performance requirements set in the present document.