Pre-clinical evaluation of the rapid diagnostic tests according to IVDR Regulation 2017/746

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Background

- **May 5, 2017** – **IVDR Regulation 2017/746** is published in the Official Journal of the European Union
- **May 26, 2022** – **IVDR Regulation 2017/746** enters into force and repeals **Directive 98/79/EC**
- **Present** – we are in the ***transitional period***, which allows the marketing of devices placed on the market before May 26, 2022, as long as they comply with the provisions of Art. 110 - Transitional Provisions (IVDR 2017/746). Marketing is still allowed until certain deadlines, depending on the new risk class of the device

Purpose of IVDR implementation

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PATIENT SAFETY

- Robust, transparent and sustainable regulatory framework
- Stricter risk-based classification system
- Extended pre-clinical performance studies
- Improved clinical safety of devices
- Implementation of the unique device identification system
- Increased involvement of the Notified Body
- Rigorous post-marketing surveillance

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Legislation
Guidelines and standards

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices, as amended

NATIONAL LEVEL

Law No. 95/2006 on health reform, republished, with subsequent amendments and additions

EMERGENCY ORDINANCE No. 137 of October 12, 2022 establishing the institutional framework and the measures necessary for implementing Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices repealing Directive 98/79/EC and Commission Decision 2010/227/EU

Law No. 289/2023 for the approval of Government Emergency Ordinance No. 137/2022

GUIDELINES AND STANDARDS

Guidelines approved by the Medical Device Coordination Group (MDCG) under Art. 99 of Regulation (EU) 2017/746

Harmonized standards

Harmonized Standards

Reference number of the standard	Title of the standard
EN ISO 11135:2014, EN ISO 11135:2014/A1:2019	Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 11135:2014)
EN ISO 11137-1:2015, EN ISO 11137-1:2015/A2:2019	Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (ISO 11137-1:2006, including Amd 1:2013)
EN ISO 11137-2:2015, EN ISO 11137-2:2015/A1:2023	Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose (ISO 11137-2:2013)
EN ISO 11607-1:2020, EN ISO 11607-1:2020/A1:2023	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019)
EN ISO 11607-2:2020, EN ISO 11607-2:2020/A1:2023	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019)
EN ISO 11737-1:2018, EN ISO 11737-1:2018/A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products (ISO 11737-1:2018)
EN ISO 11737-2:2020	Sterilization of health care products - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process (ISO 11737-2:2019)
EN ISO 13408-1:2024	Aseptic processing of health care products - Part 1: General requirements (ISO 13408-1:2023)
EN ISO 13408-6:2021	Aseptic processing of health care products - Part 6: Isolator systems (ISO 13408-6:2021)
EN ISO 13485:2016, EN ISO 13485:2016/AC:2018, EN ISO 13485:2016/A11:2021	Medical devices - **Quality management systems - Requirements for regulatory purposes (ISO 13485:2016)**
EN ISO 14971:2019, EN ISO 14971:2019/A11:2021	Medical devices - **Application of risk management to medical devices (ISO 14971:2019)**
EN ISO 15223-1:2021	Medical devices - **Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements (ISO 15223-1:2021)**
EN ISO 17511:2021	In vitro diagnostic medical devices - **Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples (ISO 17511:2020)**
EN ISO 20916:2024	In vitro diagnostic medical devices - **Clinical performance studies using specimens from human subjects - Good study practice (ISO 20916:2019)**
EN ISO 25424:2019	Sterilization of health care products - Low temperature steam and formaldehyde - Requirements for development, validation and routine control of a sterilization process for medical devices (ISO 25424:2018)
EN ISO 25424:2019, EN ISO 25424:2019/A1:2022	Sterilization of health care products - Low temperature steam and formaldehyde - Requirements for development, validation and routine control of a sterilization process for medical devices (ISO 25424:2018)

Source: https://single-market-economy.ec.europa.eu/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices_en

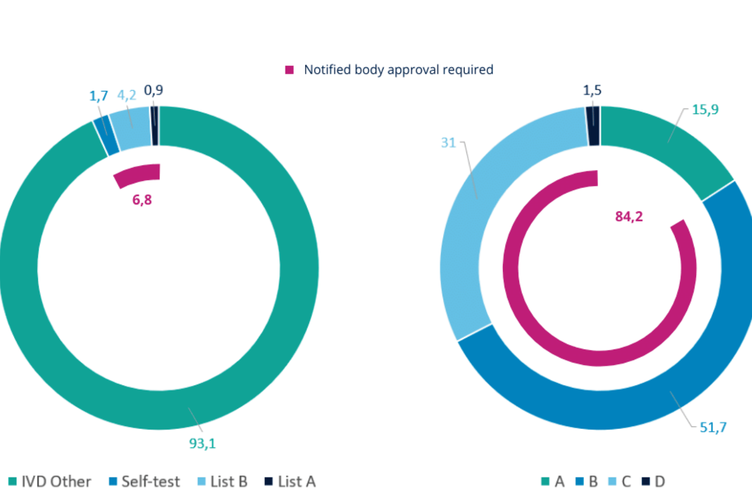
Notified Body

- **Notified Body**

  - a key pillar of the health technology regulatory system

- **Current situation**

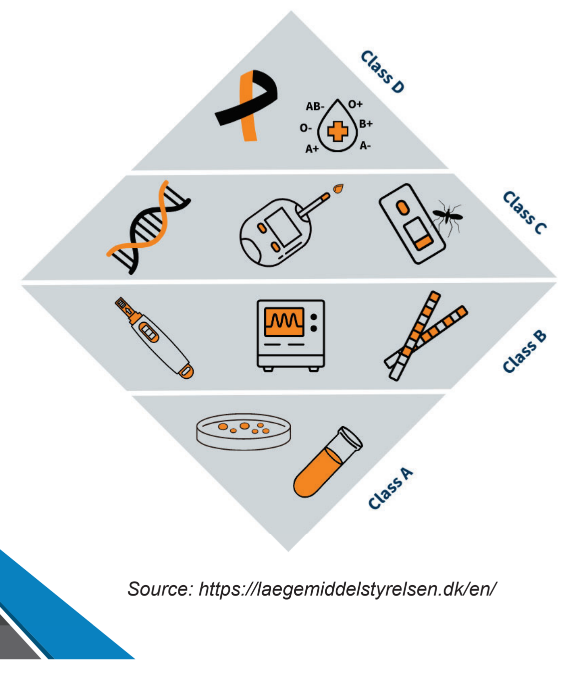
  - 17 Notified Bodies designated for the evaluation of in vitro diagnostic medical devices



Source: https://www.qbdgroup.com/en/blog/ivdr-classification-of-in-vitro-diagnostic-medical-devices-guide

Device classification

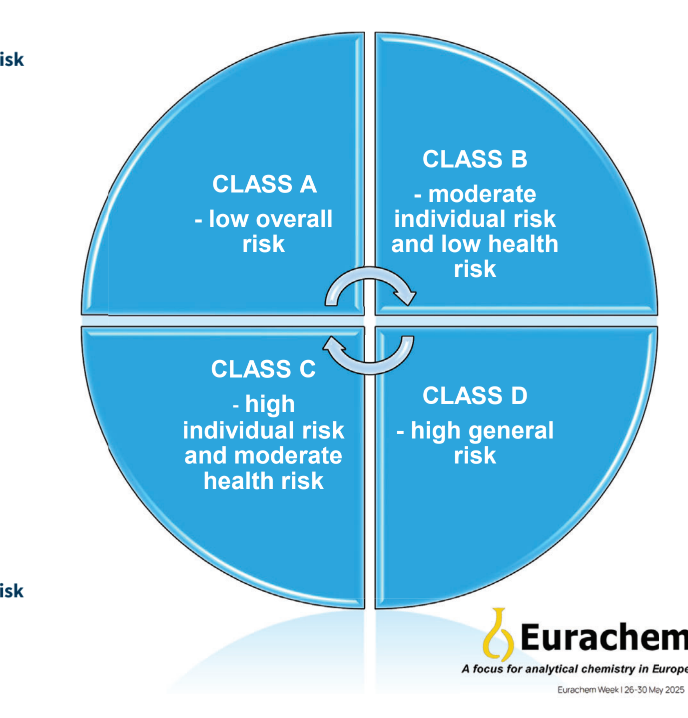
In vitro diagnostic medical devices



High risk

Low risk

Source: https://laegemiddelstyrelsen.dk/en/



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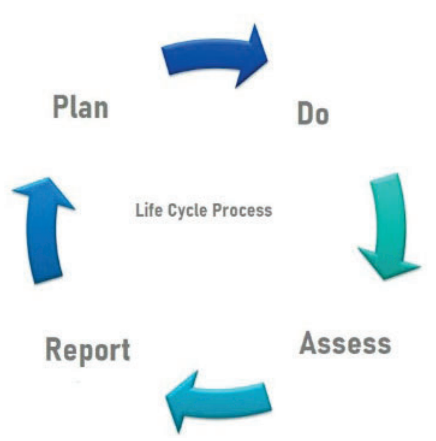
Performance evaluation

Scientific validity	• association of an analyte with a clinical or physiologic state
Analytical performance	• ability of a device to correctly detect or measure a particular analyte
Clinical performance	• ability of a device to yield results that are correlated with a particular clinical condition or physiologic or pathologic process or state in accordance with the intended target population and intended user



Analytical performance

- Analytical sensitivity
- Analytical specificity
- Trueness (bias)
- Precision (repeatability and reproducibility)
- Accuracy (resulting from trueness and precision)
- Limits of detection and quantification
- Measuring range
- Linearity
- Control of known relevant endogenous and exogenous interference
- Cross-reactivity

Standardization importance Common specifications

Performance characteristic	Specimen	Specimen numbers, features, use	Acceptance criteria
Diagnostic sensitivity	Positive specimens	≥400 including specimens from different stages of infection and reflecting different antibody patterns. HCV genotype 1-4: > 20 specimens per genotype (including non-a subtypes of genotype 4); HCV genotypes 5 and 6: > 5 specimens each;	all true positive specimens shall be identified as positive
	Seroconversion panels	≥30 panels HCV seroconversion panels for the evaluation of HCV antigen and antibody combined tests (HCV Ag/Ab) shall start with one or more negative bleeds and comprise panel members from early HCV infection (HCV core antigen and/or HCV RNA positive but anti-HCV negative).	diagnostic sensitivity during seroconversion shall represent the state of the art HCV Ag/Ab tests shall demonstrate enhanced sensitivity in early HCV infection when compared to HCV antibody only tests.
Diagnostic specificity	Unselected blood donors (including first-time donors)[1]	≥1 000	≥ 99 %
	Hospitalised patients	≥200	Potential limitations for specificity, if any, shall be identified
Cross-reactivity	Potentially cross-reacting specimens	≥200 specimens from pregnant women ≥100 other potentially cross-reacting specimens in total (e.g. RF+, from related infections)	

Source: Commission Implementing Regulation (EU) No 2022/1107 of July 4, 2022 laying down common specifications for certain Class D in vitro diagnostic medical devices in vitro diagnostics in accordance with Regulation (EU) 2017/746 of the European Parliament and of the Council

WHO guidelines

TGS 1 Standards applicable to the WHO Prequalification of in vitro diagnostic medical devices: identifies standards and guidance relating to a range of issues that are encountered in the manufacture, verification, and validation of IVDs.

TGS 2 Establishing stability of in vitro diagnostic medical devices: provides IVD manufacturers with guidance on possible approaches to determining stability and describes WHO prequalification requirements for stability testing.

- **Annex to TGS 2 Establishing component stability for in vitro diagnostic medical devices:** provides recommendations for establishing the stability of components for IVDs, with examples on the change from establishing stability for multi-use dropper bottles to establishing stability for single-use vials.

TGS 3 Principles of performance studies: identifies the key principles that apply when conducting and reporting the study design, results, and conclusion of analytical and clinical performance studies that support performance claims for IVDs undergoing assessment for WHO prequalification.

TGS 4 Test method validation for in vitro diagnostic medical devices: provides guidance to manufacturers on the validation of the test methods used in establishing the design, development and manufacture of an IVD.

Case study - Performance reports COVID-19 Antigen Rapid Test (Nasal Swab) for self-testing

Limit of Detection determination

Interfering substances

Cross-reactivity

Specificity testing with strains

Repeatability and reproducibility

Dose hook effect

Variability (inter/intra/ day to day)

Specimen volume flex study

Stability studies:

- Sample stored in VTM
- Accelerated stability
- Open pouch stability
- Real-time stability
- Simulated shipping
- Stability in provided buffer

Clinical performance studies:

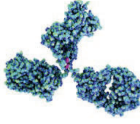
- Sample correlation study
- Lay user study

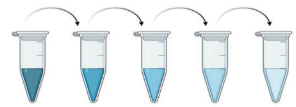
Case study

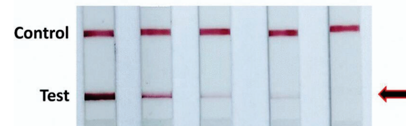
Detection limit determination – Initial assessment

Table 1: Initial Detection Limit Determination of COVID-19 Antigen Rapid Test (Nasal Swab) for self-testing

Nucleoprotein concentration (ng/mL)	COVID-19 Antigen Rapid Test (Nasal Swab) for self-testing								
	Batch 1			Batch 2			Batch 3		
	15 minutes			15 minutes			15 minutes		
14.8	+	+	+	+	+	+	+	+	+
7.4	+	+	+	+	+	+	+	+	+
3.7	+	+	+	+	+	+	+	+	+
1.85	+	+	-	+	-	-	+	+	+
0.93	-	+	-	-	+	+	-	-	+
0.46	-	-	-	-	-	-	-	-	-
0.23	-	-	-	-	-	-	-	-	-
0.11	-	-	-	-	-	-	-	-	-







Case study

Detection limit determination – Notified Body Requests

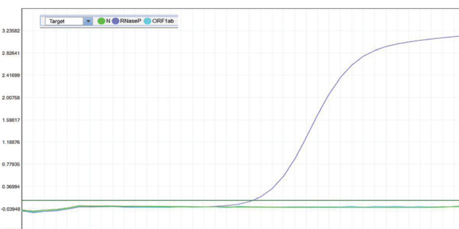


Figure 1 RT-PCR result for the matrix

Figure 2 Replicates for the final concentration set for the limit of detection: 2.4 ng/mL

Table 2: Reworked Study for Detection Limit Determination of COVID-19 Antigen Rapid Test (Nasal Swab) for self-testing

Concentration (ng/mL)	Batch 1									
	1	2	3	4	5	6	7	8	9	10
3.0	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
2.8	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
2.6	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
2.4	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
2.2	++	++	++	++	++	++	++	++	++	++
2.0	++	++	++	++	++	++	++	++	++	++
1.8	+	+	+	+	+	+	+	+	+	+
1.6	+	+	+	+	+	+	+	+	+	+
1.4	+	+	+	+	+	+	+	+	+	+
1.2	+	+	+	+	+	+	+	+	+	+
1.0	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-

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Case study
EU Common list of COVID-19 antigen tests

January 2021	*Member States have agreed to establish a common framework for the use of rapid antigen tests within the European Union*
September 2021	*The Working Group agreed on additional definitions, scope, considerations and criteria to be used in validation studies assessing the performance of these tests*
February 2022	*Publication of the MDCG 2021-21 guideline on rapid antigen-type tests for the detection of SARS-CoV-2*

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EU HEALTH PREPAREDNESS

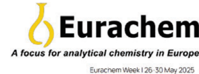
EU Common list of COVID-19 antigen tests

Agreed by the Health Security Committee

MDCG 2021-21 Rev.1

Guidance on performance evaluation of SARS-CoV-2 *in vitro* diagnostic medical devices

Revision 1 – February 2022



Case study
EU Common list of COVID-19 antigen tests

Table 4: **Antigen assays (including rapid tests) for SARS-CoV-2**

Parameter	Specimen	SARS-CoV-2 antigen	Acceptance criteria
Diagnostic sensitivity	Positive specimens	≥100[1] NAT positive samples[2] from early infection within the first 7 days after symptom onset[3]; samples should represent naturally occurring viral loads[4]; consideration of genetic variants[5] consideration of variations in specimen collection and/or specimen handling[6]	Detection of >80% (rapid tests); detection of >85% (lab-based assays[7]); relative to SARS-CoV-2-NAT[8,9]
Analytical sensitivity	Standards	As soon as available	Establishment of a limit of detection[10]
Diagnostic specificity	Negative specimens	≥300 from non-infected individuals ≥100 from hospitalised patients ≥50 potentially interfering and cross-reactive samples in total: including virus-positive samples of endemic human coronaviruses 229E, OC43, NL63, HKU1; influenza A, B, RSV, and other pathogens of respiratory diseases, eligible for differential diagnosis; including bacteria[11] present in the sampling area	Specificity >98% (rapid tests) Specificity >99% (lab-based[7]) Potential limitations for specificity should be determined

[1] If the device is intended to be used for more than one specimen type, 100 samples shall be required for each specimen type. If this is not possible in exceptional circumstances (e.g. if specimen collection is very invasive), the manufacturer shall provide a justification and evidence of matrix equivalence.
[2] Sampling should be matched for antigen and NAT testing, e.g., two simultaneous samples from each individual or optimally NAT- and antigen testing from the same sample (e.g. from the eluate of one swab); the buffer/transport medium should be compatible for both NAT and antigen testing; any volume change in the buffer/medium for sample uptake different from that of the proprietary assay, and/or between antigen and NAT test should be clearly communicated.
[3] Or time of infection, if known, taking into account the incubation time.
[4] I.e., without preselection; the viral loads and their distribution should be shown, e.g. characterized by Ct-values of RT-PCR; or transformed into viral load per ml or sample, if applicable.
[5] Depending on the design of the device and nature of the genetic variant. For the purpose of evaluation, at least 3 samples should be represented for each genetic variant.
[6] Specimen collection and extraction items such as swabs, extraction buffers, etc., should be part of the evaluation. If proprietary sampling/sample preparation is not included in the test kit, test performance should be investigated for an applicable range of sampling devices. If the sample is not tested immediately, e.g. after a certain transport time, stability of the antigen should be investigated.
[7] Other than rapid tests, i.e. formal laboratory-based assays e.g. enzyme immunoassay, automated tests, etc.
[8] The sensitivity of ≥80%, ≥85% respectively, should be for all specimen types claimed. All claimed specimen types should be compared with paired NAT results from nasopharyngeal specimens.
[9] The relationship between antigen test performance and NAT should be demonstrated; sensitivity may be shown relating to different viral load ranges and to the threshold of infectivity. The NAT and extraction method used should be described.

Case study
EU Common list of COVID-19 antigen tests

Table 6: **Additional requirements for SARS-CoV-2 antigen Self-Tests[1]**

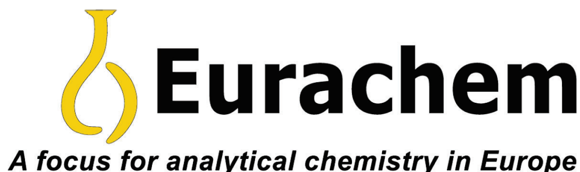
	Specimens[2]	Number of lay users	Criterion
Result interpretation	Interpretation of contrived tests[3] by lay users reflecting a range of results: • non-reactive • reactive • weak reactive[4] • invalid	≥100	Reading and interpretation of the contrived test results by 100 lay people; each lay person should be subjected to read the specified range of result reactivity levels; determination of concordance of lay reading of the same tests by professional readers
Diagnostic sensitivity	Lay users that are known antigen positive[5,6]	≥30	In comparison to the true infectious status, i.e. by RT-PCR; concordance of results with the professional test
Diagnostic specificity	Lay users that do not know their status[5]	≥60	Concordance of results with the professional test

[1] It is assumed that the underlying performance of the self-test has already been previously demonstrated with the evaluation/assessment of a professional test of the same design as the respective self-test under evaluation. In case for the self-use specimens in question there is no corresponding professional test variant, comparison should be made with the standard specimen type (e.g. nasopharyngeal swabs for antigen test, serum or plasma for antibody test) of the corresponding professional test.
[2] For each self-use specimen type claimed with the device (e.g. nasal, sputum, saliva, whole blood, etc.).
[3] Using whenever possible the original natural matrix of the respective specimen type.
[4] A higher proportion of the samples should be in the weak-positive range close to the cutoff or LoD of the test.
[5] Individuals unaware of the professional diagnostic result prior to self-testing, and performing the entire test procedure from specimen collection and specimen pre-treatment (swab, buffer extraction, etc.) to reading.
[6] Subjects up to about 7 days after symptom onset.

Conclusions

- IVDR 2017/746 establishes a robust, transparent, and sustainable regulatory framework that improves product safety and establishes fair market access for manufacturers and healthcare professionals.
- IVDR 2017/746 introduces new obligations for Notified Bodies and involves the assessment of a larger number of products than before. In vitro diagnostic medical devices are subject to a major change for certification in Europe.
- The new requirements introduce a series of changes, including the introduction of a risk-based classification system with four risk classes for in vitro diagnostic medical devices.
- Pre-clinical performance assessment under IVDR 2017/746 is much stricter and introduces new challenges for European manufacturers.
- Guidelines, common specifications, and international standards are a building block for harmonized regulatory processes to ensure the safety, quality, and performance of medical devices.
- The introduction of common requirements in the conduct of a pre-clinical study could contribute significantly to the quality assurance of medical devices.

Thank you for your attention!



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