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Classification of In-Vitro-Diagnostic Medical Devices – Comparison of Regulation (EU)2017/746 and IMDRF

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 1 first intend (IVDR) and first bullet point IMDRF			
Devices intended to be used for detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration;	First indent applies to all devices intended to assess the suitability of blood, blood components, cells, tissues or organs or their derivatives for transfusion, transplantation or cell administration, with respect to transmissible agents. The result of the test will be a major determinant as to whether the analysed donation will be used. Devices typically falling under this rule are intended for the detection of those agents for which the EU has harmonised the donor and donation testing requirements within the context of risk of transmission of infection (European Directives 2002/98/EC3, 2006/17/EC4, 2010/45/EU (corrigendum: 2010/53/EU)5). Those agents are listed in the examples below. It must be noted that: » Manufacturers may intend devices for the detection of the presence of, or exposure to, transmissible agents, other than those mentioned in the above-cited Directives, to assess the suitability of blood, blood components, cells, tissues or organs or their derivatives for transfusion, transplantation or cell administration. In that case, these devices are classified in class D according to this rule. » Some devices can detect the same agent for completely different intended purposes than the intended purposes covered by this rule. Where there is a foreseeable risk that tests may be misused to assess the suitability of blood, blood components, cells, tissues or organs for transfusion, transplantation or cell administration or their derivatives, a clear limitation of use should be included in the IFU and the technical documentation of the devices.	Devices intended to be used to detect the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs or any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration	The application of this rule as defined above should be in accordance with the rationale that follows: Devices in this Class are intended to be used to ensure the safety of blood and blood components for transfusion and/or cells, tissues and organs for transplantation. In most cases, the result of the test is the major determinant as to whether the donation/product will be used.
Examples MDCG 2020-6			
Devices typically falling under this rule are those that detect agents for which the EU has clearly harmonised the donor and donation testing requirements, as outlined in the relevant European directives. European directives 2002/98/EC (on blood), and 2006/17/EC (on tissues and cells): » Hepatitis B (HBs-Ag); Hepatitis C (Anti-HCV); Human Immunodeficiency Virus 1/2 (Anti-HIV 1/2). In addition, the European directive 2006/17/EC (on tissues and cells) references Treponema pallidum and in certain circumstances, depending on the donor's history and the characteristics of the tissue or cells donated: Human T-Lymphotropic Virus- I; Malaria (Plasmodium spp.); Cytomegalovirus; Trypanosoma cruzi; Epstein Barr virus; Toxoplasma gondii. European directive 2010/45/EU (corrigendum: 2010/53/EU) (on organs) : » Hepatitis B; Hepatitis C; Human Immunodeficiency Virus.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Tests to detect infection by HIV, HCV, HBV, HTLV; HIV blood donor screening and HIV blood diagnostics. This rule applies to first-line assays, confirmatory assays, and supplemental assays.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 1 second intend (IVDR) and second bullet point IMDRF			
Devices intended to be used for detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation;	Second indent applies to devices which are intended to be used for the detection of the presence of or the exposure to a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation. Several factors contribute to the risk of propagation of a pathogen within a population, namely: » the direct or in-direct transmissibility (i.e. the probability of infection when there is contact between a susceptible and an infected individual). This includes for example consideration of the infectious dose and route of transmission e.g. aerosol, zoonosis, vector-mediated. » the contact rate of infected and susceptible individuals (i.e. the number of contacts per time), and - the duration of infectiousness. For the purposes of this document, the risk of propagation of a pathogen within a population is considered to be the risk for the general European population. This rule applies regardless of whether the test is a first line, confirmatory or supplemental assay.	Devices intended to be used to detect the presence of, or exposure to, a transmissible agent that causes a life-threatening, disease with a high or suspected risk of propagation;	Serious diseases are those that result in death or long-term disability, that are often incurable or require major therapeutic interventions and where an accurate diagnosis is vital to mitigate the public health impact of the condition.
Examples MDCG 2020-6			
Devices intended for: » Hepatitis B Virus; Hepatitis C Virus; Hepatitis D Virus; Human Immunodeficiency Virus 1 and 2. » Haemorrhagic fever viruses (e. g. Ebola, Marburg, Lassa, Crimean-Congo Haemorrhagic fever. » Highly virulent pandemic influenza virus. » Human T-Lymphotropic Virus I and II. » SARS CoV and SARS-CoV-2. » MERS Coronavirus. » Smallpox virus. » Variant Creutzfeldt-Jakob disease (when available).			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Tests to detect infection by HIV, HCV, HBV, HTLV; HIV blood donor screening and HIV blood diagnostics. This rule applies to first-line assays, confirmatory assays, and supplemental assays.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 1 third intend (IVDR)			
Devices intended to be used for determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management	Third indent applies to devices intended to be used for determining the infectious load in the context of life-threatening infectious diseases, after the disease status of the patient has been previously determined, and for which patient management options, including specific treatment, are based on monitoring the infectious load. Viral load is typically performed by nucleic acid amplification based tests (NAT). In the case of Hepatitis B, the DNA viral load determined by molecular biology complies with the present rule due to its importance for the initiation of treatment, the evaluation of the treatment efficiency and the change of treatment, if necessary. Hepatitis B antigen tests intended for monitoring are not critical in the process of patient management and thus they do not fall under this rule.	Not availble	Not available
Examples MDCG 2020-6			
Devices intended to be used for determining the infectious load of » Hepatitis B Virus (DNA) » Hepatitis C Virus, » Human Immunodeficiency Virus.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 2			
Devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration, are classified as class C, except when intended to determine any of the following markers: » ABO system [A (ABO1), B (ABO2), AB (ABO3)]; » Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)]; » Kell system [Kel1 (K)]; » Kidd system [JK1 (Jka), JK2 (Jkb)]; » Duffy system [FY1 (Fya), FY2 (Fyb)]; in which case they are classified as class D.	Rule 2 applies equally to donor and recipient testing. This rule classifies blood grouping devices into two classes depending on the likelihood that a blood group marker could cause an immunogenic response or a severe haemolytic transfusion reaction. The red blood cell markers listed in this rule are critical for ensuring immunological compatibility and safe transfusion of blood and blood components. Devices related to these markers, either intended as screening, diagnostic, confirmatory or supplemental devices are class D devices. These class D devices includes those intended for: » The determination of the expression of ABO and Rhesus (Rh) D, Weak D, C, E, c, e in donor and recipient e.g. by serological testing or molecular genotyping. » The determination of partial D, as these D antigen positive patients are at risk of anti-D alloimmunization. » The detection of anti-A and anti-B antibodies for reverse ABO typing, as ABO blood grouping requires both forward (antigen) and reverse (antibody)typing. » Screening, detection or identification of red cell antibodies for the Rh system (anti RH antibodies), Kell system (anti-KEL1 antibodies), Kidd system (anti-JK1 and anti-JK2 antibodies) and Duffy system (anti-FY1 and anti-FY2 antibodies). » Typing of specific red blood cell antigens (KEL1, JK1, JK2 , FY1, FY2). Devices intended for identifying markers, other than the red blood cell markers listed in this rule, which are either intended as screening, diagnostic, confirmatory or supplemental devices for blood grouping, tissue typing, or to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration are class C devices. All devices intended for HLA tissue typing are classified under this rule as class C devices when they are intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration.	IVD medical devices intended to be used for blood grouping, or to determine foetomaternal blood group incompatibility, or tissue typing to ensure the immunological compatibility of blood, blood grouping for cell administration, blood components, cells, tissue, or organs that are intended for transfusion or transplantation, are classified as Class C, except when intended to determine the presence of the antigen or antibody for any of the following markers: ABO system [A (ABO1), B (ABO2), AB (ABO3)], Rhesus system [RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e), and weak or partial Rh(D)], Kell system [Kel1 (K)], Kidd system [JK1 (Jka), JK2 (Jkb)]; or Duffy system [FY1 (Fya), FY2 (Fyb)], in which case they are classified as Class D.	A high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, places the device into Class D. The rule divides blood-grouping devices into two subsets, Class C or D, depending on the nature of the blood group antigen the IVD medical device is designed to detect, and its importance in a transfusion setting.

Examples MDCG 2020-6

Class D

- Device intended for molecular RhD blood group typing, targeting directly the RHD gene alleles that code for the RBC antigens, in blood donors and recipients.
- Anti-K from clone ID, Human IgM Antibody, Blood grouping reagent for transfusion purposes.
- Red blood cell kit with A1, A2, B and O cells used to detect naturally-occurring ABO blood group antibodies in patient and donor samples, in reverse grouping.
- Red blood cell kit with O red blood cells that are homozygous for Rh, Fya, Fyb, Jka and Jkb, antigens, intended to be used as antibody type and screen procedure for transfusion purposes.
- Control red blood cells, consisting of A2B R1R2 (CcD.Ee), Kpos, intended to be used as quality control for use with ABO/Rh(D) grouping assays for transfusion purposes.
- Pre-transfusion ABO compatibility test cards intended to be used at the recipient's bedside as precaution against ABO-incompatible purposes.
- Device used for indirect antiglobulin tests used in the screening and identification of irregular antibodies, crossmatch tests and autocontrols,
- according to the markers listed in rule 2 (otherwise Class C).
- Foetal RhD typing kit.

Class C

- Device intended for HLA typing by Sanger sequencing consisting of reagents for HLA-A, -B, -C, -DRB1, -DQB1 and DPB1, for transplantation purposes.
- Medical device software for high-resolution analysis of HLA sequencing data, for transplantation purposes.
- Anti-k from clone ID, Human IgG Antibody, Blood grouping reagent for transfusion purposes.

Examples IMDRF/IVD WG/N64 FINAL: 2021

HLA, Rhesus system, Duffy system (other Duffy systems except those listed in the rule as Class D are in Class C).

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(a) Devices intended for detecting the presence of, or exposure to, a sexually transmitted agent;	Rule 3a applies to devices detecting agents whose main mode of transmission is sexual. Sexually transmitted infections are a group of infections that may be transmitted through vaginal, oral and anal sexual intercourse. The agents that cause sexually transmitted infections may pass from person to person through blood, semen, vaginal or other bodily fluids.	IVD intended for use in detecting the presence of, or exposure to, a sexually transmitted agent.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.
Examples MDCG 2020-6			
Devices intended for the detection of: » Chlamydia trachomatis; Haemophilus ducreyi; Herpes simplex virus 1&2; Human papilloma virus (HPV); Neisseria gonorrhoeae; Mycoplasma hominis; Mycoplasma genitalium; Trichomonas vaginalis; Treponema pallidum; Ureaplasma urealyticum.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Examples: Sexually transmitted diseases, such as Chlamydia trachomatis, Neisseria gonorrhoeae.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(b) Devices intended for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation;	Rule 3b applies to devices intended for detecting the presence of an infectious agent (either the agent itself or component thereof) e.g. bacterial, viral, fungal, parasitic, protozoal infectious agents, specifically in specimens derived from cerebrospinal fluid or blood. Devices intended for the detection of antibodies against the infectious agent are not covered by this rule. Several factors contribute to the risk of propagation of a pathogen within a population, namely: » the direct or in-direct transmissibility (i.e. the probability of infection when there is contact between a susceptible and an infected individual). This includes for example consideration of the infectious dose and route of transmission e.g. aerosol, zoonosis, vector-mediated. » the contact rate of infected and susceptible individuals (i.e. the number of contacts per time), and the duration of infectiousness. For the purposes of this document, the risk of propagation of a pathogen within a population is considered to be the risk for the general European population. This rule applies to devices independent of the route of transmission or source of the infectious agent. This rule also applies to microbiological media intended for the detection of relevant infectious agents in cerebrospinal fluid or blood specimen.	IVD intended for use in detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.
Examples MDCG 2020-6			
Devices intended for detecting the presence of: » Bacterial pathogens: Streptococcus pneumoniae, Group B Streptococcus, Neisseria meningitidis, Haemophilus influenza type B, Listeria spp., Borrelia burgdorferi, Mycobacterium tuberculosis. » Fungal pathogens: Cryptococcus neoformans, Aspergillus spp. » Viral pathogens: Herpes simplex virus 1&2, human herpes virus 6, varicella zoster virus, enterovirus, West Nile virus, chikungunya, Dengue, Zika, hepatitis A, hepatitis E. » Parasitic pathogen: Toxoplasma gondii. » Prion agents: sporadic Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker Syndrome, Kuru, Fatal Familial Insomnia.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Neisseria meningitidis or Cryptococcus neoformans			

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Rule 3			
(c) Devices intended for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring;	Rule 3c applies to devices intended for detecting the presence of an infectious agent (either the agent itself or component thereof) e.g. bacterial, viral, fungal, parasitic, protozoal infectious agents. Devices intended for the detection of antibodies against the infectious agent are not covered by this rule. This rule does not have any specimen type restrictions and is applicable to specimens being tested from the individual, foetus or embryo. This rule applies if there is a significant risk that an erroneous result would cause death or severe disability. It is the risk of death or severe disability to an individual that must be considered. In this context, the risk of death or severe disability to the individual should take into account that an erroneous result in a healthy individual does not carry the same risk as an erroneous result in (for example) a pregnant, immunocompromised, or vulnerable individual. This rule also applies to an embryo or foetus being tested, or the individual's offspring where an infectious agent can be detrimental to the viability/development of the embryo/foetus leading to death or disability, both current and future e.g. developmental disability.	IVD intended for use in detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested or to the individual`s offspring.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.
Examples MDCG 2020-6			
Devices intended for detecting the presence of: » Bacterial pathogens: Treponema pallidum, Chlamydia trachomatis, Haemophilus influenzae type B meningitis, Neisseria meningitidis, Listeria meningitis (Listeria monocytogenes), Mycobacterium leprae, Mycobacterium spp., Legionella spp., Streptococcus agalactiae, methicillin-resistant Staphylococcus aureus (MRSA) and multi-resistant Enterobacteriaceae (MRE). » Parasitic pathogens: Toxoplasma gondii. » Viral pathogens: Herpes simplex virus 1&2, cytomegalovirus, Rubella, Measles, Poliomyelitis, Parvovirus B19, Zika.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Examples: diagnostic assay for CMV, Chlamydia pneumoniae, Methicillin Resistant Staphylococcus aureus.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(d) Devices intended for pre-natal screening of women in order to determine their immune status towards transmissible agents;	Rule 3d applies to devices specifically intended to screen pregnant women for their immune status towards transmissible agents. These are in particular transmissible agents that may cause infections in the embryo and foetus. The term 'immune status' refers to the presence, absence or level of an immune response acquired by the women following an infection or vaccination. Devices covered by this rule are intended for the screening of pregnant women before birth in order to identify the presence of an acquired appropriately targeted immune response to transmissible agents. The absence of such acquired maternal protection is associated with an enhanced risk of transmission of the agent to the embryo/foetus upon infection of the mother. These mothers may be recommended to take preventive measures.	IVD intended for use in pre-natal screening of women in order to determine their immune status towards transmissible agents.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.
Examples MDCG 2020-6			
Devices intended to determine for prenatal screening the immune status of women towards: » Cytomegalovirus; Rubella virus; Toxoplasma gondii; Varicella zoster virus; Zika; Parvovirus B19.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Examples: Immune status tests for Rubella or Toxoplasmosis.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(e) Devices intended for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;	Rule 3e applies to devices for both the determination of the infective disease status and the determination of the immune status of a patient '**Determination of infective disease status'** The determination of the infective disease status provides information on the state, condition or evolution of a disease caused by an infective agent, which may include the effectiveness of a specific treatment. In this context, the determination of the infective disease status typically involves the measurement of infective agents, antibodies to infective agents, surrogate markers or analytes in specimens from patients. '**Determination of immune status'** The determination of the immune status provides information on the state or condition or evolution of the immune response acquired by the patient in relation to infection with a pathogenic agent, vaccinations, allergic, immunotoxic, autoimmune and alloimmune reactions such as transfusion reactions and transplant rejection reactions.	IVD intended for use in determining infective disease status or immune status, and where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation or severe disability for the patient or for the patient`s offspring.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.
Examples MDCG 2020-6			
Devices intended to determine: » Salmonella typhi in faeces, for the assessment of the carrier-status of patients. » Antibodies from lymphocyte secretions immunoassay intended for the detection of active Mycobacterium tuberculosis infection. » Quantitative virus-specific NAT tests (e.g. Cytomegalovirus, John Cunningham virus, Adenovirus, Enterovirus) to monitor an immunocompromised patient's (e.g. transplant patient) response to antiviral therapy. » Methicillin-resistant Staphylococcus aureus and Staphylococcus aureus specific polymerase chain reaction assay for pre-surgical screening of patients to determine nasal carriage. » Assays intended for the detection of IgM antibodies against rubella virus to identify an acute infection in pregnant women in order to determine whether specific treatment is necessary for protecting the foetus from virus-induced damage due to a lack of previously acquired immunity. » Assays intended for the detection of IgM antibodies against HEV. » Enzyme immunoassay intended for the quantitation of intrathecal antibodies against rubella virus in the diagnosis of rubella virus-induced encephalitis. » Assays intended for the detection of antibodies in the recipient to potentially pathogenic viruses (e.g. anti-cytomegalovirus, anti-herpes simplex virus antibodies) to determine latent disease status of viral infection prior to organ or bone marrow transplantation. » Screening assays comprising allergy panels, such as Multiple Allergen Simultaneous Tests (MAST), intended to detect IgE antibodies against several specific allergens that may lead to anaphylaxis, e.g. certain nutritional allergens or hymenoptera venom allergens. False-negative results with such MAST assays could increase the risk that the patient is not adequately managed for the occurrence of a life-threatening anaphylactic event. » Assays intended for the detection of alloantibodies in the recipient associated with transplant rejection reactions, such as antibodies against angiotensin II receptors type 1 (anti-AT1R) and against endothelin receptors type A (anti-ETAR). » Interferon-Gamma Release Assays (IGRA)for Mycobacterium tuberculosis.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Examples: Enteroviruses, CMV and HSV in transplant patients.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(f) Devices intended to be used as companion diagnostics;	Rule 3f applies to devices intended to be used as companion diagnostics. 'Companion diagnostic' (CDx) is defined in Article 2(7) as a device which is essential for the safe and effective use of a corresponding medicinal product to: a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product. The identification of patients may comprise a quantitative or qualitative determination of specific markers. Such specific markers can be present in healthy subjects and/or in patients. The emphasis 'before and/or during treatment' implies that CDxs may be intended to be applied before a treatment with a corresponding medicinal product is initiated, or during treatment, to identify if (still) the patient is (a) likely to benefit from the corresponding medicinal product or (b) likely to be at increased risk of serious adverse reactions. Devices that are intended to be used for monitoring treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be CDxs.	IVD intended for use in screening for selection of patients for selective therapy and management as companion diagnostics.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

Examples MDCG 2020-6

- CDx assay intended for the qualitative detection of the anaplastic lymphoma kinase protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung carcinoma (NSCLC) tissue, and is indicated as an aid in identifying patients eligible for treatment with crizotinib or ceritinib.
- CDx assay intended for the quantitative detection of BCR-ABL1 transcripts and the ABL1 endogenous control mRNA in peripheral blood specimens from patients previously diagnosed with t(9:22) positive chronic myeloid leukemia, intended to measure BCR-ABL mRNA transcript levels during monitoring of treatment with nilotinib.
- CDx qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, intended for use in the detection of PD-L1 protein in FFPE NSCLC and gastric or gastroesophageal junction (GEJ) adenocarcinoma tissues and is indicated as an aid in identifying patients for treatment with pembrolizumab.
- CDx in-vitro PCR assay for the qualitative detection of single nucleotide variants coding isocitrate dehydrogenase-2 (IDH2) mutations in DNA extracted from human blood or bone marrow and is indicated as an aid in identifying acute myeloid leukemia patients with an IDH2 mutation for treatment with enasidenib.
- CDx intended for the demonstration of carriers of two copies of non-functional DPYD variant DPYD*2A, that typically have complete dihydropyrimidine dehydrogenase (DPD) deficiency. The DPYD gene encodes DPD, an enzyme that catalyzes the rate-limiting step in fluorouracil metabolism. Capecitabine, a chemotherapy agent used in the treatment of colon cancer, metastatic colorectal cancer, and metastatic breast cancer, is a prodrug that is enzymatically converted to its active form, fluorouracil. Individuals who are carriers of non-functional DPYD variants, may not be able to metabolise capecitabine at normal rates, and are at risk of potentially life-threatening capecitabine toxicity, such as bone marrow suppression and neurotoxicity.

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Rule 3			
(g) Devices intended to be used for disease staging, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;	Rule 3g applies to devices where the intended purpose is for the staging of a disease. Disease staging involves the determination of distinct phases or periods in the course of a disease, or the level of severity of a disease that can be assessed by, for example, the life history of an individual, organism, markers or any biological or physiological process. The purpose of disease staging is to provide information with respect to patient management, the appropriateness and accuracy of treatment decisions, and/or for prognosis or prediction. For the majority of diseases, determination of disease stage involves taking into account the complete clinical picture which may involve investigative procedures, examining the patient/patient history and measurement of markers or analytes in patient specimens. This rule applies to devices where the information provided from the device is intended to be used for disease staging and where the patient management decision, being solely or principally based on an erroneous result, has the potential to result in a life-threatening situation. This rule does not include: » Devices for the staging of cancer as these devices are classified under rule 3h. » Devices where the result is not intended to be used for staging a particular disease e.g. markers which are indicative of the presence of an affected health condition in general.	Not available	Not available
Examples MDCG 2020-6			
» Device intended for the quantitative measurement of Brain type natriuretic peptide (BNP) in whole blood or plasma samples, for the assessment of the severity of congestive heart failure. » Devices intended for staging of enhanced liver fibrosis (ELF) for detecting the following markers: hyaluronic acid, procollagen III amino terminal peptide, tissue inhibitor or metalloproteinase. » Medical device software intended to generate an estimated glomerular filtration rate (eGFR) or albumin creatinine ratio (ACR) for staging acute kidney injury (AKI). » Medical device software intended to generate an enhanced liver fibrosis (ELF) score which correlates to the level of fibrosis. » Medical device software intended to generate a model for end stage liver disease (MELD) score.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(h) Devices intended to be used in screening, diagnosis, or staging of cancer;	Rule 3h applies to devices with the specific intended purpose to be used in screening, diagnosis or staging of cancer. Cancer is a generic term for a large group of diseases characterised by the growth of abnormal cells which can invade nearby tissues and may spread to other parts of the body through the blood and lymph systems. Other common terms used are 'malignant tumours' and 'malignant neoplasms'. The scope of this rule is limited to cancer. Two distinct cases should be considered: 1. Cancer is a term for diseases (including malignant neoplasia or malignant tumours) characterised by abnormal cells which divide without control and invade nearby tissues. Additionally, these cells can also spread to other parts of the body through the blood and lymph systems, in the process that leads to the development of secondary tumours or metastases. Many cancers form solid tumours, which are masses of tissue. Cancers of the blood, such as leukaemia, generally do not form solid tumours. 2. Cells may present hyperplasia (increased density of cells) and dysplasia (abnormal appearance) or form a carcinoma in situ (no invasion of nearby tissues). These precancerous or premalignant cells may or may not develop into cancer. This rule applies to devices for both cancerous and precancerous conditions, where the devices are intended to be used in screening, diagnosis, or staging of cancer. Disease staging involves the determination of distinct phases or periods in the course of a disease, or level of severity of a disease that can be assessed by, for example, the life history of an individual, organism, markers or any biological or physiological process. The purpose of disease staging is to provide information with respect to patient management, the appropriateness and accuracy of treatment decisions, and/or for prognosis or prediction. Non-malignant neoplasms or non-malignant tumours do not spread into, or invade, nearby tissues. Therefore, they do not fulfil the criteria of cancer. These benign tumours may grow larger, and the growth tends to be slow. Devices that are intended to be used in screening, diagnosis, or staging of cancer, may have the following functions: screening, patient management, monitoring, diagnosis or aid to diagnosis, prognosis and prediction	IVD intended for use in screening, diagnosis or staging of cancer.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

Examples MDCG 2020-6

- A faecal occult blood screening test (FOBT) or faecal immunochemical test (FIT) specifically intended to be used in colon cancer screening.
- A device intended for the quantitative/qualitative determination of IgG antibodies to Helicobacter pylori in human blood samples specifically intended to be used in gastric cancer screening.
- Papanicolaou (Pap) stain automated cervical cytology screening system, intended to process Pap cervical cytology slides and classify the cervical specimen as either normal or abnormal.
- A qualitative real-time PCR test intended for the detection of high-risk genotypes of Human Papillomaviruses for use in cervical cancer screening.
- Immunohistochemistry assay intended for the detection of c-KIT or CD117 tyrosine kinase receptor expression in normal and neoplastic formalinfixed, paraffin-embedded tissues for histological evaluation, and gene mutation testing for KIT and platelet-derived growth factor receptor alpha in (familial) gastro-intestinale stromale tumor.
- Assay for the quantitative determination of the cancer associated antigen CA 125 (celomic epithelium-related glycoprotein associated with epithelial ovarian cancer) in serum.
- Immunohistochemistry assay intended to detect progesterone receptor in breast tumours to be used as an aid in the management, prognosis, and prediction of therapy outcome of breast carcinoma.
- Fluorescence insitu hybridisation (FISH) panels intended for the diagnosis of e.g. lymphoma, multiple myeloma and leukaemia.
- Targeted next generation sequencing test intended to be used in (haemato)-oncology, to detect acquired somatic mutations in DNA isolated from formalin-fixed paraffin embedded (FFPE) tumour tissue specimens.
- BRCA1 device intended for the detection of deletions or duplications in the human BRCA1 gene in order to confirm a potential cause and clinical diagnosis for hereditary breast and ovarian cancer and for molecular genetic testing of at-risk family members.
- Device applied in testing services intended for the analysis of 35 genes relevant to digestive tract tumours (various forms of colorectal cancer, stomach cancer and pancreatic cancer), breast cancer, ovarian cancer, skin cancer, thyroid tumours, and endocrine tumours (panel), intended to provide information on whether an individual carries genetic alterations that favour the onset of specific tumour diseases, identifying these genetic predispositions.
- Circulating Tumour Cell Kit (Epithelial) intended for the enumeration of circulating tumour cells (CTC) of epithelial origin in whole blood. The test is to be used as an aid in the monitoring of patients with metastatic breast, colorectal or prostate cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring metastatic breast, colorectal and prostate cancer, to allow assessment of patient prognosis and is predictive of progression free survival and overall survival.
- Breast carcinoma cell line (SK-BR-3) CTC Cell Control Kit intended as an assay control to ensure that the sample detection and identification systems are performing when using the CTC Kit. They express epithelial cell markers recognised by the antibodies in the Circulating Tumour Cell Kit and are used as a control for the performance of the assay.
- An image analysis medical device software intended to aid in the detection and semi-quantitative measurement of programmed death ligand 1 (PDL1) protein in FFPE lung tissue. The algorithm is an adjunctive computer-assisted methodology for a qualified pathologist in the acquisition and measurement of images from microscope glass slides of FFPE patient lung tissue stained for the presence of PD-L1 protein using an associated PDL1 Assay. It scans digitised images of tissue specimens stained with the associated PD-L1 assay and provides raw numbers (scores) for immune cells and tumour cells counts in the specimen, along with a percent positivity score.

Examples IMDRF/IVD WG/N64 FINAL: 2021

Examples: PSA, CEA, and CA 125.

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(i) Devices intended for human genetic testing;	Rule 3i applies to devices for human genetic testing. Genetic testing involves the detection of specific alleles, mutations, genotypes, karyotypes or epigenetic changes that are associated with heritable traits, diseases or predispositions to disease for the individual or their descendants. Several methods can be used for genetic testing (for example): » Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify its constitution, or variations or mutations that lead to a genetic disorder. » Chromosomal genetic tests analyse whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome which causes a genetic condition. The results of a genetic test can provide a medical status, confirm or rule out a suspected genetic condition or determine a person's chance of developing or passing on a genetic disorder. Some examples include devices intended for: » Newborn Screening: Newborn screening is used just after birth to identify genetic disorders, to detect potentially fatal or disabling conditions. Such early detection allows treatment to begin immediately, which can reduce or eliminate the effects of the condition. » Diagnostic testing: Diagnostic testing is used to identify or rule out a specific genetic or chromosomal condition. » Carrier testing: Carrier testing is used to identify people who carry one copy of a gene mutation that could result in a genetic disorder in one's offspring. For some genetic disorders, two copies of the gene mutation are required to cause the genetic disorder (autosomal recessive). Whereas for others, one copy of the gene mutation is required either i) in the absence of a second normal copy resulting in the genetic disorder (X-Linked recessive) or ii) in the presence of a normal copy can result in a genetic disorder (autosomal dominant). This type of testing provides information about a couple's risk of having a child with a genetic condition. » Prenatal testing: Prenatal testing is used to detect changes in a foetus's genes or chromosomes before birth.	IVD intended for use in screening, diagnosis or staging of cancer.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
	(Continued) » Preimplantation testing: Preimplantation testing, also called preimplantation genetic diagnosis (PGD), is a specialised technique used to detect genetic changes in embryos obtained through in vitro fertilisation. Predictive and presymptomatic testing: Predictive and presymptomatic types of testing are used to detect gene mutations associated with disorders that appear after birth, often later in life. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis. Presymptomatic testing can determine whether a person will develop a late-onset genetic disorder. » Direct-to-Consumer (DTC) genetic testing: genetic testing provided through advertising and selling or (free) provision of genetic tests directly to consumers.		
Examples MDCG 2020-6			
Genetic testing may include devices intended to detect : » Chromosomal conditions e.g. trisomy 21, trisomy 18, XXX syndrome. » Abnormalities in genes associated with thrombophilia e.g. genes which code for factor V and prothrombin. » Hereditary cancer syndromes e.g. hereditary breast/ovarian cancer (BRCA1/BRCA2 genes). » Genetic risk Factors e.g. rheumatoid arthritis HLA DRB1, ankylosing spondylitis HLA B27, osteo-arthritis, pre-senilin mutation. » Monogenetic disorders e.g. hemochromatosis, Huntington's disease, Tay Sacs, cystic fibrosis. » Pharmacogenomic tests e.g. CYP liver enzymes CYP2C9 and CYP2C19. » Preimplantation genetic diagnosis. » XY disorders e.g. haemophilia, Duchenes muscular dystrophy, Fragile X.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Examples: Huntington's Disease, Cystic Fibrosis.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(j) Devices intended for monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring;	Rule 3j applies to devices intended to monitor an analyte with the purpose of adjusting patient management, such as treatments/ interventions, as required i.e. it is intended to be used for observing, checking, or keeping a record of the level, activity, presence, absence etc. of an analyte. Monitoring tests may be intended to evaluate an individual's current state and/or changes in an individual's state. This is likely to be achieved by repeated or multiple determinations of an analyte over time, at appropriate intervals. These devices are intended to determine whether results are within expectation, for the detection/assessment of disease progression/regression, disease recurrence, minimum residual disease, response/resistance to therapy, and/or adverse effects due to therapy. This rule does not apply to devices intended to be used in the diagnosis or screening of a condition where only a single measurement is required for this purpose, but would apply to diagnostic tests where multiple/ serial measurements over time are intended to be used and where an erroneous result may result in a life threatening situation for the patient or their offspring e.g. when monitoring the change in concentration of a biological compound over time to aid diagnosis, such as with troponin to help determine an acute cardiac event. Rule 3j is also applicable to the monitoring of non-life threatening conditions. It covers a wide range of analytes where the device provides an important, critical, or sole determinant for the correct patient management decision and an erroneous result may result in the life of the patient or patient's offspring being at risk due to inappropriate treatment decisions. Analytes measured by devices intended for monitoring may be medicinal products (Article 1(2) of Directive 2001/83/EC, as amended), substances (drug, chemical, or biological entity/component) or biological components (pertaining to living organisms, or components of a living organism – this would include for example: antibodies, endogenous markers, platelets, cord blood, bone marrow, stem cells etc). If the device is intended for a specific intended target population (e.g. paediatrics, pregnant women, immunocompromised individuals, etc.) then the risk to this population should be taken into account when determining if there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or their offspring. With respect to the patient's offspring, the viability/development of the embryo/foetus, both current and future shall be taken into account.	IVD intended for use to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient or for the patient`s offspring.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

Examples MDCG 2020-6

Devices intended for monitoring:

- Cardiac marker for acute presenting patients: Troponin I, Troponin T, CKMB (when intended for monitoring cardiac muscle injury).
- Cortisol levels monitoring e.g. for patients with cortisol insufficiency.
- PT/APTT when used to assess major bleeds in acute presentations or patients with acute coagulopathy or for coumadin monitoring in patients without diagnosed coagulation disorder.
- Lithium for patients being treated for bipolar disorders.
- Methotrexate when used for treating non-life threatening conditions such as vasculitis, rheumatoid arthritis and psoriatic arthritis).
- Immunosuppressive (anti-rejection) medicinal products e.g. cyclosporine, sirolimus, tacrolimus.
- Antibiotic where under/over treatment can have a serious impact on individual or offspring e.g gentamicin.
- Anti-RhD antibody levels in pregnant women given additional Anti-D.
- Blood amylase e.g. acute pancreatitis, perforated peptic ulcer, acute biliary obstruction.
- Acute phase reactants e.g. C- reactive protein (CRP), procalcitonin when intended to be used to monitor infection response to therapy for life threatening conditions such as sepsis, necrotizing skin or tissue conditions, infective endocarditis, bacterial meningitis etc.
- Full blood count when used for monitoring for the development of a life threatening haematological disorder in patients being treated for other disorders/conditions, where this risk exists e.g. monitoring of patients with a diagnosis of schizophrenia for neutropenia/agranulocytosis.
- Bilirubin in response to treatment of neonatal jaundice.

Examples IMDRF/IVD WG/N64 FINAL: 2021

Examples: Troponin, Cyclosporin, Prothrombin time testing.

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(k) Devices intended for management of patients suffering from a life-threatening disease or condition;	Rule 3k applies to devices intended for patients diagnosed with life-threatening diseases or conditions. The device provides an important, critical, or sole determinant for the correct patient management decision, and provides information for the purpose of patient management, such as treatments/interventions, as required. The classification of these devices is primarily based on the life-threatening nature of the disease or condition and the impact of the provided information on patient management (e.g. determining an initial course of therapy or erroneous decision resulting in life-threatening harm to the patient). This includes devices intended to detect drug resistant pathogens associated with a life-threatening condition (e.g. sepsis, necrosing skin or tissue condition) directly from collected specimen such as blood, skin or tissues, in order to take a patient management decision. However, rule 3k does not apply to devices used in conjunction with microbiological culture methods that are only intended to test drug resistance of an already detected pathogen including drug sensitivity testing such as sensitivity discs and tablets or Minimum Inhibitory Concentration (MIC) panels, where such devices are not intended for the management of patients suffering from a life-threatening infection.	IVD intended for use in the management of patients suffering from a life-threatening disease or condition.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.

Examples MDCG 2020-6

Devices intended for:

- Enumeration of CD4 T lymphocytes in HIV infected patients to initiate treatment and ascertain the anti-viral therapy response.
- Measurement of D-Dimers in patients with thrombotic disorders.
- Laboratory risk score calculator indicator for necrotising fasciitis in necrotising soft tissue infections.
- HbA1c and blood glucose tests for the management of patients with diabetes.
- Monitoring anticoagulant therapy e.g. prothrombin Time/INR (warfarin), APTT (unfractionated heparin), anti-Xa chromogenic assays (low molecular weight heparin (LMWH), fondaparinux, rivaroxaban, and apixaban), anti-IIa chromogenic and clot-based assays (argatroban, bivalirudin, hirudin, and dabigatran).
- Digoxin monitoring.
- Anti-retroviral resistance testing in HIV infected patients.

Examples IMDRF/IVD WG/N64 FINAL: 2021

Examples: HBV monitoring marker, HCV viral load, HIV Viral Load and HIV and HCV geno- and subtyping.

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(l) Devices intended for screening for congenital disorders in the embryo or foetus;	Rule 3l applies to devices for routine screening of embryo/foetus, and also specific screening for embryo/foetus whose families have known inherited conditions or where specific populations are at greater risk of an inherited condition e.g. Sickle cell. Rule 3i also applies to preimplantation and genetic screening tests.	IVD intended for use in screening for congenital disorders in the foetus or embryo.	Devices in this Class present a moderate public health risk, or a high individual risk, where an erroneous result would put the patient in an imminent life-threatening situation, or would have a major negative impact on outcome. The devices provide the critical, or sole, determinant for the correct diagnosis and monitoring. They may also present a high individual risk because of the stress and anxiety resulting from the information and the nature of the possible follow-up measures.
Examples MDCG 2020-6			
» Devices intended for screening of foetal aneuploidies (e.g. trisomy 13, trisomy 18 and trisomy 21), which include devices intended for the measurement of biochemical maternal serum markers. » Reagents and medical device software evaluating the risk of foetal aneuploidies based on biochemical markers and other information, in particular non-invasive prenatal tests (NIPT). » Devices intended to determine the foetal sex in cell-free foetal DNA in maternal blood, in the remit of sex-depending congenital disorders. » Genetic test for cystic fibrosis. » Genetic test for sickle cell disease. » Huntington's chorea. » Tay Sachs. » Thalassaemia and other haemoglobin disorders.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Examples: Spina Bifida, Down Syndrome, Glucose-6-Phosphate Dehydrogenase Deficiency, and Tay-Sachs disease.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 3			
(m) Devices intended for screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities.	Rule 3m applies to devices intended for screening new born babies for a defect which is present from birth i.e. a structural or functional abnormalities, including metabolic disorders, where an erroneous result could lead to a failure to detect and treat such birth disorders, which could lead to a lifethreatening situation or severe disability of the individual. This includes genetic testing where the intended purpose covers screening for congenital disorders in neonates. This rule applies to devices intended to be used for screening new-born babies shortly after birth for disorders that are treatable, but not clinically evident in the new-born period. Some of the conditions included in new-born screening are only detectable after irreversible damage has been done. New-born babies who screen positive undergo further testing to confirm whether they are affected with a congenital disorder. For these confirmatory and supplemental devices, and for congenital disorders that are clinically evident, in particular rules 3j and 3k shall be taken into consideration.	IVD intended for use in screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities.	See above

Examples MDCG 2020-6

Examples of devices intended for screening in new-born babies for congenital disorders:

- Beta-thalassaemia; Biotinidase deficiency;
- Congenital adrenal hyperplasia – e.g 17-hydroxyprogesterone (17-OHP).
- Congenital hypothyroidism – e.g thyroxine.
- Cystic fibrosis – e.g. mutation and variant screening, immunoreactive trypsin.
- Galactosaemia – e.g. total galactose or galactose-1-phosphate uridyltransferase.
- Glutaric aciduria type 1.
- Hyperphenylalaninaemia / phenylketonuria e.g phenylalanine (in blood); phenylpyruvic, phenyllactic, 2-OH phenylacetic (in urine).
- Homocystineuria (pyridoxine unresponsive) e.g. free homocystine, total homocysteine, and methionine (in blood and urine).
- Isovaleric acidaemia.
- Maple syrup disease (MSUD IA, IB, II) - e.g. branched-chain amino acids, allo isoleucine (in blood); branched-chain 2-ketoacids, branched-chain 2- hydroxy acids (in urine).
- Medium-chain acyl-CoA dehydrogenase deficiency – e.g. acylcarnitine measurement.
- Methylmalonic aciduria including cblA, cblB, cblC and cblD.
- Propionic aciduria.
- N-Acetylglutamate synthase deficiency – e.g. glutamine, alanine, citrulline, arginine (in blood).
- Sickle-cell disease.
- Tyrosinemia (I, II, III) – e.g. tyrosine (in blood); succinylacetone, 4-OH phenylpyruvic, 4-OH phenyllactic (in urine).
- Severe combined immunodeficiency (SCID) e.g. by TREC/KREC determination.

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 4			
(a) Devices intended for self-testing are classified as class C, except for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine, which are classified as class B.	Rule 4a applies to devices intended for self-testing. All devices intended for self-testing are classified as class C, except: » devices for the detection of pregnancy, for fertility, and for determining cholesterol level (in any specimen) and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine. » those classified in class D according to Annex VIII implementing rule 1.9 (e.g. HIV self-tests). If a device simultaneously detects a marker that falls under this rule as a class C in addition to a marker listed as an exception (Class B), then the device is classified in class C according to the implementing rule 1.9.	IVD medical devices intended for use by lay users (such as for self-testing or nearpatient testing) are classified as Class C, except: those devices from which the result is not determining a critical situation, in which case they are classified under Class B, and those devices which are classified under Class D by Rule 1 and/or Rule 2.	In general, these devices may be used by lay user.
Examples MDCG 2020-6			
» Devices for self-testing of blood sugar are in Class C. » Self-testing devices for blood clotting, e.g. measurement of International Normalised Ratio (INR) are in Class C.			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Example for self-testing class C: Blood glucose monitoring. Example for self-testing class B: Pregnancy self-test, fertility testing, and urine test strips.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 4			
(b) Devices intended for near-patient testing are classified in their own right.	Rule 4b applies to devices intended for near-patient testing. The classification of devices for near-patient testing follows the intended purpose of the device, as established by the manufacturer. This brings the classification of devices for near-patient testing in line with that of other devices intended for professional use. The manufacturer should check all the rules to determine the correct device classification.	Not available	Not available
Examples MDCG 2020-6			
For the below examples, the device is intended for near-patient testing: » Class D (under Rule 1): Rapid test for detection of human immunodeficiency virus. » Class D (under Rule 2): Pre-transfusion ABO compatibility test cards intended to be used at the recipients' bedside as precaution against ABO incompatible transfusion. » Class C (under Rule 3): Blood glucose reagents / strips for patient monitoring. » Class C (under Rule 3): Mobile cardiac marker monitoring test for acute presenting patients: Troponin I, Troponin T, CKMB (when intended to be used for monitoring cardiac muscle injury). » Class C (under Rule 3): Rapid test for the detection of methicillin-resistant Staphylococcus aureus. » Class B (under Rule 6): Urine dipstick to determine urinary tract infection at point of care. » Class B (under Rule 6): Quantitative test for haemoglobin as an aid in diagnosing iron deficiency. » Class B (See Rule 6): Rapid tests for the detection of Group A Strep, Respiratory Syncytial Virus, and Influenza virus(es).			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 5			
(a) The following devices are classified as class A: products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination;	Rule 5a applies to general laboratory products like pipettes, stain powders, glass microscope slides, centrifuges, pipette tips or instrument liquid collection containers, buffers which usually do not fall under the definition of an IVD medical device. However, as specified in Regulation (EU) 2017/746 Article 1 (3a) 'This regulation does not apply to (a) products for general laboratory use (...), unless such products, in view (...) are specifically intended by their manufacturer to be used for in vitro diagnostic examinations.' As a consequence, if such products are specifically intended by the manufacturer to be used for in vitro diagnostic examinations, then they are considered as IVDs and are captured by rule 5. ‚Accessory for an in vitro diagnostic medical device' as defined under Regulation (EU) 2017/746 article 2 (4), 'means an article which, whilst not being itself an in vitro diagnostic medical device, is intended by its manufacturer to be used together with one or several particular in vitro diagnostic medical device(s) to specifically enable the in vitro diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the in vitro diagnostic medical device(s) in terms of its/their intended purpose(s)'. Whilst not being an IVD in themselves, accessories are to be used in conjunction with a specific IVD. They possess one or more specific characteristics to specifically enable an IVD to be used in accordance with its intended purpose or to assist the medical functionality of the IVD. Accessories are mentioned in rule 5 (a) in combination with the attribute 'accessories which possess no critical characteristics'. This emphasizes that such products can negatively influence the benefit-risk ratio of the entire in vitro diagnostic medical device.	Reagents or other articles, which possess no critical characteristics intended by the manufacturer to make them suitable for in vitro diagnostic procedures related to a specific examination;	these devices present a low individual risk and no or minimal public health risk.
Examples MDCG 2020-6			
» General microbiological culture media containing selecting agents, antimicrobial chromogenic agents, chemical indicators for colour differentiation. » Solutions like cleaners, buffer solutions, lysing solutions, diluents specified for use with an IVD. » Pipette with a specific fixed one volume specifically intended for a particular IVD test with specified human sample, e.g. blood coagulation pipettes with automatic timing (Accessory of coagulometer). » General staining reagents like hematoxylin, eosin, pap and grams iodine; Kits for Isolation and purification of nucleic acids from human specimens; Library Prep reagents for preparation of DNA for downstream analysis by NGS sequencing; Nucleic acid quantitation kits. » General reagents (not assay specific) used with a Class A instrument, e.g. general sequencing consumable reagents used with a sequencer.			
Examples MDCG 2020-6			
General culture media (excluding the dehydrated powders which are considered not to be a finished IVD medical device), wash solutions, plain urine cup, clinical chemistry analysers, and microbiological specimen collection devices.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 5			
(b) The following devices are classified as class A: instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures;	Rule 5b applies to instruments specifically intended by the manufacturer for in vitro diagnostic procedures. These instruments are classified as class A, whereas reagents and kits are classified in their own right. Due to their interdependence, the performance of the reagent on this instrument will be part of the conformity assessment of the reagent. If the instrument has an independent measuring function which does not use any additional reagents, it is classified according to the intended purpose of the analysis (including instruments controls or instrument quality control). e.g. cell counting analysers used in haematology, ion selective electrodes, instruments measuring blood gases or glucose via its sensors, specific gravity measurements in urine analysis, mass spectrophotometer for bacteria identification, etc.	Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures.	these devices present a low individual risk and no or minimal public health risk.
Examples MDCG 2020-6			
» Enzyme immunoassay analyser, PCR thermocycler, sequencer for NGS applications, clinical chemistry analyser. » Instrument for automated purification of nucleic acids and PCR set-up. » Erythrocyte sedimentation rate analyser.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
(c) The following devices are classified as class A: specimen receptacles.	Not available	Specimen receptacles.	Not available
Examples MDCG 2020-6			
Specimen containers or evacuated or non-evacuated tubes, empty or prefilled with a fixative solution or other general reagent to preserve the condition, stimulation, transport, storage and collection of biological specimens (e.g. cells, tissues specimens, urine, faeces) for the purpose of in vitro diagnostic examinations.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 6			
Devices not covered by the above-mentioned classification rules are classified as class B.	Rule 6 applies to devices not covered by rules 1-5. An erroneous result with these devices is unlikely to have a significant negative impact on patient outcome, cause death or severe disability or put the individual in immediate danger. Depending on the intended purpose, this rule would likely capture clinical chemistry tests for hormones, vitamins, enzymes, metabolic markers, electrolytes and substrates as well as the majority of anatomic pathology immunohistochemical assays. It also includes IVDs that detect infectious agents that present a moderate risk to the individual and are not easily propagated.	IVD medical devices not covered in Rules 1 through 5 are classified as Class B.	These devices present a moderate individual risk as they are not likely to lead to an erroneous result that would cause death or severe disability, have a major negative impact on patient outcome or put the individual in immediate danger. The devices give results that are usually one of several determinants. If the test result is the sole determinant, but other information is available, such as presenting signs and symptoms or other clinical information, which may guide a physician, classification into Class B may be justified. Other appropriate controls may also be in place to validate the results. This Class also includes those devices that present a low public health risk because they detect infectious agents that are not easily propagated in a population.
Examples MDCG 2020-6			
» Device intended to detect and measure magnesium to assess electrolyte / magnesium homeostasis. » Test intended to detect and measure C-reactive protein or calprotectin to detect systemic inflammatory processes due to an active disease. » Biochemical test for establishing the identification of microbiological culture isolates or for determining antimicrobial susceptibility of microbiological culture isolates except those permitting identification or determination of MIC associated with a life threatening condition. » Test to detect Helicobacter pylori, Clostridium difficile, adenovirus, rotavirus and Giardia lamblia. » Non-typhoidal anti-salmonella antibodies to detect the exposure to an infectious agent. » FSH device for fertility testing in blood. » Device intended for the detection of Candida albicans. » Device intended for the detection of or exposure to Entamoeba histolytica. » Device intended for the detection of Sarcoptes scabiei (genital scabies). » Assay intended for the detection of autoantibodies (e.g. anti-sm/RNP and anti-SSA/Ro) associated with systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibodies [ANCAs] in systemic vasculitis), anti-aquaporin-4 antibodies (anti-AQP4) in neuromyelitis optica spectrum disorders (NMOSDs) or organ-specific autoimmune diseases (e.g. anti-Insulin antibodies in insulin-dependent diabetes).		
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Blood gases, H. pylori test, physiological markers such as hormones, vitamins, and enzymes, metabolic markers, specific IgE assays and celiac disease markers, and tests for anti-nuclear antibody, sex hormone-binding globulin (SHBG), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine and HbA1c.			

(EU) 2017/746 Annex VIII (IVDR)	Rationale MDCG 2020-16	IMDRF/IVD WG/N64 FINAL: 2021	Rationale (IMDRF)
Rule 7			
Devices which are controls without a quantitative or qualitative assigned value are classified as class B.	Rule 7 applies to controls which are described as un-assayed where control values are assigned by the user and not the manufacturer. The manufacturer may indicate whether a specific analyte is present or absent in these controls without indicating expected assay results. Controls with quantitative or qualitative assigned values are classified according to implementing rule 1.6. As a reminder, and according to Article 1 paragraph 3(c) and 3(d), "internationally certified reference material" and "materials used for external quality assessment schemes" are not IVDs.	IVD medical devices that are controls without a quantitative or qualitative assigned value will be classified as Class B.	For such controls, the qualitative or quantitative value is assigned by the user and not the manufacturer.
Examples MDCG 2020-6			
» Unassigned control sera. » Control materials used to verify the migration of immunochromatographic assays. » Unassigned QC Material as a heterozygous quality control to monitor analytical performance of the extraction, amplification and detection. » Non-assay specific control plasmas for use in coagulation. » Non-assay specific control serum containing multiple biochemical analytes. » A DNA or RNA probe supplied for use as a non-assay specific normal control for in situ hybridisation (ISH).			
Examples IMDRF/IVD WG/N64 FINAL: 2021			
Urinalysis controls and chemistry controls.			