# Is the IVD Regulation Framework ready for Class D Devices?

## Executive Summary

Under the IVD Regulation (EU) 2017/746 ('IVDR'), Class D devices rely on a complex conformity assessment infrastructure involving not only a notified body but also an EU reference laboratory, the uploading of specific information to the EUDAMED database and – for novel devices in the absence of common specifications – additional assessment by an Expert Panel.

Moreover, the EU's implementation of the IVDR has ground to a halt in the wake of the COVID-19 outbreak. The status of this transition, and the challenges it poses to all players in the IVD sector, has been discussed in a MedTech Europe position paper *published* in July 2020.[1]

With the below paper, MedTech Europe aims to identify and raise awareness of those devices that are currently self-declared under IVD Directive and will become Class D under the IVDR. These devices are especially vulnerable to the IVDR transition period, because they cannot benefit from the so-called "grace period" that extends to 27 May 2024.[2] For the purpose of this paper, these devices are referred to as 'high-risk devices'. The full range of Class D infrastructure is needed well in advance of the date of application so that these IVDs can complete their IVDR certification before 26 May 2022. These include devices which are of critical importance to healthcare systems, e.g., because they are needed to screen the European blood supply, check cells and organs for transplantation or manage infectious disease outbreaks such as COVID-19 (SARS-CoV-2).

While it already takes around 12 months today to complete a dossier and certify a high-risk device under the IVD Directive, it is reasonable to assume this process will take much longer under the IVDR, given that it is new and much more complex. These high-risk devices (Class D without grace period) will need to have successfully completed their IVDR certification in just over a year and a half from now. Therefore, they heavily depend on timely availability of the full IVDR regulatory infrastructure. However, the specific Class D conformity assessment infrastructure is limited or missing.

From a public health perspective, it is critical that high-risk tests remain seamlessly available to European healthcare systems, without the need to rely on national or European derogations (ref. IVDR Article 54), or for Europe's laboratories to address gaps in supply by creating in-house assays (ref. IVDR Article 5(5)).

**MedTech Europe therefore asks for an urgent discussion to take place with the relevant parties, including the European Commission, National Competent Authorities and interested stakeholders in order to**

[1] MedTech Europe's position paper *"Ensuring a successful transition to the new IVD Regulation in light of COVID-19"*
[2] The grace period allows certain existing devices to transition to the new Regulations later than other devices, by virtue of a valid CE marking under the current Directive.

**identify *actions to smoothly transition* these devices to the IVDR and safeguard continued access to these high-risk IVD devices.**

## Scope

This document seeks to identify and bring forward as a topic for discussion, those devices that are currently self-certified under the IVD Directive 98/79/EC ('IVDD') and which will become Class D devices under IVD European Regulation 2017/746 ('IVDR'). These high-risk devices do not have Notified Body certificates under the IVDD, nor do they have common (technical) specifications. They mainly fall into 2 areas: a) those related to blood, cells, tissues or organ screening and b) those related to management of infectious outbreaks.

a) **IVDs that present high individual risk and/or high public health risk, specifically as reflected in IVDR classification rule 1, indent 1 (IVDR Annex VIII):**

*Devices intended to be used for the following purposes are classified as class D:*
*— 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; [...]*

MedTech Europe has researched blood screening requirements in Europe and has surveyed its members (see Annex I and Annex II for more details). Devices likely exist on the market today following the above intended purpose-based rule for blood, blood components, cells, tissues or organs screening, include for example: *Syphilis, Chagas, Epstein-Barr virus, Dengue fever, Chikungunya virus, Zika virus, West Nile virus, Malaria.*

b) **IVDs that present high individual risk and/or high public health risk, specifically as reflected in IVDR classification rule 1, indent 2 (IVDR Annex VIII):**

*Devices intended to be used for the following purposes are classified as class D:*
- *Devices intended to be used for the 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*

MedTech Europe includes any device listed under this rule in the MDCG Guidance on Classification of IVDs. These are infectious diseases which do not have Common Technical Specifications today. We include the following as they relate to this rule: *SARS-CoV-2, Highly virulent pandemic influenza virus, SARS Coronavirus, MERS Coronavirus, Haemorrhagic fever viruses (e. g. Ebola, Marburg, Lassa, Crimean-Congo Haemorrhagic fever).*

This document does **not** discuss the following Class D devices, since they may benefit from an additional 2 years 'grace period' to place their devices on the market until latest 27 May 2024 under a valid IVDD certificate:

- IVD devices for detection, confirmation and quantification of HIV 1 and 2, Hepatitis B, C and D and HTLV-I and II are already subject to Notified Body certification today. This allows manufacturers to benefit from the Grace Period and to place their devices on the market until 27 May 2024, provided the transitional provisions laid down in the IVDR Article 110 are met. Besides, these agents are covered under the IVDD Common Technical Specifications (CTS) which are expected to be transposed to Common Specifications (CS) under the IVDR.

- IVD devices related to Cytomegalovirus, Chlamydia and Toxoplasma infections are part of List B of Annex II of IVDD, although not covered by CTS but have a Notified Body certificate, and therefore can be placed on the market until 27 May 2024, provided the transitional provisions are fulfilled.

## Conformity assessment procedure for Class D devices

### Requirements

For Class D devices under the IVDR, a more complex conformity assessment process is required than under the IVDD. As part of this process, Class D devices will require[3] (also see Figure 1):

- a notified body, which carries out the conformity assessment, issues IVDR certificates to the manufacturer, and notifies a considerable amount of information concerning the device and its conformity assessment to EUDAMED;
- an EU reference laboratory ('EURL'), which verifies the device performance against the common specifications or (if these are not available) against other 'at least equivalent' solutions chosen by the manufacturer. The EU reference laboratory also carries out batch release testing;
- an Expert Panel review, as an additional procedure for novel devices which do not have common specifications.[4]

### State of the infrastructure

*Notified bodies* – At the time of writing, only 4 notified bodies (1 of which is UK-based) are available to conduct conformity assessments under IVDR for Class D devices. This can be compared to 22 notified bodies available

[3] See IVDR Art. 48(3, 4 and 5) and Art 50
[4] IVDR Art. 48(6) *6. "In addition to the procedure applicable pursuant to paragraphs 3 and 4, where no CS are available for class D devices and where it is also the first certification for that type of device, the* ***notified body shall consult the relevant experts*** *referred to in Article 106 of Regulation (EU) 2017/745 on the performance evaluation report of the manufacturer. […]"*

under the IVDD today. MedTech Europe estimates that there could be ~7 notified bodies designated by mid-2021. There is cause for concern about how the available IVDR notified bodies can cover the needed conformity assessments for *all* devices, including for high risk devices. Onsite audits, which are required under the IVDR in order to certify the quality management system, are currently not possible in many countries due to travel bans in place under the pandemic – ultimately, if the notified body cannot make an onsite audit and or bring its specific experts to a particular manufacturing site then this means no EU QMS certification. At the time of writing there is no visibility on how many months the pandemic – and the travel bans in place – are likely to last. Finally – and specifically for Class D conformity assessment – another consideration is that there are many new elements, including many unknowns, in the roles and procedures between the notified body, the EURL and the Expert Panel.

*Common specifications* – At the time of writing, there is a plan to have, by Q2 2021, common specifications published for devices for detection, confirmation and quantification of HIV 1 and 2, Hepatitis B, C and D and HTLV-I and II, as well as Kidd and Duffy blood typing, and blood screening tests for Chagas, Syphilis, Cytomegalovirus and Epstein-Barr virus. There is a plan to develop common specifications for Covid-19 related tests. Other 'batches' of common specifications are planned to be developed but are likely to come only very late or even after the IVDR date of application. The adoption of even agreed-upon requirements (the common technical specifications of today) has seen repeated heavy delays due to the COVID-19 pandemic and when seen in comparison to original timelines laid down in the European Commission's 2018 Implementation Rolling Plan.

*IVD Expert Panel* – Is estimated by the European Commission to become operational in Q4 2020.

*EU Reference Laboratories* – At the time of writing, the necessary implementing acts to allow for the designation of EU Reference Laboratories have been delayed beyond the date of application of 25 November 2020 and are now foreseen to be published in early 2021. It is MedTech Europe's assessment that the designation and readiness of EURLs may come too late in the IVDR transition. Even should a sufficient number of EURLs apply on time and be designated by spring 2021, it will take several months for them to become operational, meaning that they may only be ready to operate as EURL by second half of 2021 at the earliest. Before EURL activities can start, manufacturers will need to place equipment and instruments onsite at EURL (possibly supported by the necessary training). There is also a question mark around the number of EURLs per Class D area and if the EURLs will have the capacity to do verification and batch release for all applicable tests in time for them to be certified by latest 26 May 2022. Given the short transition time which will remain for conformity assessment, another concern is that EURLs will need to conduct validation and batch release for all high-risk devices at the same time, creating a 'bottleneck' effect.

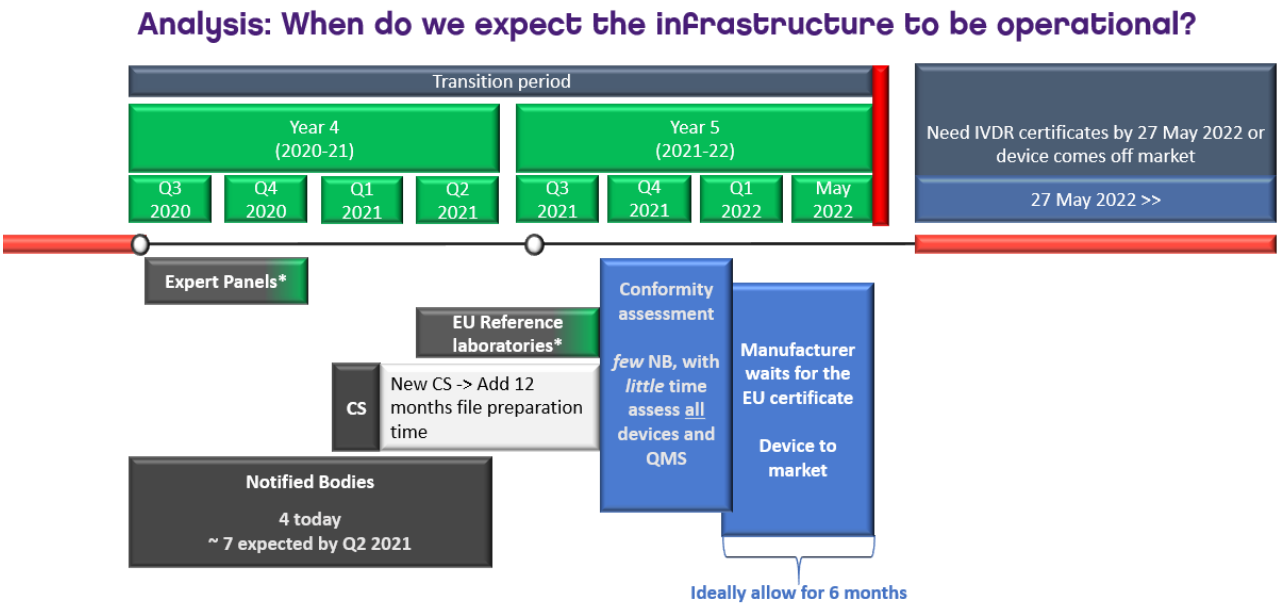


*Figure 1. The regulatory infrastructure needed for Class D, the graph gives expected timelines for each component from the moment it becomes available till the approximate date to become operational.*

## Timing

Today, it takes a manufacturer about 12 months to prepare the high-risk device file and complete the certification process with a notified body under the IVD Directive, see Figure 2. This equates to about six months to prepare the file and about six months to complete the conformity assessment (assuming there are no major non-conformities to resolve).

Under the IVDR, it can be expected that the file preparation time will be similar to today *if* the common specifications do not change from requirements under the IVDD. Any changes to the requirements or new common specifications will need at least six months of transition time to update the device file.

However, completion of conformity assessment under the IVDR is expected to take 9-12 months (or longer, in worst case scenario), particularly during the transition period when all parties (notified bodies, EURLs, Expert Panels, manufacturers, regulators) are dealing with the new and more complex system:

- Notified bodies might be expected to take longer to review devices which are newly in scope of notified body assessment (this would be the first time a notified body is reviewing the device);
- Where applicable, the opinion of the Expert Panel adds a further 60 days[5]; also an impact on the notified body assessment of additional devices of the same type can be expected;
- The scientific opinion of the EURL adds a further 60 days;
- At the end of the conformity assessment process, notification by the notified body to EUDAMED will also take time. At a minimum, the notified body will need to upload the summary of safety and performance before issuing the EU technical documentation certificate to the manufacturer in hard copy.

All of the above will take place when notified body resources will be divided amongst the thousands of other IVDs which also need to be IVDR certified by latest 26 May 2022 (the vast majority of IVDs have no so-called 'grace period'). This could potentially create a bottleneck effect, especially for the notified bodies (NB).

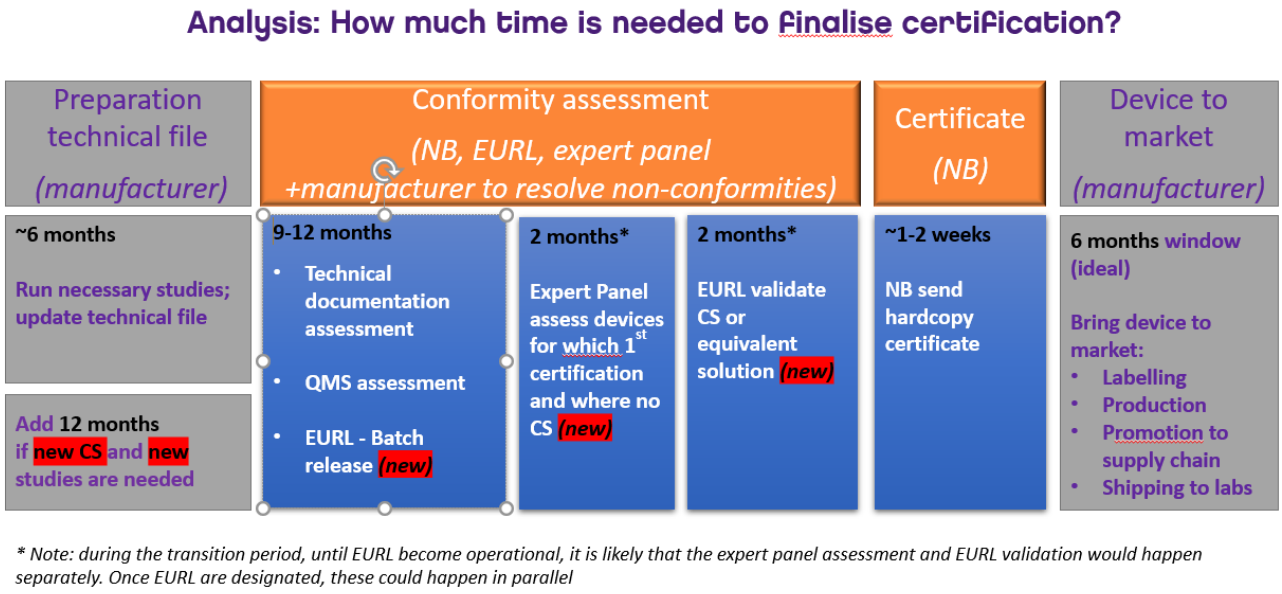


*Figure 2. Timeline to complete certification under the IVDR. The new elements add up complexity and time versus the conformity assessment of today (under the IVDD)*

For all Class D devices, there are questions around when the conformity assessment can actually start, as this depends upon the infrastructure being operational (Fig. 1). It is unknown how much time the conformity

[5] Note: once the necessary IVD expert panel and relevant EURL are in place, their assessments could run in parallel. EURL are likely to be in place only much later during the transition period. However, the expert panel assessment would take place immediately: upon receiving an application to assess a class D device, the notified body must send the performance evaluation report to the expert panel within 5 days (Art. 48(6)). Therefore, it is unlikely that the assessments of the expert panel and EURL will happen in parallel during the transition period. Of course, this assumes that conformity assessment is able to start in the absence of EURL being designated or operational.

assessment itself will take, although as explained above, this will certainly be much longer than the current estimated six months under the IVDD. For Class D devices which do not have CS nor IVDD certificates (being self-declared), will need additional time for the Expert Panel review (Fig. 2).

Class D devices which have IVDD certificates can mitigate these risks by using the IVDR grace period which extends to 27 May 2024. By contrast, Class D devices without IVDD certificates, are particularly vulnerable to the diminishing transition time, since they will need to have completed the complex conformity assessment process before 26 May 2022. The current state of the of Class D infrastructure puts the availability of devices with no grace period at great risk. Consequently, to avoid shortages of IVDs critically needed for healthcare systems, the EU regulators need to ensure a plan (and contingency plans) are in place.

## Discussion

Devices which are in Class D under the IVDR but which do not have IVDD certificates include critically-important IVDs, e.g., those intended to screen the European blood supply, and/or to screen cells and organs for transplantation, and/or to manage infectious disease outbreaks like SARS-CoV-2.

The combination of these tests' importance for public health, plus their lack of an IVDR grace period, and the lack of regulatory structure needed to ensure full IVDR compliance of these devices by 26 May 2022, constitutes a highly-concerning matter for European healthcare.

This issue deserves careful policy attention by the European Commission and national competent authorities, especially given that the devices in question may be required for mandatory testing requirements that exist in the healthcare policy space. Manufacturers are concerned by the ongoing lack of open discussion within the health policy sphere regarding this matter. Concerns continue to build that notified bodies will not have sufficient time to certify these devices under the new IVDR conformity assessment requirements, in time to meet the 26 May 2022 deadline.

MedTech Europe is calling the European Commission and national competent authorities to safeguard the availability of all Class D devices. To guarantee these *in vitro* diagnostics to the European patients, the authorities should provide a contingency plan taking into consideration the 'state of the art' of the IVDR regulatory infrastructure and the transition timeframe available now. MedTech Europe urges the European Commission, Member States and the European Parliament to enact substantive solutions to make the IVDR workable, while ensuring that all relevant stakeholders maintain maximum focus on helping healthcare systems combat and recover from the impact of COVID-19.

## About MedTech Europe

MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. Our members are national, European and multinational companies as well as a network of national medical technology associations who research, develop, manufacture, distribute and supply health-related technologies, services and solutions.

For more information, visit www.medtecheurope.org.

## For more information, please contact:

Oliver Bisazza
Director Regulations and Industrial Policy
MedTech Europe
o.bisazza@medtecheurope.org

Jessica Imbert
Senior Manager - External Affairs
MedTech Europe
(J.Imbert@medtecheurope.org)

# Annex I - *Table 1.* Blood Donor Testing Requirements – 2015 [a]

| | | Testing | Mandatory Screening[b] | Additional Screening[c] | CTS (IVDD) | Estimated timelines for CS (IVDR) |
|---|---|---|---|---|---|---|
| Basic | | **AB0 typing** | All EU countries + NO, UK | | **x** | 2021 |
| | | **RhD typing** | All EU countries + NO, UK | | **x** | 2021 |
| | | **Kell** | | BG, EE | **x** | 2021 |
| | | **Kidd** | | | | 2021 |
| | | **Duffy** | | | | 2021 |
| | | **vCJD** | | | | 2021 |
| Disease | Viral | **HIV 1** | All EU countries + NO, UK | | **x** | 2021 |
| | | **HIV 2** | All EU countries + NO, UK | | **x** | 2021 |
| | | **Hepatitis B** | All EU countries + NO, UK | | **x** | 2021 |
| | | **Hepatitis C** | All EU countries + NO, UK | | **x** | 2021 |
| | | **Hepatitis D** | | | **x** | 2021 |
| | | **Hepatitis E** | DE, NL, UK | | | |
| | | **HTLV-1** | | EL, FR, RO | **x** | 2021 |
| | | **HTLV-2** | | EL, FR, RO | **x** | 2021 |
| | | **Chikungunya virus** | | | | |
| | | **Cytomegalovirus** | | | | 2021 |
| | | **West Nile Virus** | | IT | | |
| | | **Dengue Virus** | | | | |
| | | **Epstein-Barr virus** | | | | 2021 |
| | | **Herpes simplex virus** | | | | |
| | | **Zika** | | | | |
| | Parasitic | **Malaria** | | | | 2021 |
| | | **Trypanosomiasis (Chagas)** | | | | 2021 |
| | | **Toxoplasmosis** | | | | 2021 |
| | Bacterial | **Treponema pallidum (Syphilis)** | All EU countries + NO, UK | | | 2021 |

a) **Colour coding:** "Covered" until 2024 No information retrieved online
b) Minimum requirements as set out in the 2002/98/EC Directive and its technical Directives (particularly 2004/33/EC)
c) More stringent testing - legally binding, testing applies for all types of blood donations and all donor profiles

## Annex II – Identification of IVDD self-certified devices which will become IVDR Class D

In the Netherlands, an investigation has been performed on the impact of the new IVDR classification system on the involvement of Notified Bodies, including the distribution of currently CE-marked IVDs in the aforementioned risk classes. Among 946 random database entries that were assessed, five tests which would be up-classified from Self-Certified (under the IVDD) to Class D (under the IVDR) included two tests for transmissible agents (West Nile and Epstein-Barr virus), specifically intended to test blood samples for suitability for donation or transplantation; two tests for pandemic influenza; and one HIV control.[6]

It is anticipated that the future MDCG Guidance on Classification of IVDs, soon to be published, will help manufacturers, NB and competent authorities in clarifying what are Class D devices. Any disruption in the availability of such devices would put public health at risk. MedTech Europe analysed the latest available information regarding the obligatory blood and tissue screening practices across 27 EU Member States (MS), Norway and the UK (see Annex I), to identify which devices are concerned.

### Legal framework for specific testing

The following Commission Directives on blood and blood components, human tissues and cells and organs set out the minimal screening requirements and include the following agents. For all the examples listed please consult the directives directly to ensure compliance; the below is an illustrative summary of the main tests only. For a summary of the information laid out below, please see **Table I**, in Annex I.

*Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC*

This directive provides minimum testing requirements in the context of blood donations.

[6] National Institute for Public Health and the Environment, RIVM Letter report 2018-0082, A. Van Drongelen *et al.*

Annex IV

BASIC TESTING REQUIREMENTS FOR WHOLE BLOOD AND PLASMA DONATIONS

The following tests must be performed for whole blood and apheresis donations, including autologous pre-deposit donations:

- ABO Group (not required for plasma intended only for fractionation)
- Rh D Group (not required for plasma intended only for fractionation)

Testing for the following infections in the donors:

- Hepatitis B (HBs-Ag)
- Hepatitis C (Anti-HCV)
- HIV 1/2 (Anti-HIV 1/2)

Additional tests may be required for specific components or donors or epidemiological situations. For such tests, please consult the Guide to the preparation, use and quality assurance of blood components [7,8].

*Implementing Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells*

This directive provides minimum testing requirements in the context of donated tissues and cells (excluding blood, blood components and organs), Annex II.1:

For tissues and cells, except for reproductive cells:

- HIV 1 and 2 (Anti-HIV-1,2)
- Hepatitis B (HBsAg, Anti HBc)
- Hepatitis C (Anti-HCV-Ab)
- Syphilis (see details under Annex II.1)

In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. RhD, HLA, malaria, CMV, toxoplasma, BV, *Trypanosoma cruzi*).

For donated reproductive cells:

- HIV 1 and 2 (Anti-HIV-1,2)
- Hepatitis B (HBsAg)
- Anti-HBc (Hepatitis C, Anti-HCV-Ab)

Testing for the following infections and genetic conditions in the donors if they are not the partner:

- HIV 1 and 2,

[7] European Committee on Blood Transfusion, EDQM 19th Edition 2017: Guide to the preparation, use and quality assurance of Blood components

[8] European Blood Alliance Fact Sheet on Blood Donor Selection, October 2016 (https://europeanbloodalliance.eu/wp-content/uploads/2016/11/EBA_Pos_Paper-Donor_selection-1.pdf)

- HCV
- HBV
- Syphilis
- Sperm donors must be negative for chlamydia on a urine sample tested by the nucleic acid amplification technique (NAT)
- HTLV-I antibody testing must be performed for donors living in or originating from high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas.
- In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. RhD, malaria, CMV, *T. cruzi*).

In addition to the agents specified in the aforementioned Directive, other European guidelines urge the professionals also to consider screening for agents associated with new and emerging diseases, including the Middle East respiratory syndrome (MERS), Dengue fever, chikungunya virus, Zika virus, etc.[9]

*Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation*

This directive lays out the minimum data which must be collected for the characterisation of organs and donors. The data set must include tests for:

- HIV
- HCV
- HBV

Other examples could include any device which has the intended purpose of detecting 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:

- A device intended to detect Epstein-Barr Virus (EBV) in a donated heart before it is intended to be transplanted in a patient
- A device intended to screen blood donations intended for transfusion for Creutzfeldt-Jakob disease and variants.

In 2015, the European Commission conducted a mapping exercise study to define the mandatory tests to be performed on blood donors each time they donate. In addition to the EU minimal screening requirements, Member States require blood donations to be screened for certain other agents.

For example:

[9] European Committee on Organ Transplantation, EDQM 4th Edition 2019: Guide to the quality and safety of Tissues and Cells for human application

- Syphilis represents a more stringent legally-binding testing, applicable for all types of blood donations and all donor profiles in a vast number of EU countries (see - *Table 1*);
- Hepatitis E (HEV) screening is currently known to be mandatory in two EU countries and the UK;
- West Nile Virus represents a more stringent legally binding testing, applicable for all types of blood donations and all donor profiles in Italy and a few other EU countries (see - *Table 1*).
- Chagas represents binding testing for donors travelling from or former residents from countries, where trypanosomiasis is endemic;
- Malaria represents binding testing for donors travelling from or former residents from countries, where malaria is endemic.