In vitro diagnostics for screening the blood supply: the new European regulation for IVD and the WHO IVD prequalification programme

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Blood transfusion remains a routine life-saving medical procedure that helps replace blood lost due to surgery, injury or disease. The quality of transfused blood is crucial in this process as blood donors must be free of transfusion-transmissible infections and donated blood should be compatible to that of the recipient. The quality of donated blood could be affected by the quality of in vitro diagnostic medical devices (IVDs) used in the screening process. Consequently, the need for high-quality, safe and well-performing IVDs for use in transfusion medicine arises, accompanied by the need for tight regulations in this domain. In the European Union, the new IVD Regulation will replace the existing IVD Directive within a five-year transitional period. Manufacturers of IVDs are expected to fully comply with the new Regulation by 26 May 2022. In this review, we address the major differences relating to marketing authorization and testing between this new Regulation and its predecessor. We further present the main elements of the prequalification assessment introduced by the WHO for IVDs, including disease-specific IVDs for blood screening laboratories.

Keywords: blood transfusion, IVD regulation, prequalification, TTIs.

Introduction

The delivery of healthcare today involves a huge variety of health products and technologies with wide applications ranging from disease diagnosis, prevention, treatment and monitoring. In vitro diagnostic medical devices (IVDs), also part of these health technologies, are defined as medical devices, used alone or in combination and intended by the manufacturer for the in vitro examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes [1]. IVDs play an important role in the field of blood transfusion, enabling the safety of blood and blood products through their use in the screening for transfusion-transmissible infections (TTIs) and determination of blood compatibility parameters.

Blood transfusion saves many lives worldwide. This process, if not well regulated and executed from the point of a blood donation, could be very risky due to the potential presence of TTIs [2] — the major ones being the human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotropic virus (HTLV) and Treponema pallidum (causing syphilis). A high prevalence of TTIs in the general population would pose a considerable hazard to blood safety, which may be reduced by appropriate screening tests. Good regulation of IVDs used in the field of blood transfusion is key for assurance of suitable quality, safety and performance of these devices. According to the World Health Organization (WHO) [3], globally a significant proportion of donated blood is at a lower safety level either...
because it is not screened for all the major TTIs or the screening is not done within a quality system, as some countries do not screen in a quality-assured manner. False-negative test results may occur with test systems of suboptimal sensitivity for the pathogen strains or genotypes prevalent in the region. Likewise false-positive (or false reactive) test results may cause unnecessary deferral of healthy blood donors and contribute to blood shortage [4]. False results in assessing blood compatibility marker, for example blood groups A, B, 0, testing, may cause adverse events in recipients, including life-threatening complications.

Validity of screening results is key, and IVDs of suitable quality are indispensable in guaranteeing a steady supply of safe blood and blood products.

In the global field of blood transfusion, a variety of different technologies and devices are in use, ranging from rapid diagnostic tests to fully automated systems. Serologic assays based on antigen and/or antibody detection systems to screen blood and blood products for TTIs have been available for over 50 years. With recent technological advances, nucleic acid amplification technology (NAT), such as the polymerase chain reaction (PCR), ligase chain reaction (LCR) and transcription-mediated amplification (TMA), is getting introduced into blood screening routine. These new technologies offer advantages of speed, sensitivity, specificity and accuracy in detecting nucleic acids of TTI causative agents or determining the genetic background of blood group markers.

Considering the very significant role IVDs play not only in transfusion medicine but also in general medical laboratory diagnosis, it is crucial for the design, validation, manufacture, distribution/sale and use of these devices to be thoroughly regulated. Different countries and regions around the world implement different regulations for IVDs but with the sole aim to guarantee the safety, quality and performance of these devices. In the European Union (EU), the new in vitro diagnostic medical devices Regulation (IVDR; 2017/746/EU) published in May 2017 will replace the existing in vitro diagnostic medical devices Directive (IVDD; 98/79/EC) within a five-year transitional period. The new Regulation will create a more robust, transparent and sustainable regulatory framework, recognized internationally within the EU and beyond, that improves clinical safety and creates fair market access for manufacturers [5]. The EU regulatory process for medical devices, including IVDs, begins with the correct classification of the device by the manufacturer. A quality management system implemented in all design and development phases is required for preparation of a technical documentation (TD) and documentation of compliance of the device with the ‘general safety and performance requirements’ stated in the Regulation.

Part of these requirements are confirmed during performance evaluation of the device covering both analytical and clinical performance. For IVDs belonging to higher risk categories, the manufacturer applies to a conformity assessment body, called Notified Body (NB), to audit the quality management system and to assess the technical documentation (design dossier). After a successful outcome, a European certificate confirming compliance of the device with the European requirements is issued and the CE mark may be affixed to the device.

Once IVDs have been certified for release into the market, post-market surveillance mechanisms should be implemented to ensure that they continue meeting the same quality, safety and performance requirements after placement on the market [6]. These post-market surveillance activities could either be reactive to a documented IVD event or proactive to a potential IVD issue. Incumbent upon the manufacturer is complaint evaluation related to compromised safety, quality or performance, and all necessary corrective and preventive measures, as needed [6]. A total lack of or inadequate oversight over IVDs could lead to test failures with devastating consequences, sometimes attracting public attention or generating scandals. Historical examples of such scandals in the medical device field include the silicone breast implants scandal in France where poly implant prothèse (PIP) implants made from cheaper, industrial-grade silicone not approved for medical use were rupturing, resulting in injuries. Such incidents eventually led to major regulatory updates [7]. In the IVD field, an anti-HIV test was ordered to be withdrawn from the European market by the European Commission after its low performance had become obvious [8]. Furthermore, with a considerable number of IVD products available for purchase online, their authenticity remains questionable. A recent press report has revealed that in the past 4 years, about 12,000 fake sexually transmitted infections kits were seized in the United Kingdom [9].

Although the World Health Organization (WHO) is not a regulatory body, the WHO assists Member States through its prequalification assessments in decision-making on selecting essential health products, including IVDs. The focus of the WHO prequalification is on IVDs to be used in low-resource settings for the diagnosis of life-threatening infectious diseases (including HIV, HBV, HCV, but also Malaria). In this review, we address the new aspects, which come with the new European Union IVDR, as well as the major differences between this new regulation and its predecessor, the current IVDD. We also present an overview of the prequalification process introduced by the WHO for IVDs, including disease-specific IVDs for blood screening laboratories.
Regulation of IVDs in the EU – IVD Directive (IVDD) and IVD Regulation (IVDR)

The EU Directive on in vitro diagnostic medical devices (98/79/EC) [10] adopted on 7 December 1998, is a legislative act that sets out regulatory requirements to which all EU Member States must adhere regarding the safety, quality and performance of IVDs. Prior to the year 2000, different national regulations on IVDs existed in some EU Member States. In Germany for instance, the Paul Ehrlich Institute (PEI) performed evaluation and approval of IVDs (for HIV, HBV, HCV, Cytomegalovirus, Rubella and blood group markers) under the German drug law. Since the year 2000 however, the IVDD had to be transposed into the national laws of all EU Member States, following a transitional period. Starting December 7, 2003, adherence to the IVDD became obligatory and since then only compliant IVDs have been permitted for sale and use in the EU. Only these have been allowed to bear the ‘Communauté Européennes’ (CE) mark. Summarily, amongst other rules, the IVDD prescribes essential requirements of safety, quality and performance for all IVDs in the EU market. The IVDD defines tasks performed by Notified Bodies (NBs) which are assigned by individual Member States. For so-called high-risk devices (Annex II list A and B, and self-tests), manufacturers must apply to a NB for certification of their products. The NB will assess according to predefined conformity assessment procedures. In case of the ‘highest risk’ IVDs (defined as list A in Annex II: HIV, HBV, HCV and blood group markers), each device will additionally undergo a thorough review of the Technical Documentation (TD) including assessment of its design and performance. Common Technical Specifications (CTS) have been specifically drafted, in derogation of the normal standardization mandate, to define minimal performance characteristics for these highest risk IVDs.

In the wake of the recent scandals with medical devices described in the introduction, a new Regulation was adopted on 5th April 2017 and entered into force on 25th May 2017. Regulation 2017/746 [11] of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices (IVDR) was instituted, repealing the IVDD 98/79/EC. Since a Regulation is directly binding law in the entire European Union, it prevents differences in national interpretations and increases harmonization between the Member States. This is in contrast to a Directive that needs to be implemented in the national law of the Member States, with some room for interpretation and thus for potential differences between Member States. The IVDR, which can be applied already since May 2017, and which is fully mandatory after a transitional period of 5 years, provides a modernized and more robust EU legislative framework to ensure better protection of public health and patient safety [12]. The IVDR is intended to lead to an improvement in the health and safety protection standards for EU citizens, and it will also ensure that the EU legislation is adapted to the significant technological and scientific progress occurring in this sector over the last 20 years [11]. With effect from 26 May 2022, the IVDD will be repealed and this same day marks the ‘Date of Application’ of the IVDR, with some of its provisions (e.g. regarding NB) coming into force earlier.

The IVDD and the IVDR have the same basic regulatory process with respect to their impacts on manufacturers and products. The IVDR presents important improvements, some of which include: a broader and clearer IVD definition, a new IVD classification system, augmentations to the criteria for the designation of Notified Bodies and their subsequent oversight procedures, requirements for clinical evidence to be confirmed for all IVDs, stringent rules for manufacturers regarding compliance to ensure patient safety, and the strengthening of vigilance and post-market surveillance requirements for manufacturers as well as improved coordination strategies between EU countries in this domain. The new IVD classification system is based on IVD associated risks, makes use of classification rules and replaces the predefined IVD lists of the IVDD. The classification rules differentiate devices from class A, low risk, up to class D, high risk (see Table 1 for details), with parallel increasing regulatory requirements. The intended purpose of an IVD, for example diagnosis of patients or screening of blood donors, may impact its classification and the connected regulatory burden. Therefore, for some devices manufacturers may decide not to claim ‘blood screening’ though the device would be suitable for this application. This approach may cause problems for blood safety, for example with only few devices developed in the beginning of new or emerging infections. The Regulation basically adds new requirements to the existing ones in the Directive. For example, a major new element of the IVDR is the obligatory inclusion of a European Union Reference Laboratory (EURL) for laboratory verification of the most relevant performance claims prior to marketing a new high-risk device (class D). The IVDR also highlights the continuous evaluation of products throughout their life cycles and requires evidence from manufacturers showing the existence of an effective quality management system. It requires more transparency regarding information on IVD devices and more explicit requirements for performance studies on high-risk devices; summaries of which have to be made available to the public. Furthermore, self-testing and near-patient testing devices will now be subject to a premarket approval approach, checking IVD
suitability for the respective user groups. The IVDR adopted several concepts elaborated by the International Medical Device Regulators Forum (IMDRF) to achieve on a global level regulatory harmonization and convergence. The IVDR also gives no room for ‘grandfathering’ provisions (for devices that were already on the market prior to the new Regulation) and recommends that all currently approved IVD devices need to be recertified in accordance with the new requirements. These improvements and/or differences between Directive and Regulation are summarized in Table 1. Differences between conformity assessment procedures in the IVDD and the IVDR are outlined in Table 2.

A series of technical and clinical requirements guiding the general safety and especially, the performance of IVDs is contained in the so-called Common Technical Specifications (CTS) in the IVDD or Common Specifications (CS) in the IVDR documents. These documents outline the general safety and performance requirements and minimal requirements for performance studies to which IVD manufacturers are expected to comply. Compared with the IVDD’s Common Technical Specifications (CTS), the IVDR’s Common Specifications (CS) can adopt requirements with respect to the technical documentation (IVDR – Annexes II, III), performance studies or performance evaluation (IVDR – Annex XIII) and post-market follow-up (IVDR – Annex XIII). The last revision of the CTS enlists provisions for performance evaluation (sensitivity, specificity and interferences), reference materials and batch release for manufacturers [13]. The CTS also clearly provides requirements on sensitivity, specificity and sampling, for consideration during the performance evaluation of blood screening IVDs. Such IVDs typically belong to Class D, including those for blood typing and compatibility testing, and will also be covered and extended under the IVDR by respective Common Specifications. European Union Reference Laboratories (EURL) will have to verify by laboratory testing, the performance claimed by the manufacturers of all class D devices and compliance with the CS. Results of this obligatory manufacturer-independent pre-market testing have to be used for the decision of the NB. Further tasks of EURLs are batch verification testing of class D devices and advice on IVD-related questions to the European Commission, to Member States and to NBs. With the huge diversity of class D devices, it is expected that there will be different scopes (sets of markers) to be covered by different EURLs and several EURLs per scope in order to manage the expected workload. The different EURLs have to assure uniform testing approaches and decision criteria by building an EURL network; individual EURLs may make use of specific expertise present in ‘national reference laboratories’ which may be subcontracted. Tasks and criteria of EURLs are summarized in IVDR Art 100 and will be specified in detail by implementing acts of the European Commission.

WHO prequalification of IVDs

The WHO undertakes prequalification assessments of specific IVDs to determine whether the product meets the prequalification requirements for safety, quality and performance, subjecting individual diagnostic tests through a standardized assessment procedure [14]. The prequalification requirements have been designed in a manner to meet the needs of resource-limited settings. The WHO carries out prequalification to guide interested United Nations agencies and WHO Member States without mature regulatory assessment systems for IVDs in their product selection and procurement decisions [14]. The prequalification process is governed by eligibility principles and criteria. The scope for eligibility is defined by the global need for IVDs for a particular disease or disease state, the appropriateness of the product for use in resource-limited settings, requests from WHO Member States for particular IVDs, a recommendation in WHO disease-specific testing guidelines, and the availability of prequalified products that are of a similar assay format and/or assay principle [15]. Products manufactured by original product manufacturers, which are commercially available when submitted for prequalification assessment, are of interest to UN organizations and other procurement agencies, and products for which there exists few other prequalified products all make up the eligibility criteria used for prequalification [15]. The WHO prequalification team considers applications for prequalification from manufacturers of IVDs used in the diagnosis and infection monitoring of the major TTIs like HIV, HBV and HCV, but also from manufacturers of other pathogens like human papilloma virus (HPV), toxigenic Vibrio cholerae, G6PD enzyme activity and malaria parasites.

The WHO IVDs prequalification (IVD-PQ) process begins with the manufacturer applying for prequalification through a pre-submission form, providing brief information about the product, its regulatory version and details of the manufacturer [14]. This information enables the IVD-PQ team in determining whether the product is eligible for assessment. The manufacturer proceeds to compiling and submitting a product dossier in accordance with specified requirements. Summarily, the product dossier provides information about the product’s description including variants, essential principles, risk analysis and control, design and manufacturing information, product performance specifications and associated validation and verification studies, labelling, commercial history, regulatory history and a quality management system [15]. This product dossier is reviewed by an assessor assigned by
| Subject | IVDD 98/79/EC | IVDR 2017/746/EU |
|---------|---------------|------------------|
| **MD definition** | Limited to reagent, calibrator, control material, kit, instrument, apparatus, specimen receptacle, equipment or system, intended for the in vitro examination of specimens derived from the human body, solely or principally for determining a physiological or pathological state, a congenital abnormality, the safety and compatibility with potential recipients, or to monitor therapeutic measures (Article 1) | Now expanded to also include tests intended to predict a medical condition or a disease, software and companion diagnostics (to predict treatment responses or reactions) (Article 2) Also introduces some new definitions, e.g. devices for ‘near-patient’ testing designed for use by health professionals outside a laboratory environment; devices used in direct combination with specific drug treatment (companion diagnostics) |
| **MD classification** | Classified into pre-defined high-risk devices (list A) and moderate-risk devices (list B) (both in Annex II); devices for self-testing; residual IVDs. Main involvement of Notified Bodies for list A devices, less for list B and devices for self-testing; together comprising around 10% of all devices | IVD classes<br>(a) class A (low individual risk and low public health risk)<br>(b) class B (moderate individual risk and low public health risk)<br>(c) class C (high individual risk and moderate public health risk)<br>(d) class D (high individual risk and high public health risk; ‘high risk’ IVDs)<br>CE certification of class B, C and D devices (85% of all IVDs) requires increasing levels of Notified Body involvement<br>CE certification of class D devices requires an EU reference laboratory for verification of performance and batch testing |
| **‘High risk’ IVDs** | Markers defined as list A in Annex II, difficult to extend by new markers<br>List A:<br>Viruses: HIV1 and 2, HTLV I and II, HBV, HCV, HDV<br>Blood compatibility: ABO, Rhesus, antiKell | Class D; defined by Annex VIII Rule 1 or Rule 2, flexible for future inclusion of further markers<br>Rule 1: Devices intended to be used for<br>a) safety testing of blood, tissues, cells, transplants (e.g. HIV1 and 2, HTLV I and II, HBV, HCV, HDV, HEV, Treponema pallidum, CMV, EBV, Plasmodium spp, Trypanosoma cruzii, Toxoplasma gondii);<br>b) detection of transmissible agents causing life-threatening disease (e.g. Ebola V, Marburg V, Lassa V, SARS CoV, MERS CoV, virulent influenza, vCJD)<br>c) monitoring infectious load of life threatening disease in patient management (e.g. HIV, HBV, HCV)<br>Rule 2: Blood grouping/ tissue typing systems in transfusion/ transplantation<br>ABO, Rhesus, Kell, Kidd, Duffy |
| **Notified Bodies** | Several roles listed in conformity assessment procedures, EC declaration of conformity, etc. (Articles 9, 15, 21 and Annexes III – VII) | Greater scrutiny of Notified Bodies<br>Notified Bodies have to be designated: a 12 months process involving assessors from different national and European authorities<br>More stringent criteria for scientific and technical evaluation competences |
| Subject                        | IVDD 98/79/EC                                                                 | IVDR 2017/746/EU                                                                 |
|-------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Device identification         | • No particular requirement for a harmonized device identification system in place | • More rigorous surveillance expected                                             |
|                               | • Unique device identifiers (UDIs) system now in place to improve the identification, traceability and post-market safety activities of IVDs (Article 24). |                                                                                  |
|                               | • A device identifier (UDI-DI) specific to the model and packaging of the device and a production identifier (UDI-PI) to identify the manufacturing site. |                                                                                  |
| Manufacturers’ obligations    | • Risk management and quality management systems;                               | • Risk management and quality management systems;                               |
|                               | • Conformity assessment procedure;                                             | • More rigorous clinical evidence: conduct clinical performance studies and evaluations; |
|                               | • Claiming responsibility for devices on the market (taking appropriate corrective measures, recording and reporting incidents, and providing appropriate evidence of conformity to authorities) | • Updated archive of the technical documentation;                              |
|                               |                                                                                  | • Conformity assessment procedure;                                             |
|                               |                                                                                  | • Claiming responsibility for devices on the market (taking appropriate corrective measures, recording and reporting incidents, and providing appropriate evidence of conformity to authorities) |
|                               |                                                                                  | • Common specifications with further requirements for certain devices (Article 9) |
|                               |                                                                                  | • Appointing a designated person responsible for regulatory compliance who has requisite expertise in the field of IVDs (Article 15) |
| Device category | Conformity Assessment Procedures | Notified Body Assessment of |
|-----------------|----------------------------------|---------------------------|
| MDD             |                                  | Quality Management System | Technical Dossier |
| List A devices  | Full quality assurance system (Annex IV)  
EC type-examination/ production quality assurance (Annexes V/VII)  
Option for verification of manufactured batches by testing lab | Yes | Yes |
| List B devices  | Full quality assurance system (Annex IV)  
EC type-examination/ production quality assurance (Annexes V/VII)  
EC type-examination/ EC verification (Annexes V/VII) | Yes | Yes (samples) |
| Self-testing devices | Annex III [6]  
| All other devices | Self-certification  
EU declaration of conformity | - | - |
| In-house devices | Manufactured by and used within health institution  
No specific requirements, Member States may define own requirements. | - | - |
| NDR             |                                  | Quality Management System | Technical Dossier |
| Class D | Quality management system and assessment of TD (Annex IX)  
EU type-examination (Annex X)  
Production quality assurance (Annex XII)  
new IVDs of its kind, IVDs without CS  
Scrutiny procedure (Competent Authority (CA) and Medical Device Coordination Group (MDCG))  
Lab testing by EURL  
[a] Verification of claimed performance and compliance with the applicable CS (Art 100 (2a))  
[b] Batch verification (Art 100 (2b); Annex IX (4.12), Annex XI (5.1)) | Yes | Yes |
| Class C | Full quality management system (Annex IX)  
EU type-examination (Annex X)  
Production quality assurance (Annex XII)  
companion diagnostics  
consultation of Competent Authority (CA)  
Annex IX 5.2, Annex X 3 | Yes | - |
| Class B | Quality management system (Annex IX – Chapter I) | Yes | Yes (≥1 device representative for generic device group)  
all companion diagnostics |
| Class A | Self-certification and EU declaration of conformity (Annex IV) | - | (≥1 representative device per product category) |
| In-house devices | Manufactured by and used within health institution; non-industrial scale;  
health institution justifies that the specific needs cannot be met by an equivalent device  
available on the market  
Competent authority (CA) to be informed  
QM system according ISO EN 15189  
Annex I (general safety and performance requirements) applies  
Class D IVDs: documentation of performance evaluation | - | - |
the WHO IVD-PQ team, with the purpose of assessing evidence in support of safety and performance of the product. WHO also determines whether the manufacturer’s quality management system meets the standard to warrant an inspection of the manufacturing site, and assessing the product design and manufacturing process [16].

A manufacturing site inspection is planned simultaneously to the dossier review, aiming to assess compliance of the manufacturer’s quality management system as well as manufacturing practices with international standards (ISO 13485: 2016), verification of the data supporting the claims presented in the submitted pre-submission form and product dossier, and inspection of the quality management system according to the manufacturer’s own requirements [17]. For the inspection to be adequately performed, the manufacturing site must be in active production of at least one of the products undergoing prequalification assessment [17]. Key personnel from the manufacturer (persons in charge of the quality management system, quality control and production line) and from the inspection team (whose competence should match all the parameters of inspection) must be present on the agreed date(s) of inspection. Inspectors from the local national regulatory authority are usually invited as observers.

In addition to the product dossier review and manufacturing site inspection, evaluation of the product in question takes place. This evaluation, which aims at assessing the operational and performance characteristics of the product, is carried out by a WHO performance evaluation laboratory [18]. At the WHO Collaborating Centre in Antwerp, Belgium, for example, test kit evaluations are carried out with the use of a WHO HIV reference panel of well characterized serum/plasma specimens of geographically diverse origin, seroconversion panels and low titre panels [18]. Similar evaluations for hepatitis B and C virus test kits are done by the WHO Collaborating Centre – Public Health England, in London, United Kingdom. A summary of the prequalification assessment is published in the prequalification public report [19]. Manufacturers of prequalified IVDs have post-market surveillance obligations to ensure that these IVDs continue meeting the same quality, safety and performance requirements.

With the increased variety and widespread use of IVDs globally, cooperation between IVD medical device regulators becomes essential. Different models of regulatory collaboration can be observed between some countries and regions around the world. Reliance is one of such processes, defined by the WHO as one wherein a regulatory authority considers or relies upon the evaluations performed by another regulatory authority or trusted institution to make its own decision about a device [20]. Through this model, under-resourced and/or less-experienced regulatory bodies can rely on decisions from more advanced regulatory institutions. However, a sound understanding of the regulatory system on which reliance is based upon is very crucial. This also comes with trust building, confidence and confidentiality on information exchange especially for mutual reliance between authorities.

Recognition, a very similar model to reliance, is a process whereby certificates issued by one regulator or NB to a manufacturer is recognized or accepted by the regulatory authority of another importing country, without necessarily repeating the audit process [20].

In countries with limited access to quality health products especially IVDs, progress towards addressing high-burden diseases is seriously hampered. In addition, the prevalence and incidence of some of the major TTIs are high in these countries. Since the WHO IVD-PQ focuses on IVDs for priority diseases such as HIV/AIDS, hepatitis B and C, and their suitability for use in resource-limited settings, regulatory authorities in these countries may choose to rely on evaluations conducted by the WHO [20]. Consequently, the IVD-PQ assessments take into consideration the regulatory version of the product marketed on the global market, make sure the scrutiny level reflects individual and public health risks in resource-limited settings, and guarantee that data submitted by the manufacturer is assessed from the perspective of such settings so as to reflect the environment and user in these places – including for example, real-world transportation conditions, temperature or humidity [20].

The WHO prequalification service has the main focus on IVDs for so-called priority diseases; however, if an IVD device is submitted for prequalification with claims including for use in screening blood donors, then the IVD is assessed for this claim following WHO requirements. In this regard, several products for screening blood donors have been prequalified, and the public reports for all prequalified IVDs can be accessed online [19].

Summary and conclusion

Transfusion-transmissible infections remain a major concern when it comes to blood products. TTIs have diagnostic window periods, which further make their detection difficult; sensitivity of high-quality IVDs is key. Therefore, effective screening systems are required to eliminate blood donations and derivatives that may contain TTIs, to guarantee a safe supply of blood and blood products. However, this cannot be achieved without the use of highly sensitive and specific, safe, high-quality IVDs. Good quality manufacture and supply of such IVD devices can only be guaranteed through a robust regulatory process, which encompasses the product’s life cycle.
The European Union approached this goal by introducing the IVD Directive in 2000, together with the CTS defining requirements for devices that are important for assessing the virus safety of blood, human tissues and organs. The new IVD Regulation, which is gradually being transitioned into force since May 2017 and is expected to take full effect from May 2022, will increase respective requirements. It provides the new European regulatory basis for manufacturing, placing on the market, distribution and putting into use of IVD devices, including those for blood screening.

In resource-limited settings however, regulation of IVD medical devices is either completely absent, just being introduced or already existing but often not functioning optimally. In such instances, the WHO’s IVD prequalification provides support to WHO Member States by listing prequalified IVD products for priority diseases, on which these countries can rely for product selection and procurement. It however remains important for countries in resource-limited settings to have at least basic effective regulatory systems in place for IVDs so that they can guarantee the safety, quality and performance of IVD devices circulating in their countries. Such regulatory authorities could collaborate with regulatory bodies from other countries or regions through the concept of reliance and recognition when it comes to certain products, hence reducing the burden originating from lack of resources. The WHO IVD prequalification process is known to provide a good opportunity for regulators especially in resource-limited settings to rely upon assessments of IVD medical devices already performed by this WHO service.

References

1. Global Harmonization Task Force: Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’, 2012. http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf. [Last Accessed 30 June 2020]

2. Böning H, Schmidt M, Hourfar K, et al.: Sufficient blood, safe blood: can we have both? BMC Med 2012; 10:29

3. World Health Organization: Screening donated blood for transfusion-transmissible infections, 2010. https://www.who.int/bloodsafety/ScreeningTTI.pdf. [Last Accessed 30 June 2020]

4. Candotti D, Assennato SM, Laperche S, et al.: Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose. Gut 2019; 68:313–321

5. European Commission: Factsheet for Manufacturers of in vitro Diagnostic Medical Devices, 2018. https://ec.europa.eu/growth/sectors/medical-device_s_en. [Last Accessed 30 June 2020]

6. World Health Organization. Post-market surveillance of in-vitro diagnostics, 2015. https://www.who.int/diagnostics_laboratory/postmarket/en/. [Last Accessed 30 June 2020]

7. Hegyi T: PIP Breast Implant Scandal: A Story That Triggered Change, 2017. https://www.imarcresearch.com/blog/pip-breast-implant-scandal. [Last Accessed 30 June 2020]

8. Official Journal of the European Union: European COMMISSION DECISION of 2 December 2008 on the application of Article 8 of Directive 98/79/EC of the European Parliament and of the Council (notified under document number C (2008) 7378), 2008. http://data.europa.eu/eli/dec/2008/932/oj. [Last Accessed 30 June 2020]

9. Badshah N: About 12,000 fake STI kits seized in past four years, figures show, 2019. https://www.theguardian.com/society/2019/oct/20/fake-sti-kits-seized-counterfeit-devices. [Last Accessed 30 June 2020]

10. Official Journal of the European Communities: Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, 1998. https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices_en. [Last Accessed 30 June 2020]

11. European Commission: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, 2017. https://ec.europa.eu/growth/sectors/medical-devices/new-regulations_en. [Last Accessed 30 June 2020]

12. European Commission: Manual on borderline and classification in the community regulatory framework for medical devices, 2017. http://ec.europa.eu/DocsRoom/documents/12867/attachments/1/translations/en/renditions/native. [Last Accessed 30 June 2020]

13. European Commission: Commission Decision of 27 November 2009 amending Decision 2002/364/EC on common technical specifications for in vitro diagnostic medical devices, 2009. https://up.europa.eu/en/publishing-detail/-/publication/2b2ecf2-65c5-490c-885a-bc8b210902d8/la nguage-en. [Last Accessed 30 June 2020]

14. World Health Organization: Essential medicines and health products. In Vitro Diagnostics (IVDs) Prequalification Process, 2019. https://www.who.int/medicines/regulation/prequalifica tion/prequal-in-vitro-diagnostics/ivd-prequal-process/en/. [Last Accessed 30 June 2020]

15. World Health Organization: Eligibility criteria for WHO prequalification of in vitro diagnostics, 2019. https://apps.who.int/iris/bitstream/handle/10665/259170/WHO-EMP-RHT-PQT-2017.03-eng.pdf?sequence=1&ua=1. [Last Accessed 30 June 2020]

16. World Health Organization: Prequalification of in vitro diagnostics product dossier review: Product Dossier Checklist, 2014. https://www.who.int/diagnostics_laboratory/evaluations/FQDxInfo/en/. [Last Accessed 30 June 2020]
17 World Health Organization: Prequalification of in vitro diagnostics: site inspections, 2019. https://www.who.int/diagnostics_laboratory/evaluations/PQDxSiteInspection/en/. [Last Accessed 30 June 2020]

18 World Health Organization: In vitro diagnostics laboratory evaluation, 2019. https://www.who.int/diagnostics_laboratory/evaluations/Labeval/en/. [Last Accessed 30 June 2020]

19 World Health Organization: WHO list of prequalified in vitro diagnostic products, 2019. https://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/. [Last Accessed 30 June 2020]

20 World Health Organization: WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices, 2017. https://www.who.int/medical_devices/publications/global_model_regulatory_framework_meddev/en/. [Last Accessed 30 June 2020]