AgPlus diagnostics

The impact of implementing the new *In Vitro* Diagnostic Regulations on SME's

May 2020

CONTENTS

KEY POINTS

From 26 May 2022, all new IVD (*In vitro* Diagnostics) products will have to comply to the IVDR (*In vitro* Diagnostics Regulations-IVDR). Certificates issued under the IVDD may be valid up to 27 May 2024, while the requirements of the new Regulation relating to post-market surveillance, vigilance, and the registration of economic operators and devices shall apply from the DoA (Date of Application).

The requirements of the IVDR need to be fulfilled by the manufacturer (non-exhaustive list – see table 1). However, exceptions/adaptations are possible/necessary, particularly because EUDAMED may not be fully functional before the DoA.

Important challenges for SMEs ahead while implementing IVDR include - not enough designated notified bodies, the volume of technical documentation and constantly updating documentation throughout the lifecycle of the product

INTRODUCTION

The EU Regulation 2017/746 of the European Parliament and of the Council on *In vitro* Diagnostic medical devices IVDR entered into force on 26 May 2017 and this regulation will replace the EU's current Directive on *In vitro* Diagnostic medical devices (98/79/EC).

All currently approved manufacturers of *In vitro* Diagnostic devices must be recertified in accordance with the new requirements by 26 May 2022. Products already certified by the Notified Body (NB) may be placed on the market for further 2 years under some conditions, e.g. the certificate issued under the IVDD is still valid and subject to surveillance by the Notified Body who had issued it and no significant changes to the product are made.

However, these new regulations have a huge impact on *In vitro* Diagnostics industry especially for Small and Medium Enterprises (SMEs). While the *In vitro* Diagnostics Directive (IVDD) required devices to be CE marked before placing on the market, the regulatory requirements were lenient for most devices, with no clinical evidence required.

The new IVD requirements have changed significantly. The new Regulations demands clinical evidence to demonstrate the claimed benefits and safety of the devices against the scope and intended purpose. This increases the manufacturer's work significantly.

IVDR gives the opportunity to select from a series of conformity assessment routes, but most manufacturers will likely use Conformity Assessment Based on a Quality Management Systems and on Assessment of Technical Documentation-Quality Management System. In other words, design and development will also be performed and documented for placing a product on the EU market. Also, a Notified Body will be required to perform audits and review the technical documentation including clinical performance, scientific validity, and analytical performance evidence before issuing CE certificate.

Performance Evaluation Article 56:

Performance Evaluation

Scientific validity of an analyte means the association of an analyte with a clinical condition or a physiological state.

The scientific validity of the analyte shall be demonstrated and documented in the scientific validity report

Example Evidence:
- Proof of concept studies
- Scientific peer review
- Relevant information on the scientific validity of devices measuring the same analyte

Analytical performance means the ability of a device to correctly detect or measure a particular analyte. Analytical performance shall be demonstrated and documented in an analytical performance report.

Example Evidence:
- Temperature
- Limit of detection and quantitation
- Range
- Accuracy
- Sensitivity
- Specificity
- Precision or trueness of the test

Comparative assessment to current available products in the market

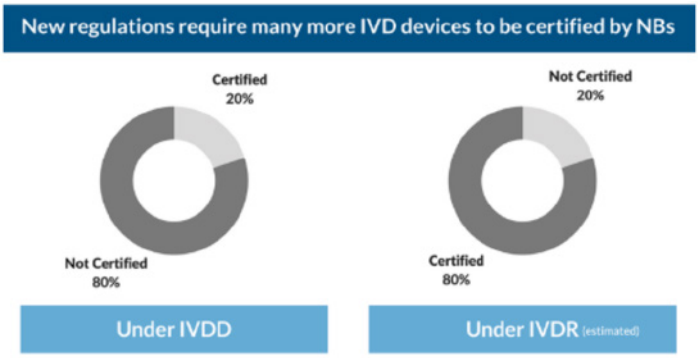
Clinical performance means the ability of a device to use results that are correlated with a particular clinical condition. The physiological or pathological process or state in accordance the target population and intended user.

The clinical performance parameters can be show by example Evidence:
- Diagnostic sensitivity
- Expected values in normal and affected population via Scientific literature
- Diagnostic specificity

IMPACT OF THE CHANGES

In terms of their impacts on manufacturers and products, the IVDD and the IVDR largely share the same basic regulatory process. No existing requirements have been removed, but the IVDR adds new requirements, which increases manufacturer's work in generating the additional documentation. This will be a large amount of work for SMEs who have limited number of resources. The IVDR also clarifies the obligations of economic operators (manufacturers, authorised representatives, importers, and distributors). Listed below are some of the challenges that the manufactures face.

Challenge 1: One of the biggest challenges during the transition is finding a designated Notified Bodies: The IVDR brings more stringent requirements for the designation of Notified Bodies, with increased control and monitoring by the national competent authorities and the joint assessment committee.



According to IVDR all IVD's must be reviewed by Notified Bodies of which there are only 3 compliant to IVDR as of MAY 15, 2020.

Challenge 2: In UK MHRA guidance says - we must follow EU regulations i.e IVDR regulations 2017/746.
"During the transition period, devices can be put on the market under the current EU Directives, or the new Regulations (if you fully comply with the new Regulations). During the transition period, the registration process remains unchanged for devices that comply with the Directives (the MDD, AIMDD and IVDD). However, if you wish to register devices under the new EU Regulations, you will need to tick the relevant box on the registration form to indicate that your devices fully comply with the new Regulations and not the Directives.."[1]

You could be IVDD certified by a Notified Body, but there is a possibility that a Notified Body will ask you to justify why you chose IVDD and not IVDR. If a manufacturer decides to follow IVDD (certificate expires on 27 May 2024) the product on the market might have to be recertified. Therefore, the manufacturer must reinvest time and money in IVDR compliance while the product is already in the market under IVDD.

Challenge 3: The IVDD took a list-based approach to assigning risk classes, which in turn determined the process for assessing conformity and the level of supervision required from Notified Bodies. The IVDR instead uses rules recognised at international level to assign each device to one of the four risk categories (Article 47), ranging from class A (lowest risk) to class D (highest risk). As a result, around 80% of all IVDs will need Notified Bodies oversight. This is a significant impact on the IVD market as all SMEs will need to generate required documentation and go through assessment for all classes except the exempted list.

Challenge 4: For Companion Diagnostics, the Notified Bodies shall consult the competent authorities for medicinal products (Article 48). The conformity assessment of class D devices will require the involvement of an EU Reference Laboratory (if designated for that type of device) to verify the performance claimed by the manufacturer and compliance with the applicable Common Specifications (article 48.5). In addition, for innovative class D devices where no Common Specifications currently exist, an independent expert panel must provide its views on the performance evaluation report of the manufacturer (Article 48.6). Class D devices produced must be tested by an EU Reference Laboratory (if designated for that type of device).

WHAT IS IN IT FOR SME'S

Advantages:

- **Risk-based approach:**
  Using a risk-based approach is the better way to run a compliance program. The risks are identified and mitigated by implementing adequate policies and procedures that are proportionate to these risks, once you've identified low-risk items, you can focus on just those items that truly need to be remediated. The core of the risk-based approach to vulnerability management is making decisions; this not only helps in diverting the limited available resources to high-risk but also ensures long term stability for small businesses.

- **In-line with the rest of the world:**
  IVDR regulations are stricter, tighter, and rigorous as compared to IVDD. UK/EU regulation is closing the gap with rest of the world. Especially with Companion Diagnostics, there are products that are self-certified in UK which in other markets are highly regulated.

  Even though initially a lot work will be required to generate the technical documentation and getting processes in place, the readiness will be established for future outcomes ensuring business continuity.

Disadvantages:

- **Cost:**

The IVDR is a large set of regulations as compared to IVDD.

Documentation	IVDR	IVDD
Articles	113	24
Annexes	15	10
Introductory comments	101	35
Pages	157	37

The IVDR calls for living documentation, requiring updates as the product journeys through its life cycle. Careful consideration is required to establish the technical documentation for your products and maintaining technical file. Annex II states: "the technical documentation shall be presented in a clear, organized, readily searchable and unambiguous manner."

IVD device documentation must:
- Comply with the technical documentation in Annex II of the IVDR,
- Conform harmonized standards/common specifications as described in articles 8 and 9 of the IVDR, (ISO 14917, ISO 13485 and many more)
- And most importantly, the technical documentation list must comply the general safety and performance requirements (Annex I of the IVDR), where benefits must outweigh risks and achieve the claimed performance.

Apart from generating an exhaustive list of documents (as listed in the table below), IVDR also expects all the manufacturers to complete and document activities like software validation, Unique Device Identification (UDI) labelling, clinical validity, post market surveillance etc.
All these activities consume a lot of time and money which may be a scarcity from an SME Although IVDR is a step in the right direction in terms of compliance it can adversely affect the SMEs with limited resources.

WHAT IS IN IT FOR SME'S

Documentation list for IVDR (not limited to)	
Table 1. Technical Documentation Outline	Table 2. Design Dossier Outline
Regulatory information	Introduction
Trade name	Summary Information
Classification	Device Description, Variants and Accessories
UDI	Device Description
Device Description, Variants and Accessories	Market History
General Safety and Performance Principles Checklist	General Safety and Performance Principles Checklist
Intended use and indications for use	Benefit-Risk Analysis and Risk Management
Summary and Explanation	Design and Manufacturing Information
Principles of Procedure	Device Design
Components, reactive ingredients	Manufacturing Processes
Specimen collection (if applicable)	Manufacturing Sites
Instruments (if applicable)	Product Verification and Validation
Software (if applicable)	Analytical Performance
Variants/ Configurations	Clinical Performance
Accessories	Performance Evaluation Report[2]
Market History	Stability
Overview of Previous Generations	Claimed shelf life
Overview of Similar Devices	In use stability
Design and Manufacturing Information	Shipping stability
Design Information	Software Verification and Validation
Manufacturing Information	Labels and IFU
General Safety and Performance Requirements	Post-Market Surveillance
Device description and specification	Conclusion
Measuring Function Accuracy (if applicable)	Draft Declaration of Conformity
Benefit-Risk Analysis and Risk Management	List of Technical Standards
Product Verification and Validation	
Analytical Performance	
Clinical Performance	
Performance Evaluation Report	
Stability	
Software Verification and Validation (if applicable)	
Sterilization (if applicable)	
Origin of tissues, cells and substances of animal, human or microbial origin (if applicable)	
System Performance (if applicable)	
Post-Market Surveillance	
Labeling	

CONCLUSIONS

IVDR sets criteria which can be an instrument for SMEs to achieve high-quality standards and more control over their product. Although, there is a cost involved for this, it ensures that a high-quality product get to the market and ultimately to the consumer. In a way, only the companies with excellent quality processes and regulatory compliance will survive the transition taking out the elements of competition and poor quality. With the implementation of IVDR, SMEs can target global markets for new collaborations and ventures as the quality of the work adheres to international standards.

Comparison of IVDR and IVDD documentation list			
IVDR		IVDD	
Chapter I (Articles 1-4)	Introductory provisions	Article 1	Scope, definitions
		Article 2	Placing on the market and putting into service
Chapter II (Articles 5-21)	Making available on the market, and putting into service of devices, obligations of economic operators, CE Marking, free movement	Article 3	Essential requirements
		Article 4	Free movement
Chapter III (Articles 22-30)	Identification and traceability of devices, registration of devices and economic operators, summary of safety and clinical performance, European database on medical devices	Article 5	Reference to standards
		Article 6	Committee on Standards and Technical Regulations
Chapter IV (Articles 31-46)	Notified Bodies	Article 7	Committee on Medical Devices
		Article 8	Safeguard clause
Chapter V (Articles 47-55)	Classification and conformity assessment	Article 9	Conformity assessment procedures
		Article 10	Registration of manufacturers and devices
Chapter VI (Articles 56-77)	Clinical evidence, performance evaluation and performance studies	Article 11	Vigilance procedure
		Article 12	European databank
Chapter VII (Articles 78-95)	Post-market surveillance, vigilance and market surveillance	Article 13	Particular health monitoring measures
		Article 14	Amendments to Annex II, and derogation clause
Chapter VIII (Articles 96-101)	Cooperation between member states, medical device coordination group, EU reference laboratories and device registers	Article 15	Notified Bodies
		Article 16	CE marking
Chapter IX (Articles 102-106)	Confidentiality, data protection, funding and penalties	Article 17	Wrongly affixed CE marking
		Article 18	Decisions in respect of refusal or restriction
Chapter X (Articles 107-113)	Final provisions	Article 19	Confidentiality
		Article 20	Cooperation between Member States
		Article 21	Amendment of directives
		Article 22	Implementation, transitional provisions
		Article 23	Enforcement
		Article 24	Addressed

Comparison of IVDR and IVDD documentation list			
IVDR		IVDD	
Annex I	General safety and performance requirements	Annex I	Essential requirements
Annex II	Technical documentation	Annex II	List of devices referred to in article 9(2) and (3)
Annex III	Technical documentation on post-market surveillance	Annex III	EC DECLARATION OF CONFORMITY - Technical documentation
Annex IV	Eu declaration of conformity	Annex IV	EC declaration of conformity
Annex V	Ce marking of conformity	Annex V	EC type-examination
Annex VI	Information to be submitted upon the registration of devices and economic operators in accordance with articles 26(3) and 28, core data elements to be provided to the UDI database together with the UDI-di in accordance with articles 25 and 26 and the UDI system	Annex VI	EC verification
Annex VII	Requirements to be met by Notified Bodies	Annex VII	EC declaration of conformity (Production quality assurance)
Annex VIII	Classification rules	Annex VIII	Statement and procedures concerning devices for performance evaluation
Annex IX	Conformity assessment based on a quality management system and on assessment of technical documentation	Annex IX	Criteria for the designation of Notified Bodies
Annex X	Conformity assessment based on type-examination	Annex X	CE marking of conformity
Annex XI	Conformity assessment based on production quality assurance		
Annex XII	Certificates issued by a Notified Body		
Annex XIII	Performance evaluation, performance studies and post-market performance follow-up		
Annex XIV	Interventional clinical performance studies and certain other performance studies		
Annex XV	Correlation table		

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