THE NEW EU IN VITRO DIAGNOSTIC MEDICAL DEVICE REGULATION (IVDR):
Practical Implications for Manufacturers

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Introduction

After a prolonged and challenging political process, agreement was finally reached over the new European Union In Vitro Diagnostic Medical Device Regulation (IVDR), which was approved by the European Parliament on 5th April 2017 and published in the Official Journal of the European Union on 5th May 2017.


‘The existing regulatory framework for in vitro diagnostic medical devices has demonstrated its merits but has also come under criticism in recent years... This revision aims to overcome these flaws and divergences and to further strengthen patient safety. A robust, transparent and sustainable regulatory framework for in vitro diagnostic medical devices that is ‘fit for purpose’ should be put in place.’

It is important to note that the Regulation has binding legal force throughout the EU and enters into force simultaneously in all Member States (by contrast, Directives lay down a set of specific results that must be achieved, but each Member State is free to decide how to transpose these Directives into national laws).

The IVDR is a complex and lengthy document and the changes embodied therein are significant. The purpose of this white paper is three-fold: firstly, to analyse the most influential changes, and secondly, to highlight their implications of these changes not only for regulated companies, but those companies who, for the first time, must comply with IVDR. Most of all, however, this white paper aims to provide practical steps that manufacturers should take as soon as possible to prepare for this substantial and unprecedented change in the European regulatory environment for in vitro diagnostic medical devices.

NOTE: The consolidated text of the new EU Medical Device Regulation (MDR) has been published in parallel with the IVDR. While this also merits the full attention of regulated manufacturers of Medical Devices and also involves significant changes, this Regulation is not in the scope of this white paper.

Phil Brown
Director - Technical & Regulatory,
Association of British Healthcare Industries

“With the introduction of the new IVDR, medical device companies are going to need to re-evaluate their regulatory and compliance strategies, ensuring they properly plan for effective implementation. Maetrics’ white paper is essential reading for companies producing devices under the IVD classification. It outlines the key points of change and guidance from the many years of experience they have. The challenge of new regulation can also be seen as an opportunity to bring operational and commercial improvements; this paper highlights how to implement IVDR for business success whilst ensuring compliance.”

Phil Brown
Director - Technical & Regulatory,
Association of British Healthcare Industries
Significant Changes in the In Vitro Diagnostic Medical Device Regulation and the Implications for Manufacturers

Significant changes for consideration include:

Scope and Definitions

**CHANGE**

The number of definitions of an IVD has been expanded to 74 and the text is now more specific in defining different types of diagnostic procedures, such as:

+ Tests providing information about the predisposition of a medical condition or disease, such as genetic tests.
+ Tests providing information to predict treatment responses to medicines, such as companion diagnostics.
+ Single use devices.
+ Medical software is introduced within the definition of IVDs.

**IMPLICATION FOR MANUFACTURER**

Manufacturers need to review the scope and definitions in conjunction with the classification rules to understand what conformity assessment route they will need to apply.

Some manufacturers will now come under Notified Body scrutiny for CE marking that was not previously regulated.

Classification and Conformity Assessments Requirements

**CHANGE**

A new risk-based classification system is introduced that considers the impact on the patient. This replaces the general IVD category and uses seven implementing rules, according to Annex VII, to divide IVDs into four classes, with A being the lowest risk and D being the highest. Classification should be determined by reviewing all rules, and the rule deemed to have the highest risk class applies. For IVDs with multiple intended uses, all uses must be classified, and the highest risk class is applicable.

+ Class A IVDs will not require the involvement and oversight of a Notified Body. For these devices it will be the responsibility of the manufacturer to declare conformity with the regulation.
+ Class A sterile IVDs will require an assessment by a Notified Body of the sterile aspects, according to Annex VIII.
+ Class B IVDs require a quality systems audit (Annex VIII, except chapter II) with a Notified Body and sampling of at least one technical file per generic device group, unless these devices are self-testing or near-patient testing, in which case the technical documentation of all devices need to be assessed.
+ Class C IVDs require either a full quality management system with a review of technical documentation of a least one device per generic device group (Annex VII, except chapter II), or an EC-type examination (Annex IX) together with production quality assurance or EC verification (Annex X).
+ Class D requires the same procedure as Class C, plus batch verification and reference laboratory involvement (Annex VIII).
IMPLICATION FOR MANUFACTURER

Under the existing directive, a significant proportion of IVDs on the EU market are self-declare (equivalent of new Class A) and do not have Notified Body oversight – under the IVDR, that proportion will change inversely. Manufacturers of IVD medical devices should carefully examine the IVDR Classification rules in Annex VII to determine whether new conformity assessment routes are now applicable to their product portfolio. If so, they should engage their Notified Body (where necessary) and take steps to evaluate the required timescales involved in implementing this change. In cases where reclassification has occurred, this may be the first time that such relationships and agreements with a Notified Body have been required. Meanwhile, this will also have an enormous impact on Notified Body resource capacity and their ability to service clients in a timely manner.

Market Access of Legacy Products

CHANGE

There is no provision for grandfathering certification (CE marks) obtained under the previous Directives – all products have to be CE marked under the new Regulation 2017/746 in order to be placed on the market or put into service (IVDR Article 5), after the transition period.

IMPLICATION FOR MANUFACTURER

A comprehensive plan needs to be put in place to ensure that all products that will be maintained on the EU market are CE marked in accordance with the full requirements of the new IVDR. This should include products currently under development. This review may provide an opportunity for rationalisation of the product portfolio and elimination of any marginal products.

Technical Documentation

CHANGE

The IVDR is significantly more prescriptive about the required content of technical documentation (IVDR Annex II and Annex III):

- Essential Requirements (ERs) are replaced by “General Safety and Performance Requirements” (IVDR Annex I) and the number of requirements has been expanded.
- A ‘Presumption of Conformity’ still applies for IVD medical devices that are in conformity with relevant harmonised standards, but the Commission may define Common Specifications where no harmonised standards exist or where they are considered insufficient.

Additionally, there are more detailed requirements for Quality Management Systems (QMS) (IVDR Annex IX). EN ISO 13485:2016 was rewritten and issued in 2016 with the new MDR and IVDR in mind. It should be noted that while EN ISO 13485:2016 is not an absolute requirement, there will be a general expectation that this standard will be used.

IMPLICATION FOR MANUFACTURER

The required technical file/design dossier documentation is heavily based on the current GHTF STED Guidance document\textsuperscript{2} reflecting the harmonisation intent of global regulators. Accordingly, the continuing sufficiency of the Technical File including associated checklists will need to be checked in detail. Manufacturers will need to remain alert to the publication on new Common Specifications. In addition, manufacturers should be aware of a new sub section related to required Post Market Surveillance (PMS) information.

\textsuperscript{2} Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices GHTF/SG1/N011:2008

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Clinical Evidence, Performance Evaluation, and Performance Studies

CHANGE

The IVDR will require clinical evidence and post-market performance follow-up, therefore providing a life-cycle approach. This will require a performance evaluation plan and report, and will describe how to demonstrate scientific validity, analytic performance, and clinical performance.

For Class C and D IVDs, performance evaluation reports must be updated annually as part of their post-market surveillance plans. Performance evaluation reports are required for Class A and B IVDs but do not need to be updated annually.

IMPLICATION FOR MANUFACTURER

This may require manufacturers to obtain additional clinical data from clinical studies. There will be scrutiny of Performance Evaluation Reports by Notified Bodies and this will be a new experience for many manufacturers.

Vigilance and Post Market Surveillance (PMS)

CHANGE

Under the new Regulation 2017/746, IVD medical device manufacturers will be required to collect post-market clinical data as part of their ongoing assessment of potential safety risks. An electronic database called EUDAMED will be introduced where manufacturers can report serious incidents, safety corrective actions, field safety notices, and periodic summary reports. This information will be available to national competent authorities, giving greater oversight and scrutiny and the ability to highlight potential risks to the wider public.

Manufacturers will need to analyse this data to determine if trends in individual incidents that are not classed as serious have an impact on the risk/benefit analysis due to the frequency of occurrence, and therefore need reporting.

Additionally, reporting timeframes are tightened from 30 days to 15 days for reporting serious incidents (IVDR Article 82). There will be new electronic vigilance reporting (IVDR Article 87) and Periodic Safety Update Reports (PSUR) for all IVDs (IVDR Article 81) subject to differing frequency and submission requirements.

IMPLICATION FOR MANUFACTURER

Manufacturers need to review their procedures for PMS and ensure that the responsibility for the provision of this additional data and associated support is clearly established. This is likely to require additional resources in functions that support products on the market such as Regulatory and Medical Affairs.

“Patient safety has always been a critical part of the products and services associated with in-vitro diagnostics. The industry welcomes these important new regulations and will take this as an opportunity to enhance quality systems and create compliance strategies that continue to put patients first, whilst reducing business risk. Maetrics’ expertise and guidance on this topic can help companies navigate what might seem like an overwhelming exercise. They provide a positive and pro-active outline of the key points to plan for, as well as practical tips for successful IVDR implementation.”

Jim Filer
VP of Global Quality & Regulatory
at a leading diagnostics firm
Mandatory Product Liability Insurance

CHANGE

Manufacturers must be able to provide sufficient financial coverage for their potential liability. This provision will be based on risk class, type of device, and the size of the enterprise (IVDR Article 10.15).

IMPLICATION FOR MANUFACTURER

Manufacturers need to review their Product Liability provisions under advice from legal counsel.

Transparency

CHANGE

Transparency is one of the guiding principles expounded in the IVDR preamble, “transparency and adequate access to information, appropriately presented for the intended user, are essential in the public interest, to protect public health, to empower patients and healthcare professionals and to enable them to make informed decisions, to provide a sound basis for regulatory decision-making and to build confidence in the regulatory system.”

This will (eventually) take the form of a European Data Bank on Medical Devices (EUDAMED) (IVDR Article 33) which will also be made public for certain devices. On their part, manufacturers will need to notify all products to EUDAMED database.

IMPLICATION FOR MANUFACTURER

Manufacturers should closely follow the continuing evolution of the EUDAMED system and prepare for its implementation so as to be able to notify all products to the EUDAMED database.

Supply Chain

CHANGE

Each manufacturer will be required to appoint a Person Responsible for Regulatory Compliance (PRRC). In early drafts of the IVDR this was first referred to as a “Qualified Person” however this was deemed to be confusing with the pharmaceutical industry QP and is now PRRC (IVDR Article 15). The PRRC must have a university degree or equivalent in a relevant scientific discipline, and at least one year of professional experience; or four years of professional experience.

There are also more prescriptive and onerous requirements placed on EU Authorised Representatives (EUAR) (IVDR Articles 11 & 28). The IVDR also states that “the authorised representative should be jointly and severally liable with the importer and the manufacturer.” The EUAR will also be required to be registered and must also have a PRRC.

The IVDR extends the scope of the regulation beyond the IVD manufacturer to other Economic Operators in the supply chain. Distributors and Importers are now specifically regulated (IVDR Articles 16 and 22) and have specific regulatory obligations as well.

IMPLICATION FOR MANUFACTURER

Manufacturers should consider their entire Supply Chain to ensure that these provisions are adequately addressed and agreed with their business partners. In addition, they should identify a person who is suitably qualified to assume the PRRC role. Agreements with EUARs, if used, should be revisited and updated together ensuring that EUARs have defined plans to be registered and also have appropriate levels of insurance to cover their new liability.
Labelling

CHANGE

Requirements for product labelling are more prescriptive under IVDR than before. For example, information supplied by the manufacturer shall be made available and kept up to date on the manufacturer’s website (IVDR Annex I Chapter III). Examples of some other requirements:

+ Specific details for labels and for sterile packages.
+ Inclusion of information on residual risks and shall be included as limitations, contra-indications, precautions or warnings.
+ For devices that may incorporate dangerous substances or mixtures, relevant hazard pictograms and labelling requirements are prescribed.

IMPLICATION FOR MANUFACTURER

Manufacturers should carefully review the adequacy of their product labelling and precautionary statements and consider how this will be reflected on their web-sites.

UDI System

CHANGE

The IVDR requires the traceability of all IVDs placed on the EU market (except custom-made devices) by means of a Unique Device Identification system (UDI System) based on international guidance to significantly improve the effectiveness of post-market safety related activities for devices (IVDR Articles 24, 25, and 26 and IVDR Annex VI).

Each IVD will need to have an assigned UDI obtained from a UDI supplier and this information must be uploaded into EUDAMED. The UDI must be established before the product is placed on the market, and the UDI carrier must be provided on the device label/packaging and, in the case of reusable IVDs, on the device itself.

It should be noted that, for logistical reasons relating to EUDAMED and a Delegated Act on UDI, the UDI requirements cannot be immediately implemented and will be phased in beginning in 2021, starting with the highest-risk devices.

IMPLICATION FOR MANUFACTURER

Detailed project planning for UDI Implementation in the EU (additional to that currently required by the FDA in the US) will be required. While the detailed specification of the EU UDI system is still under discussion, current information suggests it will not differ significantly from the newly established US system. Manufacturers who do not supply their products to the US will have the steepest learning curve on EU UDI, however they can also learn from the successes and mistakes of US UDI implementation.

Some Important Practicalities of Implementation

Timeline

Following its recent formal adoption, the IVDR was published in the Official Journal of the European Union on 5 May 2017. The new regulation is associated with a five-year transition period following its publication and therefore enters fully into force in 2022 (the “Date of Application”). After this date it will no longer be possible to put a new IVD on the market with a CE mark issued against the former Directive 98/79/EC.
Projected Timeline of Implementation of IVDR

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<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2016</td>
<td>Entry into force May 2017</td>
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<td>2017</td>
<td>EC Certificate Validity Prior to Entry Into Force</td>
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<tr>
<td>2018</td>
<td>NBs can apply +6 months for re-designation</td>
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<tr>
<td>2019</td>
<td>Readiness of EUDAMED? UDI?</td>
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<tr>
<td>2020</td>
<td>Date of application 26 May 2022 IVDD certificates can no longer be issued</td>
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<td>2021</td>
<td>All unexpired IVDD certificates now expire May 2024</td>
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<td>2022</td>
<td>5 year transition period</td>
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<td>2023</td>
<td>EC Certificate Validity During Transition Period</td>
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<td>2024</td>
<td>Future EU regulation for medical devices and for the UK remaining part of the CE marking regime. Nonetheless, the possibility that additional bureaucratic overheads may be encountered in the UK going forward certainly exists. Manufacturers should closely monitor further developments in the UK so as to anticipate any significant consequences for their business.</td>
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**UK BREXIT**

The decision of the UK to exit the EU (Brexit) following a referendum held in June 2016 and formalised by the triggering of Article 50 in March 2017 complicates the situation for UK based manufacturers, non-EU companies with Authorised Representatives in the UK and companies wanting to continue to access the UK market. However, it seems unlikely that the UK government will devise any sort of national regulatory regimen that differs significantly in its requirements from that of the EU IVDR. Thus, any future UK regulatory regimen is likely to closely mirror that of the EU.

To this end, the UK Association for British Health Industries (ABHI) has recently published a white paper on its web site advocating a pragmatic UK approach to compliance with the current and future EU regulation for medical devices and for the UK remaining part of the CE marking regime. Nonetheless, the possibility that additional bureaucratic overheads may be encountered in the UK going forward certainly exists. Manufacturers should closely monitor further developments in the UK so as to anticipate any significant consequences for their business.

**NOTIFIED BODY CAPACITY**

After some well publicised safety issues in recent years that have strongly influenced the evolution of the IVDR, Notified Bodies (NBs) are themselves under considerable pressure from their respective Competent Authorities to heighten scrutiny of their client IVD medical device manufacturers. Notified Bodies will themselves need to seek designation under the IVDR in the months after the IVDR is adopted.

Notified Bodies across Europe are already encountering capacity issues and this is expected to continue. There has been a significant decrease in the number of Notified Bodies accredited to deal with in vitro diagnostic medical devices in spite of a substantial increase in workload and, with the IVDR coming into play, Notified Bodies will also need time to prepare and train their own staff. In the EU there are currently just 56 Notified Bodies in total (including three MRAs from Australia and Switzerland), reduced from more than 70 Notified Bodies.
Bodies in 2014. Germany and Italy have 10 Notified Bodies each, the UK has five and the remaining countries have four or less each, the majority having just a single Notified Body.

This suggests there will be significant over-demand from the industry for Notified Body services as manufacturers compete for their services during the transitional period. It is vital that manufacturers engage with their Notified Body early and ensure they have the capacity to assist them and that they agree on timescales.

UNANNOUNCED INSPECTIONS
Notified Bodies have already started to conduct unannounced inspection of manufacturers, their critical subcontractors and suppliers. For example, TÜV SÜD has carried out more than 400 unannounced audits worldwide since March 2014. Under the new IVDR such inspections must be performed at least once every five years. Manufacturers should put in place procedures to deal with these, should they not already have done so, and always be prepared for an audit.

DELEGATING ACTS
The harmonising standards and Delegating Acts that will make the IVDR operational are still under active discussion and development at the EU level. It is important that manufacturers closely follow these developments by actively engaging with their Trade Associations, and where possible, lobbying to influence their final form.

ISO 13485 QUALITY SYSTEM
In addition to needing to comply with Regulation 2017/746 requirements, the medical devices industry is currently transitioning to the newly revised ISO 13485:2016 standard required for medical device QMS which is itself a de facto requirement for medical devices placed on the EU market. This new standard has a transition period that ends 1st March 2019, overlapping closely with the IVDR transition period. In practice, manufacturers must phase in these two transitions together, further complicating the implementation of the IVDR.

Steps Manufacturers Should Take Now
It is evident that conformance with the IVDR is a significant business issue; all products on the market must be phased into the new system no later than at the end of the grace period following the five year transition period. All new products being placed on the market after the transition period must be compliant with the IVDR. Furthermore, regulatory control over conformance with the requirements of the IVDR is ever-increasing.

Additional Costs and Resource Requirements
IVDR conformance will place a considerable additional administrative burden on manufacturers. Both staffing and external cost budgets should be carefully considered and adjusted to ensure that timely access to the EU market is not compromised and that regulatory compliance is maintained in the face of significantly enhanced regulatory scrutiny.

Many manufacturers will rely on additional resources to assist with the workload at a time when there is a shortage of skilled professionals. Manufacturers who plan and implement sooner rather than later will have the best access to limited resources and will be able to cherry-pick the best personnel. Whenever there is demand and a lack of resources, prices increase, so there is also likely to be an increase in labour costs over the next few years. When budgeting, manufacturers must allow for this fluctuation and also be aware that it is a candidate’s market so they will need to act fast to secure top professionals.

Programmatic Approach
It is imperative that IVD manufacturers and other economic operators be proactive and adopt a programmatic approach to conformance. It is recommended that a cross-functional project team is formed to manage this Program. The Program should ensure that the following are addressed:
MAETRICS IVDR PROGRAMMATIC APPROACH

+ Brief Executive Management to ensure they gain a clear understanding of the importance and business implications of the IVDR;
+ Ensure that overall responsibility for IVDR implementation has been established and that a cross-functional program team is formed in order to cover all aspects;
+ Study the detailed requirements of the IVDR;
+ Perform a detailed gap analysis for products and the whole organization against the IVDR requirements;
+ Give special consideration to certification expiry dates versus transition period and enforcement date;
+ Review the IVDR Implementation plan, identifying and addressing key areas of risk;
+ Consider organizational challenges: management awareness, staffing capability and availability, budget implications;
+ Continue to actively monitor the still-developing European Regulatory environment;
+ Check classification rules and verify conformity assessment routes for existing and future products and take steps to address any changes;
+ Contact the selected Notified Body and determine their capacity and availability to service the implementation plan;
+ Review the changes needed in existing technical documentation (Technical File);
+ Determine the adequacy of clinical evidence, performance evaluation and studies and address any gaps;
+ Review the adequacy of Quality Management System (QMS) processes and plans to transition to ISO 13485:2016 and build in the new regulatory requirements into the QMS;
+ Identify Person Responsible for Regulatory Compliance (PRRC) and be sure they are adequately qualified and trained and plan their training, if applicable, as early as possible;
+ Review product labelling;
+ Ensure product liability provisions are adequate;
+ Ensure PMS arrangements are adequate;
+ Review supply chain provisions and clarify roles and responsibilities of business partners;
+ Prepare for unannounced inspections from Notified Bodies;
+ Ensure regular review of progress versus the IVDR Implementation program plan are held and included in the management review process.
Summary

Conformance with the IVDR is a significant business challenge that must be overcome in order to enjoy continued access to the EU market. To meet this challenge manufacturers must be proactive and begin preparing now.

Some of the underlying details of the IVDR implementation process are not yet fully defined. Manufacturers must closely follow the emerging regulatory landscape, keeping alert for the detailed Implementing and Delegating Acts that are required in order to make the IVDR operational.

In this challenging and competitive environment, the availability of resources, both internal and external, are likely to prove rate limiting. Executive support and proactive program management of IVDR implementation is a prerequisite for a manufacturer’s success in this regard.

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