ARE YOUR COMPANION DIAGNOSTIC PARTNERS READY?

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The new *In Vitro* Diagnostic Medical Devices Regulation (IVDR) EU 2017/746, was published in the Official Journal of the European Union in May 2017[1] with full implementation by the date of application, 25th May 2022. It is envisaged that the new regulations will create a robust, regulatory framework which will be internationally recognised to improve clinical safety and improved market access. It appears, however, that the majority of stakeholders are not ready for the increased challenges of obtaining and maintaining compliance to the new requirements.

The IVDR will have significant impact on the regulation of companion diagnostics (CDx) and manufacturers of CDx devices are facing some of the greatest regulatory challenges in order to become compliant by the date of application. While the IVDR uses the same basic regulatory processes as the current In vitro Diagnostic (medical device) Directive (IVDD), including the continued need for technical documentation to demonstrate device performance, there is now a requirement for considerably more detail. The Essential Requirements remain but have been renamed to the General Safety and Performance Requirements and updated to include new requirements as well as additional requirements for clinical evidence. Existing requirements for Post Market Surveillance have been reinforced and expanded.

Due to the lack of clarity in some key aspects of the text; the associated difficulty in uniform interpretation; along with an apparent lack of understanding or consideration of the global companion diagnostic clinical validation paradigm already established in the US, Japan and S. Korea, many Rx/CDx sponsors are unsure of how to develop or move forward with their compliance plans.

In this whitepaper, we will provide an overview of the transitional activities required under the IVDR and their status, as well as examine the most significant new requirements and assess their impact on companion diagnostic manufacturers and their pharma collaborators. While preparations should now be well advanced to ensure compliance with the new requirements, the reality may be otherwise, particularly for smaller companies and laboratory test providers with limited resources. We will outline the steps that the manufacturers of targeted therapies who rely on CDx availability in the EU to select patients for whom their therapy is safe and effective, should take now to ensure that their CDx vendors are as prepared as possible for the new regulatory paradigm and that their CDx devices are available for use at clinical laboratories by the date of application.

Transitional Provisions

In order to prepare for the new regulatory model in the EU, many changes must be implemented by the EU Commission and National Competent Authorities to ensure that the systems are ready to submit and assess the conformity of existing and new medical devices being placed on the EU market (both for clinical use and for clinical research) by the date of application. Transitional provisions for *in vitro* diagnostics are drafted by the Medical Devices Coordination Group (MDCG), whose members are drawn from representatives of member state competent authorities and who provide input to the commissions programme of implementation of the new regulations. These transitional provisions include the following;

- Scope & Designation of Notified Bodies
- EUDAMED (European Databank on Medical Devices)
- UDI (Unique Device Identification)
- Implementing Acts (including Common Specifications for Class D IVDs)
- EU Reference Laboratories (for class D IVD devices)
- Establishment of Expert Panels
- Development of Guidance Documents

As of the end of 2018, progress has been made in some of the transitional provisions above, however this progress has been slow, and fears are growing that key provisions will not be in place in time for the date of application of the MDR in May 2020. As a result of the size of the medical device sector, the focus of attention at Commission/MDCG level has been largely confined to working to ensure that the needs of the general medical device sector are met on time, albeit some of these provisions will equally apply for *in vitro* diagnostic medical devices.

In relation to designation of Notified Bodies, only 7 (out of an existing 22 designated under the directive) applications have been received for designation under the new IVDR. This figure includes Notified Bodies who have applied for designation in more than one member state. Since Companion Diagnostics shall require the involvement of a Notified Body in the Assessment of Conformity, the capacity of the Notified Bodies to review and approve (CE mark) CDx device technical documentation will be seriously constrained. Given that around 85% of IVD devices will require approval by a notified Body, this represents a serious risk to the availability of CDx devices, approved for their intended use, by the date of application. It is currently

Figure 1: Impact of IVDR on CDx Device Classification

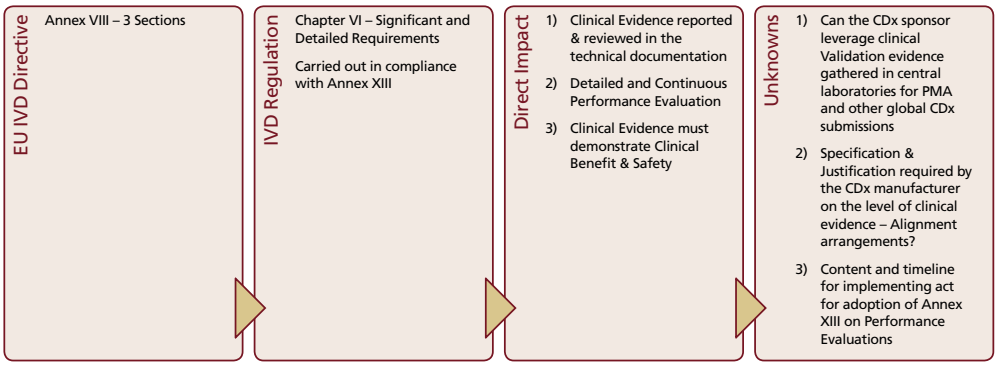

Figure 2: Performance Evaluations and Clinical Evidence under the IVDR

unknow by industry whether there are additional Notified Bodies who intend to apply for designation under the IVDR.

Another transitional provision permits the continued placing on the market of IVD devices that have a valid CE certificate issued by a Notified Body under the current directive at the date of application. These devices can be supplied until this certificate expires or until May 27th, 2024 whichever comes first. Since CDx devices CE-marked in compliance with the directive are self-certified (i.e. no Notified Body involvement in the CE-marking and therefore no CE-mark certificate), this provision will not apply to Companion Diagnostics.

Additionally, the commission has agreed to a 'sell-off' provision, permitting devices that are in the supply chain (already placed on the market) on the date of application to be used by their final user up to 26 May 2025. Devices must, however, have been transferred outside of the manufacturers' ownership by the date of application. This provision is clearly of limited utility to IVD manufacturers resulting from manufacturing capacity and device stability constraints.

Overview of the Conformity Assessment Process for Companion Diagnostic to the requirements of IVDR

The introduction of the IVDR brings with it many changes for manufacturers of Companion Diagnostics. In addition to meeting the applicable general safety and performance requirements in Annex I of the regulation, Companion Diagnostic devices must additionally follow a conformity assessment process in compliance with Annex IX or Annex X combined with Annex XI.

The requirements of Annex IX are based around implementing a robust quality management system that will control development; manufacturing; and release of the IVD device with additional requirements detailed in Annex IX section 5.2, specific for Companion Diagnostics including consultation by the Notified Body with the EMA or National Competent Authority for Medicines in the country where the Diagnostic manufacturer has a registered place of business.

In combination with the numerous changes to the way in which the performance testing of the Companion Diagnostic device is planned and conducted, along with the remaining uncertainties in the text and many areas requiring further clarification for CDx stakeholders, the procedures for conformity assessment represent a significantly increased burden on manufacturers and Notified Bodies.

IVDR Effects on the Development and Validation of Companion Diagnostics

As outlined earlier, the changes in the IVDR represent a challenge to many CDx stakeholders to ensure:

- The continued availability of devices for patients in the EU at the date of application and;
- The level and nature of device performance data is adequate
- That current and ongoing development programmes are considering and meeting the requirements of the new regulation.

Below, we consider the most significant changes between the existing directive and the regulation affecting companion diagnostics, their direct impact and explore the 'known unknowns' that will affect the development and approval of CDx devices in the EU.

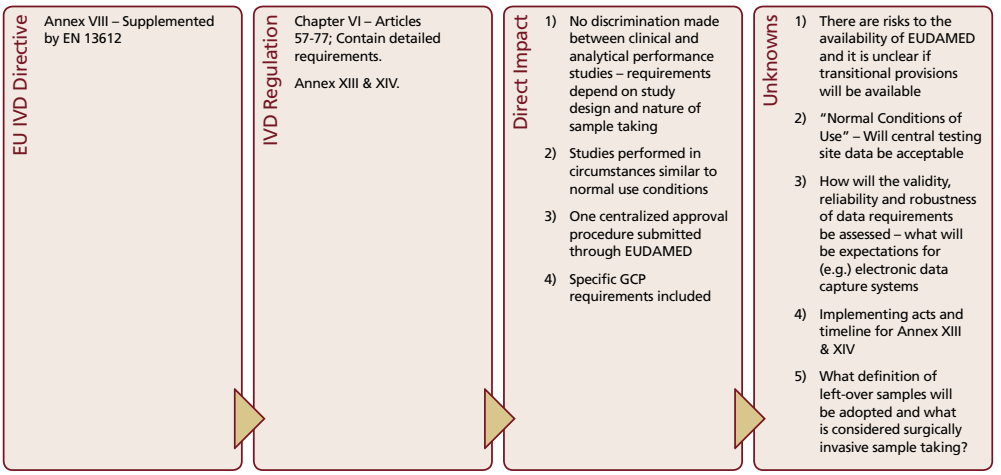

Figure 3: Comparison of Requirements for Performance Evaluations conducted under the IVDD and IVDR

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1. Companion Diagnostic Classification

As shown in **Figure 1**, one significant aspect of the new regulation is the introduction of a risk-based classification system based on the IMDRF (formerly GHTF) system of device classification. This, in combination with a specific definition for Companion Diagnostics, results in a change in the classification from self-certified general IVD devices to high risk class C devices. CDx devices will require conformity assessment by a Notified body in consultation with the European Medicines Agency (EMA) or Member State Competent Authority for Medicines.

2. Performance Evaluation and Clinical Evidence

Figure 2 indicates that there are substantially more activities to be carried out under the IVDR to plan and conduct a performance evaluation. The performance evaluation process per Annex XIII, is a continuous process throughout the life-cycle of the device (documented in the Post-Market Performance Follow-up), carried out according to the Performance Evaluation Plan and presented in a Performance Evaluation Report. The Performance Evaluation must be developed and planned such that it generates adequate evidence that demonstrates Scientific Validity, Analytical Performance and Clinical Performance based on a Clinical Performance Study Plan (CPSP). The CPSP contains twenty-six specific elements, any considered not appropriate for inclusion in the CPSP due to chosen study design (e.g. use of left over samples versus interventional clinical performance studies) must be justified. The Clinical Performance documented in the Clinical Performance Study Report should be transparent, free of bias and clinically relevant.

As a general rule Clinical evidence should be sourced from performance studies under the responsibility of the study sponsor (manufacturer).

3. Requirements for Performance Studies

As shown in **Figure 3**, there are significantly increased requirements to demonstrate the performance of companion diagnostic devices requiring a performance evaluation study to be conducted. The definition of a performance study includes both analytical and clinical performance studies. Requirements for planning, executing and reporting on the studies is dependant only on the nature of the study design (observational/interventional/etc.) and whether surgically invasive sample-taking is done only for the purpose of the performance study. For all performance studies involving companion diagnostics, excluding those that use exclusively left-over samples, sponsors must meet the additional requirements for performance studies detailed in Article 58, Articles 59-77 and Annex XIV. These studies are subject to authorisation by the member state competent authority and approval by an ethical committee in accordance with national law.

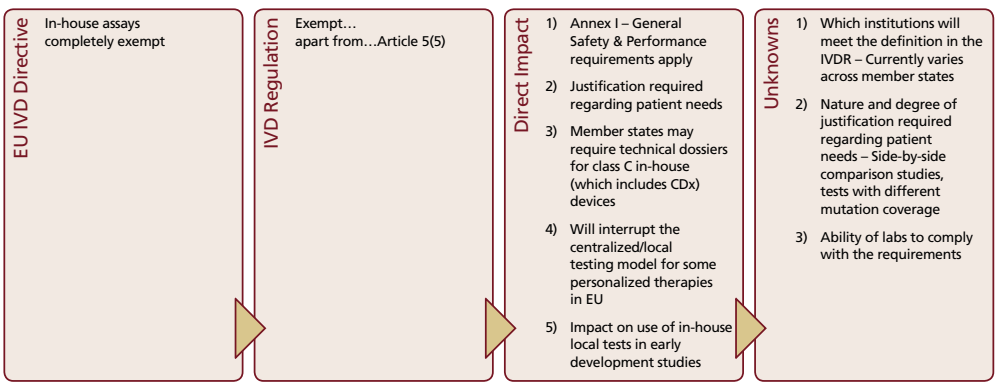

Figure 4: IVDR Requirements for In-house Tests Developed & Used Within a Health Institution

In addition, clinical performance studies carried out in accordance with the applicable sections of Annex XIII must be conducted unless it is duly justified to rely on other sources of clinical performance data. For companion diagnostic devices already cleared through the PMA process or by Japan's PMDA and where the clinical performance data has been gathered in a central testing laboratory that does not represent the normal conditions of use, questions remain over the validity of this data under the IVDR.

4. Health Institution Exemption

As shown in **Figure 4**, requirements for Health Institutions are now included in the IVDR, requiring manufacturers of in-house assays (that meet the definition of the Health Institution in the exemption) to, inter alia, provide justification for use of their tests and a declaration of compliance to the General Safety and Performance Requirements. Any changes to the manufacturers' specification by a Health Institution will make them the manufacturer of the modified device, and subject them to the requirements in Article 5(5). In addition, laboratories are required to compile a product dossier for class D devices and to have this available for review by member state competent authorities. Competent Authorities are free to apply this requirement to laboratories who manufacture class A, B and/or C device which will include devices used as companion diagnostics.

5. EMA/Medicines Competent Authority Review

Figure 5 shows the involvement of the medicines agencies in the approval of companion diagnostics, which represents an additional layer of scrutiny as well as an additional challenge to the sponsors of the new drug and companion diagnostic. In addition to the lack of any clear picture on how the alignment of the multiple stakeholders might occur, there are concerns as to the capacity and technical capability

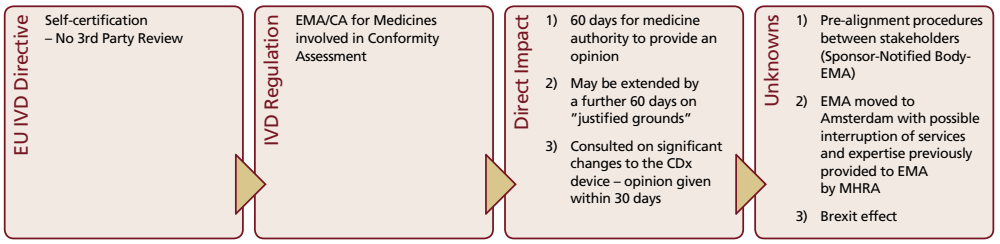

Figure 5: Requirement for Medicines Authority Review

of the agencies to adequately review the information provided. The lack of any performance criteria related to the device efficacy relevant to the treated patient outcome in Annex I of the IVDR present a further challenge and does the need to demonstrate clinical benefit address this.

Conclusion:

Is your diagnostic partner ready?

While many areas remain unclear, there are activities that CDx sponsors/manufacturers should already have started and be progressing throughout the transition period. Many drug development programmes run to and beyond the date of application, meaning that by the time the drug is being submitted, the companion should also have all of the data requirements under the IVDR in place for review and approval.

Some of the questions you should now ask of your CDx development partner(s) include;

- Have they reviewed and confirmed, based on the intended use, that the device meets the definition of a Companion Diagnostic under the IVDR?
- Do they already have a Notified Body identified for CE marking and has this Notified Body confirmed their intent to or their completion of an application for designation under the IVDR that includes Companion Diagnostics?
- Have they conducted an assessment of the gaps in their clinical evidence for the device? Have they discussed this with their Notified Body and considered a plan as to how those gaps might be filled?
- Have they confirmed the need for a clinical performance study to generate the clinical performance element of clinical evidence and discussed this with their Notified Body? Are they able to leverage any clinical performance data already gathered through studies conducted for other market approvals?
- Do they have the necessary processes and systems in place to manage a clinical performance study that assures valid, robust, verifiable clinical data and protects the health, safety and welfare of patients?
- Do they have adequate liability protections in place for defective devices both in commercial distribution and in interventional clinical performance studies?
- Do they have the necessary resource capacity and expertise in place to meet the requirements of the new regulation?

It is clear that the introduction of the IVDR represents a challenging shift in the regulation of Companion Diagnostics in the EU. It should be advised however, that for many CDx devices already cleared in, for example, the US or Japan, much of the clinical evidence will already exist from studies undertaken for these submissions and might be leveraged to meet the clinical evidence required for CE marking under the Regulation. The clinical use of the CDx device and feedback from clinicians regarding patient reported results and outcome data is another important source of real-life clinical evidence that can be leveraged towards CE marking for existing marketed CDx devices.

ARC Regulatory Ltd. is a leading regulatory and clinical consulting company and niche CRO, providing specialised services to the global precision medicine industry. Our clients include leading names in the development of targeted therapies and their diagnostic vendors/partners, whom we have helped to navigate the complexities of global regulatory and clinical research paradigms. ■

Reference

1. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1542301249315&uri=CELEX:32017R0746

Seamus Kearney has been working in the medical device industry for almost 20 years. After graduating from The Queen's University of Belfast with a BEng Honours Degree and a Master Degree, also in Engineering, he started his career as a design engineer for a US-based medical device company. He has held various roles of increasing seniority in device development from Project Management, Design Quality and Risk Management to Regulatory and Clinical affairs. Seamus founded ARC Regulatory in 2010 and has focused on the *in vitro* diagnostic sector working with many leading names in the global IVD and CDx industry and their partner companies to bring targeted therapeutics to the US, EU and global markets.

Maud Smyth has over 20 years of experience in the global IVD industry. Maud graduated with an honours degree in Biological Sciences from the University of Ulster and was later awarded a D.Phil in 1995 from the same institution for her research in scanning force and correlative microscopy in the study of epithelial cells. Maud's early career was spent as an R&D scientist in immunoassay development, later moving in to a global regulatory role gaining global regulatory market access for a broad range of IVDs through submission and clearance of numerous US FDA 510(k) submissions. Maud has spent almost 4 years working in the area of companion diagnostics development, aligning with various stakeholders and US FDA through the Q-Sub programme, developing and submitting IDE's as well as Regulatory Authority approvals in other markets.