The In Vitro Diagnostics Regulation and the role of medical writers

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Abstract
Even though in vitro diagnostic medical devices (IVDs) occupy only a very small market segment in the healthcare sector, they have a vital role to play. The importance of diagnostics was strongly underlined during the COVID-19 pandemic. In the EU, IVDs are regulated under the In Vitro Diagnostics Regulation 2017/746 (IVDR), with the planned date of application in May 2022. This article gives an overview of IVDs and the regulatory requirements under the IVDR in comparison to the more well-known Medical Device Regulation 2017/745. Considering the similarities in the regulatory landscape and the document requirements of the two regulations, medical writers well versed in mainstream medical devices have the skills and competencies to support IVDs under the IVDR.

About IVDs
When a patient visits a doctor, the doctor usually collects blood to evaluate basic blood parameters, e.g., biochemistry, haematology, and biomarkers. As simple as it sounds, basic information obtained from blood samples can provide the physician with general information on the patient's health status. Taken together with a physical examination, the test results are able to guide the physician's treatment decisions. For instance, high C-reactive protein levels are indicative of an infection, or high levels of blood glucose hint towards diabetes. But what is behind these tests? Behind these tests is the in vitro diagnostics industry. It develops and provides test systems, solutions, and rapid tests, and these products are commonly known as in vitro diagnostic medical devices (IVD).

The The In Vitro Diagnostics Regulation 2017/746 (IVDR) defines an IVD as:

> *… any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:*
>
> a. *concerning a physiological or pathological process or state;*
> b. *concerning congenital physical or mental impairments;*
> c. *concerning the predisposition to a medical condition or a disease;*
> d. *to determine the safety and compatibility with potential recipients;*
> e. *to predict treatment response or reactions;*
> f. *to define or monitor therapeutic measures.*[1]

IVD tests are considered to be non-invasive and meant to support the physician in identifying the patient's underlying disease. They are used to analyse human samples such as blood, saliva, urine, or tissue by measuring the concentration of specific substances (e.g., cholesterol, sodium) or detecting the presence or absence of a particular marker (e.g., DNA, RNA, or protein). Figure 1 shows the diversity of IVDs in terms of products, therapeutic areas, applications, and users.[2]

Nowadays, in addition to diagnosing conditions, clinicians also use IVD tests to provide important information for therapy decisions. Screening tests help to stratify patients into drug-responsive vs non-responsive populations based on the expressed biomarker(s), whether protein-, DNA-, or RNA-based to ensure that patients benefit from the appropriate or future therapies. For example, PCR-based IVD tests such as the

OncoBEAM RAS CRC Kit detects rat sarcoma (RAS) gene mutations from plasma of late-stage colorectal cancer patients. It has been shown that patients with colorectal cancer harbouring wild-type RAS genes will benefit from therapeutic approaches that target the epidermal growth factor receptor (EGFR) by antibodies such as cetuximab or panitumumab.[3] However, patients carrying mutations in the RAS genes do not respond to anti-EGFR therapy.

In another example,[4] breast cancer patients overexpressing the human EGFR receptor 2 (HER2) gene will benefit from anti-HER2 therapy while patients overexpressing oestrogen receptor alpha 1 gene (ESR) will benefit from ESR antagonists. Gene expression assays like the Mamma Typer, which is an in vitro molecular diagnostic test, measures the expression levels of biomarkers in surgical breast cancer samples to guide the right therapy.[4]

The developmental life cycle of the IVD industry is fast-paced compared to that of the pharmaceutical industry. The current COVID-19 pandemic, which has brought the importance of IVD tests to the forefront, shows how suddenly a need for IVD can arise and how fast this need can be fulfilled. Already, a plethora of diagnostic tests have been rapidly developed in a matter of months by several companies. Some have received a **CE** mark in the EU while others are for research use only.[5]

IVDs that play a central role in companion diagnostics ("devices essential for the safe and effective use of certain medicinal products"[1]) and personalised medicine need to be co-developed along with their pharmaceutical counterparts. The new IVDR,[1] with a more streamlined approval process similar to the existing pharmaceutical market approval, will provide an opportunity for co-developing these products.

About the IVDR

Everyone in the healthcare sector would have heard about the MDR which stands for EU Medical Device Regulations 2017/745.[6] Less known but equally important, especially in the current pandemic scenario, is the IVDR that regulates IVDs. IVDR can be considered as the "younger sibling" of the MDR, shorter in length and scheduled for application in May 2022. The two regulations are quite similar in structure,

An IVD is "any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended … to be used in vitro for the examination of human biological specimens".

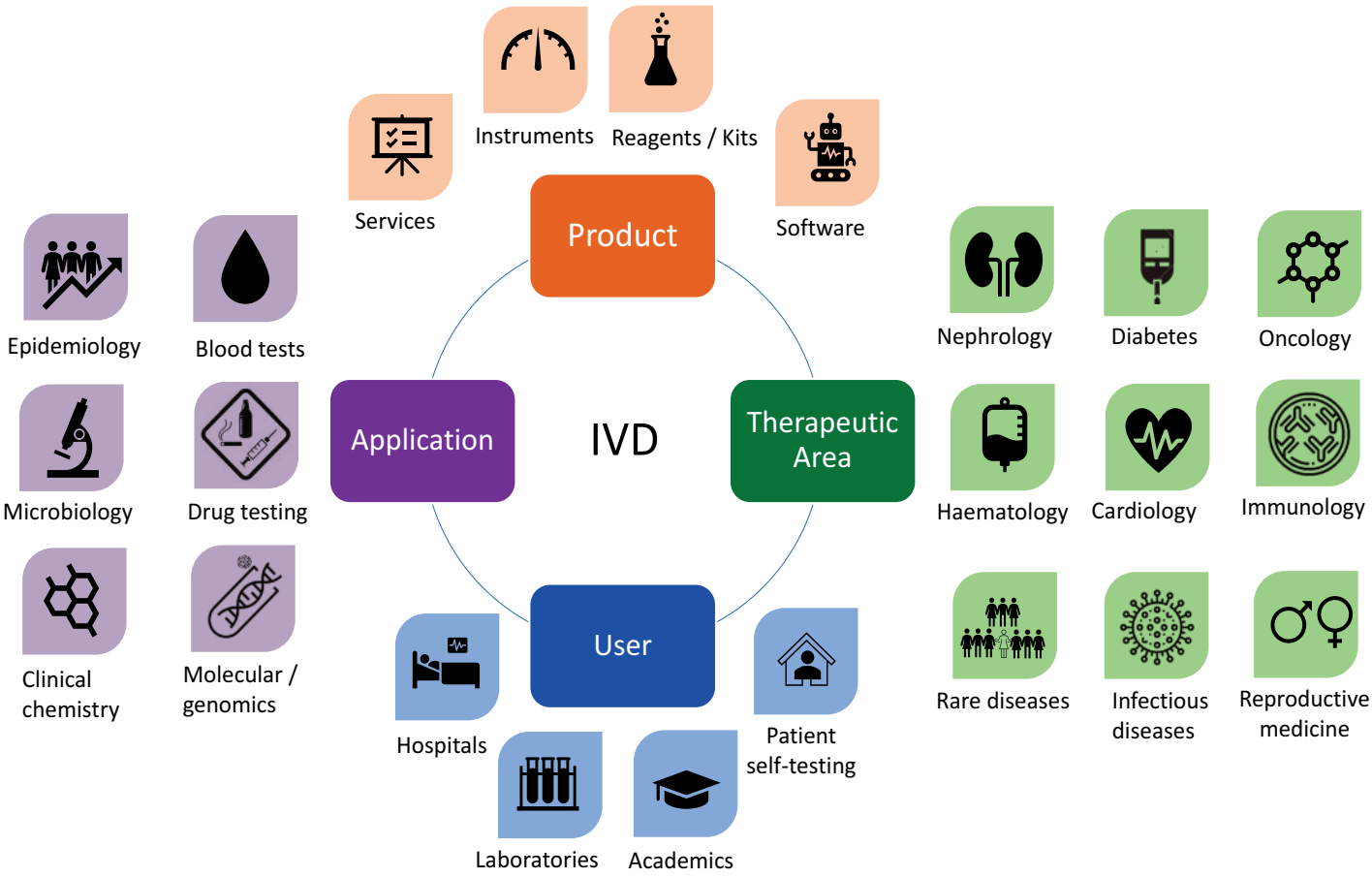


Figure 1. In vitro diagnostic medical devices by product, therapeutic area, application, and user (not an exhaustive list)

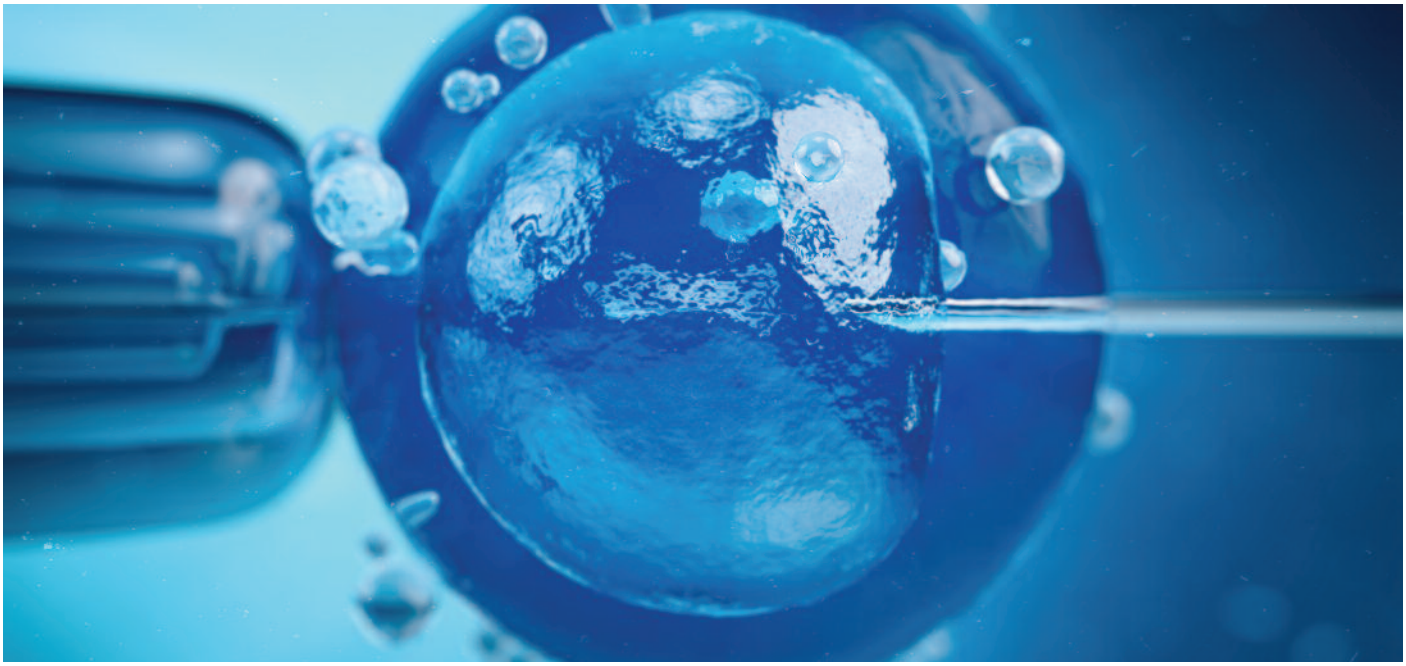
Table 1. Tables of contents of the MDR and the IVDR showing the similarities and key differences

Chapter/ section number	Chapter/section heading in the MDR	Chapter/section heading in the IVDR
Chapter I	Scope and definitions	
Chapter II	Making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement	Making available on the market and putting into service of devices, obligations of economic operators, reprocessing, CE marking, free movement
Chapter III	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices
Chapter IV	Notified bodies	Notified bodies
Chapter V Section1 Section 2	Classification and conformity assessment • Classification • Conformity assessment	Classification and conformity assessment • Classification • Conformity assessment
Chapter VI	Clinical evaluation and clinical investigations	Clinical evidence, performance evaluation, and performance studies
Chapter VII Section1 Section 3	Post-market surveillance, vigilance, and market surveillance • Post-market surveillance • Market surveillance	Post-market surveillance, vigilance, and market surveillance • Post-market surveillance • Market surveillance
Chapter VIII	Cooperation between member states, MDCG, expert panels, and laboratories and device registers	Cooperation between member states, MDCG, expert panels, and laboratories and device registers
Chapter IX	Confidentiality, data protection, funding, and penalties	Confidentiality, data protection, funding, and penalties
Chapter X	Final provisions	Final provisions
Annexes	17 Annexes	15 Annexes

Rows highlighted in grey are the key differences. Abbreviation: MDCG, Medical Device Coordination Group

Table 2. Key differences between the MDR and the IVDR Annexes

Category	MDR	IVDR
General safety and performance requirements (Annex I)	Requirements 1 to 23	Requirements 1 to 20
Technical documentation structure (Annex II)	Less granularity	More granularity Details include specimen types, assays, accuracy, sensitivity, specificity, shelf-life. and stability
Device classification rules (Annex VIII)	22 rules that cover non-invasive (4), invasive (4) and active devices (5) and special rules (9)	7 rules
Device classes (Annex VIII)	Class I, IIa, IIb, III	Class A, B, C, D
Clinical evidence	Based on clinical evaluation, post-market clinical follow-up, andclinical investigations (Annexes XIV and XV)	Based on performance evaluation, post-market performance follow-up, and clinical performance studies (Annexes XIII and XIV)



content, and the requirements therein.

Table 1 compares the high-level headings of the two regulations. Table 2 summarises the key differences as detailed in the Annexes of the regulations.

The role of medical writers in IVDs under the IVDR

On p. 24, our EMWA colleagues expound on the role of medical writers and some of the documents they develop for medical devices under the MDR.

Considering the similarity in the regulatory landscape for mainstream devices and IVDs, medical writers can also have a key role in complying with documentation requirements in the development and market authorisation of IVDs under the IVDR. The terminologies may differ between mainstream medical devices and IVDs but the principles governing the two sets of products and the requirements for compliance are very similar. Hence, medical writers who are familiar with medical devices and the MDR have skills and competencies that are highly transferrable to IVDs.

For example, Table 1 and Table 2 highlight the similarities and key differences between the two regulations. Further, Table 3 lists the key documents and their purposes as required under the MDR and the IVDR.

In order to develop these documents, a medical writer needs to draw on knowledge and competencies that include, but are not limited to, scientific writing, good clinical practice, data analysis, safety surveillance, public disclosure, and plain language writing. These are very similar to the skill set that medical writers use in other healthcare sectors such as those dealing with mainstream devices and medicinal products.

Table 3. Key documents that medical writers may develop as required by the MDR and the IVDR

Purpose	MDR	IVDR
Clinical evidence	Clinical evaluation plan Clinical evaluation report	Performance evaluation plan Performance evaluation report
Clinical studies	Clinical investigation plan Clinical investigation report Investigator's brochure Informed consent	Clinical performance study plan Clinical performance study report Investigator's brochure Informed consent
Post-market surveillance	Post-market surveillance plan Post-market surveillance report Periodic safety update report Post-market clinical follow-up plan Post-market clinical follow-up evaluation report	Post-market surveillance plan Post-market surveillance report Periodic safety update report Post-market performance follow-up plan Post-market performance follow-up evaluation report
Disclosure for the lay public	Clinical investigation results summary understandable by the end user Summary of safety and clinical performance	Clinical investigation results summary understandable by the end user Summary of safety and performance

In terms of structure and content of these documents, it is expected that the EU Medical Device Coordination Group will eventually provide clear guidance in addition to what is laid out in the IVDR. However, it is important that IVD companies should start the preparatory work to comply with the IVDR requirements as soon as possible. And the role of medical writers should be considered seriously.

Conclusions

IVDs occupy only a small segment of the healthcare industry. Yet, they play a vital role in healthcare as demonstrated during the COVID-19 pandemic. Medical writing for IVDs is still considered a "niche" and non-mainstream field that requires specialised training and experience. However, it is also clear that the regulatory landscape for mainstream devices and IVD is quite similar. The information provided in this article about IVDs and the IVDR demonstrates that medical writers can easily transition their skills set to support the IVD industry to comply with the IVDR requirements.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their respective employers or EMWA.

Conflicts of interest

Both authors are employed in the pharmaceutical industry.

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Raquel Billiones has more than 14 years' experience as a regulatory medical writer that spans the pharma and medical devices industries in the freelance, clinical research organisation, and pharmaceutical environments, from entry level to leadership positions. An EMWA member since 2006, she has served in various roles, currently as an associate editor for *Medical Writing*, workshop leader, MD SIG lead, and Education Committee member.