edma DIAGNOSTICS FOR HEALTH

Position Paper

A NEED FOR SEPARATE LEGISLATION

EDMA analysis of proposed Regulation on in vitro diagnostic medical devices

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INTRODUCTION

The European Diagnostics Manufacturers Association, EDMA, welcomes the Commission Proposal for a Regulation on in vitro diagnostic medical devices (IVDs) and its intention to strengthen the current system for the sake of patient safety, while still guaranteeing a competitive and innovative environment for manufacturers. EDMA supports in particular the choice of a Regulation as the legal instrument, in order to ensure the harmonised application and interpretation across all EU Member States.

In this position paper, EDMA suggests further improvements to the Proposal, which aim to strengthen patient safety, facilitate the effective use of IVDs by healthcare systems and support the industry to develop and bring IVDs to patients.

We encourage the European Parliament and the Council of the EU to integrate these improvements as the Proposal moves through the legislative procedure.

EDMA also seizes this opportunity to clarify what IVDs are, their role in healthcare and how they are different from other healthcare products.

WHAT ARE IN VITRO DIAGNOSTIC MEDICAL DEVICES?

In vitro diagnostics (IVDs) are tests that determine medically relevant information based on samples derived from the human body. Such samples typically include blood and urine, although saliva, tissue or cerebrospinal fluid can also be analysed. The IVDs themselves commonly include an instrument that performs the test, a reagent that is able to specify the information under question, and possibly a specimen receptacle to help collect and transport the specimen.

IVDs are used for predictive testing, screening, diagnosis, disease characterisation and monitoring of patient conditions. IVDs range from large complex automated laboratory systems that are capable of analysing hundreds of samples for dozens of parameters per hour, to relatively portable near-patient testing kits that deliver rapid results to healthcare professionals. Easy to use self-testing systems are another type of IVD which provides information directly to the individual performing the test.

Unlike other forms of medical technology, IVDs are unique in that they never interact directly with the human body. They provide information on a medical condition, but without having a direct therapeutic effect. The absence of direct contact and the absence of a direct therapeutic effect are key characteristics of IVDs, setting them apart from medical devices and pharmaceuticals. This distinction also creates a different assessment structure for IVDs: any risk associated with their use is exclusively *indirect* as it stems from the information they provide and *how this information is acted upon*. The expertise of the healthcare professional using the IVD is crucial to ensure the correct decision making for patient treatment and care.

To minimise even such indirect risks, IVDs must demonstrate compliance with strict product safety and performance requirements, through clinical evidence. Procedures are in place to closely monitor the product once on the market.

Some IVDs are used in clinical laboratory testing, where users routinely verify the performance of the test. These laboratories generally operate under external control schemes including external quality assessments, ring trials and internal quality management systems.

These mechanisms aim at proactive, rapid identification of potential technical problems before they become clinically relevant for the patient.

ROLE IN HEALTHCARE

IVDs are imperative to many therapeutic decisions and patient safety, but are not well known by the public as their work remains 'behind the scenes'. IVDs have transformed healthcare thanks to faster and more accurate diagnosis, improving patient outcomes and having the potential to present significant savings to healthcare systems, as unnecessary treatment and multiple hospitalisations can be avoided. The critical information provided by IVDs can take several forms, including:

- **Predictive testing** – As one of the key applications of genetics, these assays determine the predispositions that a healthy person has for developing a disease in the future.
- **Screening** – Controlling a sub-population for a specific underlying condition, which does not yet show any symptoms. Examples include colorectal cancer screening and screening of the blood supply for potential pathogens.
- **Diagnosis** – Identifying the medical condition a patient is suffering from and potentially, its stage of development. Tests have been developed for diseases as varied as hepatitis and metabolic disorders.
- **Characterisation of diseases** – After receiving the initial diagnosis, the patient's condition can be further analysed to determine the most appropriate measures to be taken. Viruses can be genotyped to pinpoint the exact strain and companion diagnostics guide selection of the appropriate treatment in complex diseases, especially when dealing with cancers.
- **Monitoring** – Used in the management of certain diseases, especially chronic conditions, that require consistent monitoring to ensure optimal patient outcomes. Blood glucose monitoring in diabetes, for example, allows patients to maintain an independent lifestyle.

The information gathered through these testing approaches is used to take decisions on how to best treat the patient. Our understanding of the concept 'disease' has begun a paradigm shift from a symptom-based definition to an understanding based on the underlying genetic mechanisms. A special type of IVDs – companion diagnostics – ensures that patients receive the treatments that will effectively combat their condition. IVDs can further empower patients to better take control of their own health by allowing them to manage their condition on a day-to-day basis.

IVDs' key role in public healthcare is apparent not only at the individual patient level, but also to a wider extent because IVDs ensure the safety of the blood supply – both in screening for infectious agents and by blood typing. Such IVDs enable transplantation procedures that match donors to recipients, and survey outbreaks of diseases and emerging health threats.

WHERE AND HOW ARE IVDS USED?

IVDs are strictly reliant on patient samples and lack any direct interaction with patients themselves. It is a growing trend in healthcare that more and more clinically relevant information is obtained through the in vitro testing of such samples.

The three main instances of use can be classified as:

- **Clinical laboratory testing** – Certain complex tests can only be run in controlled laboratory environments, which also tend to handle larger numbers of tests. To ensure accuracy, these laboratories operate under an external control scheme. The trend in Europe is to move towards the accreditation of clinical laboratories within their own quality system management.
- **Near-patient testing** – Testing carried out by trained professionals, such as nursing staff, physicians or emergency response personnel, outside of a controlled clinical laboratory setting, is a developing area of IVDs. While not all tests are available in a near-patient format, those that are, provide information on the management of patient conditions or are used for screening and preliminary diagnosis.
- **Self-testing** – Designed for lay persons, these tests are often, though not exclusively, performed by the affected individual usually for management of health conditions (e.g. diabetes) or to provide relevant health information (e.g. pregnancy tests).

RISK OF IVDS AND CONTROL MECHANISMS

The distinction between IVDs and other medical devices rests in the way they are used on patients. Unlike most medical devices, IVDs do not come into direct physical contact with the patient. IVD risk classification is therefore made on the basis of the impact that the provision of inaccurate information would have on patient care decisions. Patient care decisions are ultimately taken by healthcare professionals, often in cooperation with pathologists, patients and other experts on tests. Thus the risk posed by the IVDs is determined by the value of the information they provide, rather than by any direct effect which they have on patients.

Another dimension to understanding the risk posed by IVDs is determined by the role an IVD test plays in public health. For example, IVDs may present a risk that is not specific to any individual patient, but to healthcare systems at large. This is particularly true of tests used in ensuring the safety of the blood supply,

such as those involved in determining blood type, which does not threaten the health of the donor, but could put the recipient at risk.

Because the risks posed by IVDs are related to the information they provide, they can also be controlled in different ways. For instance it is common practice for the information that IVD assays provide to be verified at the time of use through the testing of control materials whose properties are known. If a test gives an incorrect result on the control materials, the issue is investigated, but the patient does not actually receive an incorrect result.

The distinction between direct and indirect risk is why IVDs are subject to the new classification system in the Commission's Proposal ranging from A to D (lowest to highest), according to the impact their malfunctioning would have on public health. Class D IVDs (considered to be the highest risk IVDs) are classified as such because their failure would have an impact beyond that of the individual patient, while classes C, B and A are based on decreasing individual health risks. One important consequence of this is that even though both IVDs and medical devices have four risk classes, the classes are not comparable, as, for instance, a class D IVD represents a substantially different risk from a class III medical device.

These distinctions in risk classification are also reflected in the current legislation's fundamentally different approaches towards the control of safety and performance of IVDs. This distinction has also been kept intact in the Commission's Proposal for an IVD Regulation.

A NEW REGULATORY FRAMEWORK

The European Commission's proposal for a Regulation on in vitro diagnostic medical devices acknowledges the important role of in vitro diagnostics for public health and the quality of life of patients. The changes proposed to the current legislation are intended to take into account the need for protection of health, without sacrificing an innovative and competitive market environment.

GENERAL REMARKS

EDMA welcomes the Commission's continued acknowledgement that IVDs need a different assessment approach than other medical devices, and the decision to adopt a separate Regulation for IVDs.

It is imperative that the final Regulation continues to respect the unique characteristics of IVDs. It must also ensure efficient procedures for putting IVDs on the market, to enable patients and clinicians faster access to these life-saving technologies. The Regulation must also be flexible enough to respond to rapid technological and research advancements.

EDMA notes some new aspects that are particularly well suited for IVDs:

Common Technical Specifications (CTS) – CTSs are documents that describe the details that a device must meet in terms of performance and the way in which this must be tested. IVDs are particularly well suited for such performance tests as when an adequate set of samples can be used, the IVDs will be controlled in conditions that are identical to those in which they would be used in live healthcare systems.

Clinical evidence – As a relatively new way of explicitly stating the requirements for IVDs, clinical evidence is composed of three elements: analytical performance, scientific validity and clinical performance. Together they form the foundation of clearly defined control for all IVDs:

- Analytical performance ensures that the IVD is capable of assessing what it intends to measure;
- Scientific validity ensures that the measured analyte is relevant to the condition under investigation; and
- Clinical performance ensures that the IVD will actually perform as intended in a clinical setting.

Post-market controls – The nature of IVDs makes them particularly well suited for post-market controls as it is possible to compare results from the same patient as attained through different testing systems. As such, discrepancies or problems become immediately evident.

EDMA supports the new classification system as it follows international GHTF/IMDRF classification system thereby contributing towards global harmonisation, which helps IVD companies.

However, some provisions in the proposal could be improved. Below, EDMA suggests changes that aim to strengthen patient safety, to facilitate the effective use of IVDs by healthcare systems and to support the industry to develop and bring IVDs to patients.

SUGGESTED IMPROVEMENTS

COMPANION DIAGNOSTICS ANNEX VIII SECTION 6.2

Article 2 (6) - Definition

Under the new proposal companion diagnostics are defined as a unique category of IVDs that are used in personalised medicine. This is a welcome step as a definition that was missing in the past.

The Commission's proposed definition is:

> *"A device specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy."*

EDMA fully supports this definition as it accurately reflects the nature and extent of companion diagnostics.

Classification and assessment by medicines agencies

It is appropriate that the majority of companion diagnostics will be classified as Class C. This ensures that they will be subject to a stringent level of control through an assessment which will include an in depth review of the clinical and scientific evidence which justify the use of the companion diagnostic tests.

It is essential that the regulatory processes account for the relationship between the companion diagnostic and its related medicine. The proposal contains some clarification on how Notified Bodies would work with the competent (medicines) authorities or the European Medicines Agency (EMA). However, there is a lack

of clarity on how this consultation process would work in practice, and the roles and responsibilities of each actor.

The Commission Proposal states that the authority responsible for the approval for a medicinal product be consulted during the approval process of a companion diagnostic.

However, the European Medicines Agency has neither the mandate nor the expertise to assess in vitro diagnostics. On the other hand, at the time of approval of a medical product that relies on a companion diagnostic, it is to be expended that the medicines agency would want to have an assurance that the companion diagnostic used performs as required, ensuring that patients are correctly selected for treatment. It would therefore seem reasonable that at that time EMA would consult with the competent authority and/or notified body responsible for the companion diagnostic.

It should also be noted that when a drug and a companion diagnostic are developed in parallel, a medicines agency is already involved in the oversight of the clinical trial and therefore has access to data that reflects how well a companion diagnostic can select patients. If this is not accounted for, there is a risk of serious delays to patient access to treatment. EDMA therefore seeks clarifications of the text to the effect that duplication of regulatory submissions and efforts to generate evidence are avoided.

In order to ensure transparency in the system and guarantee the performance of the companion diagnostics, the development of common technical specifications for companion diagnostics would allow for a system with clear performance requirements which would provide transparency to all authorities involved as to the suitability of use for a given companion diagnostic.

EDMA therefore asks for a review of section 6.2 of Annex VIII so as to reflect:

- The need for EMA to consult with notified bodies and/or IVD competent authorities during the approval process of a medicinal product that relies on a companion diagnostic.
- A pragmatic approach to approval of companion diagnostics themselves that does not add undue delays allowing the companion diagnostic and the medicinal product it is related to, are available at the same time for use.

Articles 2 (54), Article 4.5, Article 59.4, - In-house tests

Companion diagnostics are unlike other class C IVDs as their specific association with a particular medicinal product means that they are essential to the use of these life-saving medicines. To ensure their safety, additional measures are described in Annex VIII section 6.2, which other class C devices do not have to comply with.

For class C in house assays*, the safety and performance requirements are substantially lower than those of normal IVDs. Specifically for companion diagnostics the need to demonstrate that the IVD can successfully select patients for treatment is not required for in house assays, nor is the need for an external design review of the product.

In this context, EDMA would like to emphasise as a general principle that any companion diagnostic test – whether commercialised or not – should fulfil high safety and performance requirements in the interest of patient safety and optimal care. Due consideration shall always be taken to the risk that the test in question poses to the patient.

Therefore, 'assays developed by clinical laboratories for in-house use should meet the same quality, safety and regulatory requirements as IVDs in order to ensure they perform to the same level as the companion diagnostics they replace[1]'.

EDMA thus asks that companion diagnostics should not benefit from the in-house exemption under Article 4 paragraph 5.

* IVDs that are manufactured and used within a single health institution, but not commercialised (such as within a hospital).

CONTROL OF IVDS – CHAPTER II, ARTICLE 7

The classification for an in vitro diagnostic is chosen according to the risk it poses to the population, with the highest, Class D, devices reflecting an indirect threat beyond the individual (e.g. blood typing for blood donations). These types of IVDs are subject to control through the Common Technical Specifications (CTS), which detail the intended performance of a device and the processes that have been undergone to demonstrate the accurate performance. This approach is well-suited to IVDs because the conditions for CTS assessment are identical to those in which a specific diagnostic test will be used in practice.

Under the new proposal, the mechanisms of control are strengthened through a combination of higher risk classification for most IVDs and more stringent pre-market, CTS and post-market controls, in particular in relation to the clinical evidence associated with IVDs, and the introduction of reference laboratories, which will enable authorities to have access to an independent scientific resource for assessment of devices.

EDMA is in support of post-market controls because pre-market controls cannot account for all of the potential issues that may arise, some of which are only apparent at time of use. As IVDs are additionally controlled at the moment of use, rapid identification of any problems is possible to guarantee patient safety.

TRANSITION PERIOD – CHAPTER X, ARTICLE 90

EDMA strongly supports the five-year transition period for IVDs. This provides a sufficient amount of time for manufacturers to achieve full compliance and, assuming that a systematic approach is taken, will also ensure that all of the necessary processes – both compliance and manufacturing – are in place.

The proposed Regulation introduces many new requirements for IVDs. The new classification system will force the majority of IVDs to shift from a self-certification system to one which requires involvement of the Notified Bodies. The Notified Bodies must also be re-designated and qualified to perform conformity assessments on the specific IVDs.

Other areas of significant impact are the requirement for clinical evidence reports and post market surveillance plans for every IVD. Thus, a five-year transition period is justified for IVDs.

The provision of a five-year transition period presumes that certain measures have been completed and are functional at the start of the transition period, in

[1] European Alliance for Personalised Medicine : New Perspectives for Patients in Europe for Patients in Europe http://img.euapm.eu/resources/eapmmanifesto.pdf

particular the re-designation of notified bodies, and a European databank with all of its subparts (electronic systems for UDI, registration, clinical performance studies, vigilance and market surveillance). EDMA believes these steps are integral to the success of the new system and mechanisms for these must already be in place at the start of the five-year transition period.

FINAL REMARKS

EDMA emphasises the need for a strong regulatory framework that places emphasis on patient safety, encourages the responsible use of IVDs in healthcare systems and fosters innovation without undue delays. With the suggested improvements, there is an opportunity to do precisely that, giving patients and healthcare providers the chance to take a proactive approach to healthcare through accurate diagnosis that can guide decisions on which is the best medical response for a specific patient. EDMA thus encourages the European Parliament and the Council of the European Union to integrate these improvements into the Proposal as the legislative procedure moves forward.