

PROPOSED REGULATION ON IN VITRO DIAGNOSTIC MEDICAL DEVICES

Comments on Council Partial General Approach

25 August 2015

Executive summary

EDMA, the voice of the in vitro diagnostic manufacturers in Europe, welcomes the progress in the development of an EU Regulation on In Vitro Diagnostics (IVD), which intends to strengthen the current approval system for in-vitro diagnostics. This regulation will introduce substantial changes to the existing legislation, first introduced in 1998. The Council's partial general approach of June 2015 still falls short, and requires improvement to fulfil the overarching objective of creating a new specific regulation for in vitro diagnostic medical devices.

In order to achieve a successful outcome of the trilogue negotiations between the European Parliament, Council and the European Commission, EDMA calls for an emphasis on a high level of protection to patients and fostering innovation in the EU. This can be done by focusing on delivering effective safety and performance requirements for products, alongside a clear and highly efficient approval system.

At this stage the text is not specific enough to in vitro diagnostic products and their characteristics, which are distinct and different from other health technologies, such as medical devices, pharmaceuticals and biotechnology. In addition, there are significant amount of technical anomalies. As a result the regulation as proposed would put an excessive and unnecessary administrative burden on SMEs – which make up 95% of this sector.

Six key areas requiring further attention include:

- I. **Clinical Evidence** requirements must be adapted to the specificities of IVDs, and be broadly appropriate for all IVDs, not just companion diagnostics and interventional technologies, which make up only a few percent of all IVD products. Acknowledging this is especially important when defining requirements for studies, post-market assessment, and criteria for assessment of IVDs.
- II. **Conformity Assessment** should reflect the risk-based approach with proportionate regulatory controls increasing alongside the risk class.
- III. **Quality Management Systems** should establish only those requirements applicable and feasible for IVDs, as opposed to those applicable for other health technologies. In addition, specific IVD technology and requirements (e.g. self-tests) should adequately reflect the nature of these devices.
- IV. **The Companion Diagnostics** definition is not specific enough and should only include those IVDs selecting patients for a specific therapy. In addition, the mechanism for clinical evidence requirements for companion diagnostics, especially scientific validity and intermediate assessment, must be adapted.
- V. **Classification** principles for IVDs must be consistently applied to ensure a system of controls that is proportional to the risk class of the IVDs, while at the same time adhering to the internationally agreed classification scheme.
- VI. **Labelling Requirements** need to be clear and uncluttered, focusing on the information that is essential for the safe use of the IVDs to deliver relevant results and adhering to globally harmonized labelling requirements.

Analysis per topic

I. Clinical Evidence (Articles 47-58 & Annexes XII and XIII)

EDMA proposals with regards to clinical evidence:

- a) **Study type:** Better separation between the requirements for general studies (applicable to more than 95% of the IVDs) and those which involve a risk to patients (less than 5% of the IVDs) (Annexes XII & XIII)
- b) **Concept of clinical benefit:** Criteria for assessment of clinical evidence based on the output of the diagnostic technologies, not on subsequent healthcare pathways or patient outcomes
- c) **Post-market assessment:** The Council text on continuous assessment must be clarified to enable a feasible and appropriate post-market surveillance system for IVDs.
- d) **Pre-market evidence gathering:** Information and data driven clinical evidence requirements, rather than process driven requirements.

The introduction of clinical evidence requirements for all IVDs is at the heart of the new IVD regulation. The greatly increased requirements that IVD manufacturers would have to meet were first established in the European Commission proposal and now further expanded in the Council position. These requirements must be clear, applicable, feasible and appropriate for implementation.

EDMA has the following concerns:

a) Defining study requirements: Most studies on IVD are conducted without any involvement of patients, e.g. by using samples from biobanks. The requirements for these studies are defined in Annex XII. It is only in exceptional cases that patients are directly involved in the study, i.e. where patient management decisions are taken as part of the study or the specific type of specimen collection poses some risk. Requirements for these studies are defined in Annex XIII, including more rigorous requirements.

Concern: Council text does not clearly differentiate between the requirements for studies where no patients are involved (Annex XII, General requirements for studies), greater than 95% of the IVD studies; and those where patients are involved and potentially at risk (Annex XIII, Specific requirements for interventional studies), less than 5 % of all IVD studies.

Proposal: Requirements for Annex XII (general requirements for studies) and Annex XIII (specific requirements for interventional studies) need to be adequately differentiated. In addition, in the implementation phase, a more precise definition of which specimen collection practices are considered to be a risk for patients needs to be developed.

b) Concept of clinical benefit: Clinical benefit refers to a patient outcome. However, IVDs provide purely diagnostic information. They cannot directly determine a patient outcome or a care pathway for the patient, as these are determined by healthcare professionals, the national healthcare system and the national clinical care guidelines.

An appropriate requirement would be to assess IVDs against other diagnostic options and technologies, but not specifically against patient outcomes.

Concern: The Council text introduces a need for all IVDs to be assessed against a clinical benefit. Assessing against a patient outcome as required by clinical benefit is not a feasible measure for IVDs, nor is this the role of IVDs.

Proposal: Criteria for assessment of clinical evidence applicable for IVDs should be based on the output of the diagnostic technologies, not on subsequent healthcare pathways or patient outcomes.

c) Post-market assessment: An IVD result is relevant for a given patient at a single point in time. The test is not indicative of any future result for that patient. For instance, a Hepatitis B test reflects the status of the patient at the specific moment when the test is performed. That single test cannot follow the future condition of that patient. Continuous assessment of that test is irrelevant for the monitoring of the safety and performance of the IVD. Rather, this is done through post-market assessment, whereby IVD manufacturers need to monitor developments in epidemiology (emergence of new strains) and changes to clinical evidence, for instance through the emergence of new interference (e.g. caused by a new therapy).

Concern: The Council text introduces the concept of a 'continuous assessment' for all IVDs. It leaves unclear whether this concept refers to the following-up of patients or the post-market surveillance of the IVD. Only the latter would be the appropriate method.

Proposal: The Council text on continuous assessment must be clarified to enable a feasible and appropriate post-market surveillance system for IVDs.

d) Pre-market evidence generation: The method of how to gather clinical evidence and information can vary significantly depending on the IVD, e.g. there are significant differences in gathering data for a urine cup and an HIV blood screening assay. Rather than the process, it is the endpoints of evidence generation that are critical for IVDs.

Concern: Instead of the output-oriented concept as proposed by the European Commission, the Council text proposes uniform procedural requirements on how data must be gathered.

Proposal: Information and data driven clinical evidence requirements, rather than process driven requirements are more appropriate to which avoid unnecessary burden for manufacturers and ensure adaptability to embrace innovative approaches.

II. Conformity Assessment (Article 40)

EDMA proposals with regards to conformity assessment:

- a) **Class C Devices:** Amend article 40 to remove references to assessment by generic device group – assessment should be done on a representative basis.
- b) **Class B Devices:** Amend article 40 to ensure that assessment of class B devices focusses on the quality management system requirements (this is also in line with the global approach as suggested by GHTF).

Conformity assessment routes are dependent on the principle that the higher the risk presented by a device, the more detailed the control mechanisms should be. Such a basis is important for two key reasons:

- It focusses the regulatory system resources on the control of high risk and high impact devices, such as HIV screening assays;
- It supports a practical system for the effective development of all classes of IVDs.

The Commission, in Article 40 of its proposal, lays out how different IVDs will be controlled following a risk based approach increasing in line with their risk classification. The text greatly increases the control mechanisms for IVDs by including interventions of Notified Bodies for the vast majority of IVDs in the conformity assessment processes. Under the proposal in contrast to the 20% of IVDs that are subject to Notified Body controls today, over 80% of IVDs will undergo controls from NBs.

Concern: The Council erodes the risk based approach by further proposing increased control mechanism requirements for class C IVDs virtually identical to those of class D, simultaneously also increasing the control requirements for class B. This creates a disproportionately heavy regulatory burden.

For example, according to such a proposal, for a midsize company with approximately 100 class C IVDs, approximately 75 of them would be de facto regulated as if they were class D and need to undergo design dossier examinations, as stipulated by the requirements of assessment for each generic device group. The reason for such a large impact is that generic device groups for IVDs (as defined by the Global Medical Device Nomenclature [GMDN]) are substantially more detailed than for most other medical devices. In practice, this would require auditors to be permanently assigned to the company to review its documentation. This is disproportionate when considering the risk of class C IVDs.

Similarly, for class B IVDs, the requirement for technical documentation assessment on a representative basis goes far beyond what is practical and needed for these IVDs.

III. Quality Management Systems (Annex VIII)

EDMA proposals with regards to quality management systems:

- a) **Self-Tests:** Amend Annex VIII section 6.1 to better reflect the nature of self-tests, in particular full review of all essential requirements should be determined by the risk class of the self-test, not only the fact they are self-tests.
- b) **Near-Patient Tests:** Article 40 and Annex VIII should be consistent – section 6.1 of Annex VIII should only apply to self-tests.
- c) **Requirements not applicable to IVDs:** Requirements that are not applicable for IVDs should not be included in the IVD Regulation, e.g. preclinical evaluation is not valid for IVDs as these do not serve a therapeutic purpose; instead of assessing the clinical application of IVDs, which varies based on health systems, IVDs should be assessed for a high standard of safety and performance.

Under the new regulation, the Quality Management System requirements described in Annex VIII will be the conformity route applicable to the vast majority of IVDs. As such, it is critical that it reflects the nature of IVDs and that it allows for a clear and effective conformity assessment. In particular for:

a) Self-tests: The Council proposes that all self-tests be subject to a full technical documentation review, including an assessment of compliance with every essential requirement, irrespective of the risk class of the self-testing device.

While self-tests have long been considered to be a special sub-set of IVDs, the particular risks posed by self-tests focus on the ability of the patient to perform the test and be able to understand the results. As such, while the information to be provided to patients has always been carefully assessed, the new proposal will include a design dossier review.

Concern: Applying a uniform approach to all self-test IVDs, with no regard for their actual risk class, does not reflect the nature of self-tests. For instance, there is a significant difference in risk between a self-testing device for HIV, which due to its risk class (D) would already be subject to a technical documentation assessment, and a urine cup (class A) that is only intended to enable the patient to collect a urine specimen. Such differences need to be respected as reflected in the Commission proposal, which effectively increases the requirements for all IVDs while still reflecting the nature of self-tests.

b) Near-Patient Tests: Annex VIII needs to be consistent with article 40 – article 40 was amended to reflect that near-patient tests will be subject to conformity requirements based solely on their classification and therefore not subject to Section 6.1 of Annex VIII. Thus section 6.1 of Annex VIII applies only to self-tests. Annex VIII section 6.1 should also reflect this.

c) Requirements not applicable to IVDs: Several requirements that have been put in place by the Council are not applicable for IVDs. For instance:

i. Preclinical evaluation: This is a specific term used to describe a stage in the development of therapeutic technologies whereby animal testing and toxicological screens are carried out.

Concern: As IVDs have no therapeutic effect this requirement is not applicable to IVDs.

ii. Clinical application of IVDs: The proposal requires NBs to assess against the clinical application of the IVD.

Concern: IVDs are diagnostic technologies and as such their clinical application is dependent on the patient management pathways available in a given health system. As these vary across different health systems, it would be both unfeasible and irrelevant to do an EU wide assessment of the clinical application to support a CE mark.

IV. Companion Diagnostics (Article 2 & Article 48)

EDMA proposals with regards to companion diagnostics:

- a) **Definition:** The definition of companion diagnostics should reflect the small subset of devices that are truly acting as gatekeepers for advanced therapies. The European Parliament proposal constitutes a good definition, though further guidance may be needed in secondary legislation.
- b) **Scientific Validity for companion diagnostics:** Article 48 should not require the establishment of scientific validity prior to conducting interventional studies, whose purpose is usually to establish the scientific validity.
- c) **Mechanism for intermediate assessment:** A clear mechanism for intermediate assessment of companion diagnostics once the analytical performance has been established needs to be put in place to ensure the safety of patients involved in trials and a clear path to market for companion diagnostics.

Companion diagnostics are an innovative and growing portion of the IVD sector, holding great promise as enablers of personalised healthcare solutions for patients across Europe. Because of their particular role as gatekeepers of access to advanced therapies, they are given special consideration under the new Regulation and are subject to additional requirements and controls.

a) Definition of Companion Diagnostics: The proposed definition of the Council includes all IVDs that identify patients likely to benefit from a medicinal product. There is also a specific mention of devices that monitor a response to treatment for the purpose of adjusting the treatment (dosage, frequency, etc.).

Concern: The proposed broad definition of a companion diagnostic would encompass many basic diagnostic tests that are not generally considered to be a companion diagnostics. For instance, HIV tests, which identify patients who will benefit from anti-retroviral therapies, or cholesterol tests that identify patients who will benefit from statin treatments would be considered companion diagnostics. Yet, these are not novel assays that require additional treatment or intervention from the European Medicines Agency.

As regards to monitoring, the definition includes assays that have a different risk profile. Such tests are not gatekeepers of a specific therapy whereby a single mistake could lead to patients not receiving therapy. Rather, monitoring tests help to adjust treatment decisions, as is the case for cholesterol tests. Unlike with companion diagnostics, a single error by such a test can be corrected by the next monitoring check or by other indications on the condition of the patient.

b) Establishing Scientific Validity for Companion Diagnostics: Scientific validity for companion diagnostics demonstrates that the biomarker being measured really corresponds to the adequate selection of patients for a therapy. This is generally determined through interventional studies, which are part of larger clinical trials for the associated pharmaceutical.

Concern: In Article 48, Council has included a requirement stating that interventional studies can only be conducted after scientific validity has been established. This creates an illogical loop – the study cannot be conducted until the scientific validity is established, while scientific validity can only be established by conducting the study.

c) Missing mechanism for an intermediate assessment: According to the Regulation text, analytical performance of companion diagnostics must be fully established before the tests are used in interventional studies. There is currently no mechanism for intermediate assessment of analytical performance.

Concern: An intermediate assessment mechanism is crucial as the authorities responsible for supervising the conduct of the pharmaceutical trial – which includes the interventional study for the IVD – need to consult the authorities on the analytical performance of the companion diagnostic.

V. **Classification (Annex VII)**

EDMA proposals with regards to classification:

- a) **Rule 1:** Revert back to the Commission proposal – Class D should be kept only for IVDs with a public health impact.
- b) **Rule 4:** Self-tests that are low risk should remain in class B.
- c) **Rule 5:** While Rule 5 may need clarification, classical diagnostic technologies such as culture media or histological stains should remain in class A.

The new classification system is one of the core changes introduced in the IVD Regulation. Based on an international consensus, it places IVDs whose failure could result in a risk at the level of health systems (e.g. resulting in contaminated blood supply, outbreak of a deadly disease) in the highest class (D), while the rest of the classes (C through A) reflect IVDs that have an impact on individual patients (from high to low risk). The basis for the classification is the intended use of the IVD. This is substantially different from the classification system used for medical devices because there are no health system effects.

For all classification changes, there are concerns that a deviation from the international consensus will increase the burden on the industry, have a detrimental impact on competitiveness, and reduce availability – all without a clear justification:

a) Rule 1 – Upclassification of viral load assays: Council proposes that assays for the monitoring of HIV and hepatitis C infections be classified as class D.

Concern: These assays have no impact on healthcare systems as they are used to determine the status of individual patients. In line with the general risk approach, which is also used at a global level, these should remain in the class with high individual risk, which is Class C.

b) Rule 4 – Upclassification of devices for self-testing: The Council has classified all devices for self-testing as class C.

Concern: Not all self-tests present the same risk to patients. For instance, a pregnancy self-test has a lower risk class than a self-test for syphilis, both because of the consequences of the test and because of the impact of an erroneous result.

c) Rule 5 – Class A devices: The Council proposal changes the way in which Rule 5 for Class A devices is defined. As a consequence of the change classical diagnostic technologies with minimal risk, such as certain culture media and histological stains, are no longer covered by rule 5 (this was the primary intention of the GHTF guidance documents as also implemented for example in Australia).

VI. Labelling Requirements (Annex I)

EDMA proposals with regards labelling:

- a) **Requirements not relevant for IVDs:** Requirements not relevant for IVDs such as the requirement regarding the effects of therapeutic radiation should be removed.
- b) **Duplication of traceability information:** Requirement for including the single registration number on the labelling should be removed as the information is accessible through the UDI.
- c) **Batch Specific instructions for use:** Instructions for use should not have batch specific requirements.
- d) **Use of Electronic instructions for use:** The use of electronic instructions for use should be permitted as it is today in particular for devices for professional use.

Labelling requirements as defined in Annex I are a critical way of communicating relevant information to users on the nature of the device. It is a means to understand the function, operation and risks of an IVD. In order to be effective, labelling requirements need to focus on that which the user needs to know – information which is not relevant for the identification and safe operation of the IVD detracts from the effectiveness of labelling.

It cannot be understated that developing and maintaining labelling in conformity with legal requirements is a major cost factor for IVDs due to the complexity of the products and of the information which needs to be supplied. Thus the addition of labelling requirements which do not improve the safety or the use of a device can add a significant cost, a burden which is disproportionately heavy on SMEs.

a) Requirements not relevant for IVDs: A number of requirements have been introduced by Council which are not relevant for IVDs – these may be relevant for some therapeutic devices (e.g. Risks associated to the effects of therapeutic radiation) but should not be considered for IVDs.

Concern: Labelling requirements which are not relevant for IVDs should be removed – such requirements are an unnecessary burden and detract from critical information.

b) Duplication of traceability information: The council adds a requirement to include the single registration number (which is relevant for the manufacturer) into the labelling of the IVD. The single registration number is a means of relating data within Eudamed, however it is of very little value to users and can in any case be obtained through the UDI (unique device identification).

Concern: UDI is the system for tracing devices and their manufacturers. Adding a second tier to the system is confusing and unnecessary.

c) Batch Specific instructions for use: Instructions for use (IFU) are developed for IVDs to provide an insight into how to use them safely and how users can achieve the intended performance. IFU do not contain batch specific information – their development and updates are linked to product design, not to batch specific aspects which are normally included on the label (e.g. expiry date).

Concern: The inclusion of batch specific performance information in the IFU as a general requirement is not needed for the safe use of devices, since the performance of all batches falls within the stated performance for the IVD. Inclusion of batch specific IFUs would significantly increase the costs of developing IFUs for IVDs.

d) Use of Electronic instructions for use: Electronic distribution of IFU for professional use IVDs has been a reality since January 2007 when Commission published clear guidelines (MEDDEV 2.14/3) which allowed this practice. This has been very well accepted by users and enables rapid and clear dissemination of information which is relevant for the use of IVDs. This practice should be continued.

Concern: In their proposal Council has made a number of modifications which could be interpreted as restricting the electronic distribution of IFU (e.g. by removing the statement that IFU might be presented in different media). Electronic distribution of IFUs should continue.

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