

## REVISION OF DIRECTIVE 98/79/EC ON IN VITRO DIAGNOSTIC MEDICAL DEVICES

### EDMA Position Paper January 2014

#### Overview

EDMA, the voice of the in vitro diagnostic manufacturers in Europe, welcomes the revision of the EU In Vitro Diagnostics (IVD) Directive and the intention to strengthen the current approval system for in-vitro diagnostics for the sake of patient safety, whilst still guaranteeing a competitive and innovative environment for manufacturers.

In light of the position the European Parliament took in October 2013, EDMA looks forward to working closely with Member States in the forthcoming months and would like to draw your attention to several key areas of significant importance. These points are essential for achieving a final outcome that can ensure effective safety gains for products as well as high levels of performance from the approval system, without compromising the innovative nature of the sector, which is needed for the early diagnosis of patients.

The industry's large SME sector - 95% of the IVD industry is SME-based - would welcome a balanced approach in the final outcome of the trilogue negotiations between the European Parliament and Council.

Nine key areas require further discussion:

- I. **Transition period** – A five-year transition period is paramount to enable all involved players to successfully implement the necessary changes.
- II. **Clinical Evidence and Post-market Follow-up** – Clinical requirements need to be adapted to reflect the specificities of in vitro diagnostics.
- III. **Classification system for IVDs** – Classification rules support the introduction of a more harmonised classification system that is based on the international GHTF model, which will lead to global competitiveness of the European IVD sector.
- IV. **Transparency** – A more balanced approach to transparency of information is suggested, keeping in mind the possibility of a breach of intellectual property rights.
- V. **In-house exemption and companion diagnostics** – Companion diagnostics should only be benefit from the in-house assay exemption when no equivalent commercial test is available.
- VI. **Conformity assessment for companion diagnostics** – The EMA, along with other relevant stakeholders, should contribute to the development of Common Technical Specifications for companion diagnostics. It should not be involved in the assessment of each individual test as this would cause unnecessary bureaucratic delays.
- VII. **Reference laboratories and batch release testing** – The governance of reference laboratories needs to be clarified, specifically to whom they will be responsible and how conflicts on assessments should be resolved.
- VIII. **Scrutiny procedure** – The 'Additional Assessment Procedure of Extraordinary Circumstances' procedure is better adapted to realities of IVDs.
- IX. **Definition of an IVD** – The scope of the IVD definition must remain as the in vitro diagnostics products that run tests on samples taken from the human body.

Detailed analysis of the above nine key areas can be found in the following pages.

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**Detailed Analysis**

***I. Transition Period (Article 90)***

The proposed IVD Regulation promises widespread changes to the IVD landscape in Europe. Manufacturers and importers, Notified Bodies, Competent Authorities, reference laboratories and the European Commission itself will have to adapt to significant changes to comply with the new requirements expected from the future Regulation. While the intended harmonisation of rules and checks across Europe is warmly welcomed by the IVD industry and will greatly benefit patient safety, **sufficient time needs to be allowed for all involved players to successfully implement the immense changes.**

While the European Commission has proposed a transition period of five years for IVDs, the European Parliament voted for a transition of only three years. EDMA strongly supports the five-year transition period for IVDs. This timeframe is needed for manufacturers to be able to fully comply with the various new requirements and place all of the necessary manufacturing processes in place. The three year time period proposed by the European Parliament is simply not realistically achievable.

***Why five years?***

- There are over 40,000 IVD products on the market today, ranging from tests performed in clinical laboratories to tests carried out by medical professionals ('near-patient testing') to tests carried out directly by the patient or consumer ('self-testing'). In this diverse sector, manufacturers require appropriate time to have all the proposed requirements in place.
- The system of risk classification will change for all IVD products. With that, the majority of IVDs will be 'classified upwards'. Guidance will have to be developed by regulators on how to apply the classification rules. As a consequence, manufacturers will have to upgrade their 'conformity routes', including the amount of evidence and the manufacturing and documentation processes.
- The majority of IVDs will shift from a 'self-certification system' to one which requires the involvement of Notified Bodies (NBs). According to the new proposal, in the future 90% of all IVDs will fall under some level of control by NBs. They must also be re-designated and qualified to perform conformity assessments for IVDs. This uplifting in the work of NBs is a challenge for both IVD manufacturers and NBs. While NBs will need to audit and control many more manufacturers and IVDs, IVD manufacturers will need to implement stricter control and documentation processes to enable the new conformity assessments to be carried out.
- The new requirements for providing clinical evidence reports and post-market surveillance plans for every IVD means that all manufacturers need to prepare accordingly. This includes adherence to a methodology to carry out the needed clinical studies, which is yet to be developed and, subsequently, adopted across the IVD sector.

**EDMA proposal to Council:**  
**Support the five-year transition period as proposed by the Commission.**

## ***II. Clinical evidence and post-market follow-up (Annex XII)***

Most IVDs are tested on already collected samples from patients, for example the samples available in a biobank. Additionally the information that the test collects from the sample is not provided to patients nor is it used in patient management decisions, thereby removing direct consequences of the clinical investigation.

The European Commission approach to clinical evidence and post-market follow-up establishes the means for collecting clinical evidence information and conducting performance studies. **EDMA believes the Commission approach provides an adequate balance of safety and efficiency by acknowledging that studies for IVDs are conducted without a direct impact on patients**, as they rely on leftover samples or samples taken from biobanks. This approach also reflects the guidance provided by the Global Harmonisation Task Force (GHTF), a body that fostered international harmonisation in the regulation of medical devices. The GHTF promoted this approach to ensure that patients are not subject to unnecessary studies and best practice in the presentation of clinical evidence is achieved.

However, there is concern about some aspects of the proposed Commission text, with regard to a new requirement to perform *direct* post-market follow-up on each individual IVD. This requirement is not useful or relevant for IVD products. IVDs are fundamentally different from other medical devices as they never come into direct contact with the patient. The information provided by an IVD is reflective of the patient's state of health at the time the test is carried out, and does not account for any possible future variations to a patient's health.

For instance, a patient testing 'negative' for a chlamydia infection in April, but testing 'positive' for chlamydia in October is not a reflection of the test itself and rather a reflection of the evolution of the patient's status. There is generally no long-term effect from having a test carried out, unlike the long-term effects that therapies might have. This makes the impact and risks of IVDs specific to the sector.

As a general rule, because of the unique nature of IVDs, their assessment and control, and the regulatory process, the requirements applicable to other medical devices on clinical evidence and post-market follow-up are not transferrable to IVDs.

### **EDMA proposal to Council:**

**The Commission proposal needs to be adapted to reflect the specificities of in-vitro diagnostics. Currently the concept of post-market follow-up is nonsensical for IVD products. Clinical requirements need to reflect the lack of direct impact that IVDs have on patients in the proposed clinical evidence studies, i.e. collecting clinical evidence information and conducting performance studies.**

### ***III. Classification system for IVDs (Annex VII)***

The European Commission proposal regarding the classification for IVDs is based on the globally developed and accepted GHTF standard for classification, which aims to foster convergence of any international classification system. With manufacturers working globally, international standardisation is critical as manufacturers export their products for patients around the world and thus need to comply with various regulatory systems.

Australia, Canada, Saudi Arabia and other countries are already moving towards harmonisation with the GHTF standard for classification. There is huge potential for creating a new system that allows relevant data to be comparable globally and can greatly facilitate vigilance procedures. This is essential for patient safety and enhances the distribution of diagnostic technologies across markets and regulatory jurisdictions, promoting the European IVD sector on the global market.

**The IVD industry strongly supports the introduction of a more harmonised classification system that is based on the international GHTF model, as reflected in the European Commission text.** As such, the Commission text is warmly welcomed, enhancing the global competitiveness of the European IVD sector and facilitating access to new technologies in European healthcare systems.

For specific categories of IVDs that raise particular risks, the concerns can be addressed either through the inclusion of specialised requirements for these IVDs or by implementation of different controls at the level of the 'conformity assessments'. This approach already exists in the Commission proposal for self-tests, companion diagnostics and point-of-care assays, all of which are subject to specific requirements and/or conformity routes.

**EDMA proposal to Council:**

**Support the European Commission proposal on classification rules. Any deviation would be detrimental for the European IVD sector on the global market, as the European system would diverge from the internationally accepted, harmonised GHTF system.**

#### ***IV. Transparency (Preamble 32a, Article 23)***

Transparency in the healthcare sector is very important and the industry considers an increase in transparency and relaying meaningful information to patients as a step in the right direction. The European Parliament has proposed to significantly strengthen the transparency provisions for the IVD industry in its amendments, but has done so to an extent that EDMA believes does not maintain a balance between the level of information needed for safety reasons and the protection of intellectual property rights. By requiring the disclosure of all raw data of clinical studies, and full public access to the technical file of manufacturers, the Parliament position results in the disclosure of commercially sensitive information, which would be detrimental to the IVD industry.

Permitting access to the raw data from studies or to the full manufacturer's technical documentation will inevitably result in revealing commercially sensitive information. With the majority of our industry consisting of SMEs, this would be detrimental, adversely and severely affecting the continuously needed investment in research and development to ensure innovative products are created for patients.

**EDMA calls for a more balanced approach to transparency of information than suggested by the European Parliament. An example could be the transparency rules applied by the US FDA**, which provides an appropriate and relevant level of information regarding an overview of available IVDs on the market, background on the products, access to safety and performance information summaries, as well as vigilance incidents.

There is a need to balance legitimate expectations of transparency and the data protection necessary to drive innovation. Unlike the pharmaceutical sector, the IVD industry does not benefit from data exclusivity following studies. Thus if the study data becomes public, it is of immediate benefit to all competitors. Additionally, the patent protections are generally weaker in the IVD sector. For example, while the pharmaceutical industry can patent 'active substances' in medicines, when a sample is taken from human body to determine the status of health, the relevant gene sequence or a hormone cannot be patented.

**EDMA proposal to Council:**

**Rather than allowing access to the full technical file and full raw study data by third parties, which has been proposed by the European Parliament, EDMA strongly recommends calling for a summary of the study report to be made publicly available. Such an approach is, for example, applied by the US FDA, protecting innovation and considering the possibility of a breach of intellectual property rights.**

***V. In-house exemption and companion diagnostics (Recital 9a)***

The European Commission proposal introduces a so-called ‘in-house exemption’ allowing high-risk in vitro diagnostics – those falling into Class D according to the new classification system – to be developed and used within a single health institution. The qualified tests do not have to provide the normally required clinical and performance studies, provided that no comparable test is yet commercially available. This measure is intended to encourage innovation and the development of more cost-effective approaches to healthcare. Furthermore, the in-house exemption has been generally expanded to all companion diagnostics, as a means of encouraging new therapeutic technologies and treatment of various cancers.

Though the general principle of an in-house exemption carries much potential in terms of providing new possibilities to patients, it poses some concern in the context of companion diagnostics. Different to other tests, companion diagnostics are subject to specific requirements in order to demonstrate that patients are being appropriately selected for the use of life-saving therapies. As such the clinical evidence requirements for companion diagnostics are substantially higher than those for most other IVD assays. This high level of clinical evidence is not required of tests developed in-house, making commercial companion diagnostics substantially safer than in-house alternatives.

**EDMA proposal to Council:**

**Companion diagnostics should only be permitted to benefit from the in-house assay exemption in instances where no equivalent commercial test is available. This is in line with the requirements for class D devices.**

## ***VI. Conformity assessment for companion diagnostics (Article 40, Annex VIII, Chapter 2)***

The European Commission proposal sets out a procedure for the assessment of companion diagnostics that involves the European Medicines Agency (EMA) in each individual review alongside the designated Notified Body. EDMA considers that the involvement of EMA in these cases will be ineffective as it would most likely create unnecessary regulatory and administrative burden with no evident safety gain. This, in turn, could create a situation whereby a medicinal product is already available but cannot be used, as the supporting companion diagnostic is stuck in the approval process, causing major delays.

Key concerns include:

- The degree of review by the EMA is not defined, neither in timing nor desired outcomes;
- Interaction between the EMA and notified bodies is not clear; and
- The level of expected evidence for demonstrating the ability of the companion diagnostic to appropriately select patients is not clarified.

The European Parliament has expanded the control of companion diagnostics compared to the Commission text, by including the mandatory development of Common Technical Specifications (CTS) for companion diagnostics, which would outline the prerequisite targets and expectations that these devices must satisfy. These CTS would be developed by regulators with input from EMA, physicians, patients, notified bodies and manufacturers and would provide a high level of detail and transparency of prerequisite safety and clinical requirements. These CTS would furthermore cut down on time and red tape whilst ensuring a high level of safety and performance.

### **EDMA proposal to Council:**

**Companion diagnostics should undergo consistent conformity assessments, a task that is possible through the creation of Common Technical Specifications (CTS) by relevant entities (i.e. regulators, EMA, physicians, patients, notified bodies, manufacturers). Inclusion of the EMA in the assessment of each individual companion diagnostics, however, is not supported as its role and scope of responsibility is unclear. Instead, rather than safety gains, unduly administrative burdens and delays are anticipated.**

***VII. Reference laboratories and batch release testing (Article 78; Annex VII, section 5.7)***

The European Parliament adopted several amendments to further improve the European Commission text as regards the role of reference laboratories, their control of high-risk devices and the related post-market follow-up. However, there is still a lack of clarity in relation to how reference laboratories will be governed and their involvement in post-market follow-up activities.

In the Parliament position, reference laboratories have been given a significant role in the market surveillance of IVDs, alongside notified bodies and competent authorities, including:

- Pre-market batch release laboratory testing for all cases;
- Unannounced onsite visits; and
- New requirements in terms of knowledge, experience and in-house skills.

Additionally, reference laboratories will further provide input on the development and implementation of CTS, as well as having additional oversight to that of notified bodies on how manufacturers are implementing CTS requirements.

The biggest concern with the European Parliament text rests with the follow-up actions beyond the CTS, as the proposal for pre-market batch release testing has proven to be resource-intensive, without any additional provisions of safety, which would only be exacerbated if it applied to all cases.

**EDMA proposal to Council:**

**The governance of reference laboratories needs to be clarified, specifically to whom they will be responsible and how conflicts on assessments should be resolved. Furthermore, the way in which reference laboratories would contribute to the CTS and the specificities of their role in batch release testing must be defined.**

### ***VIII. Scrutiny procedure (Article 42a; Article 44a)***

The European Parliament has amended the European Commission proposal on scrutiny of in vitro diagnostics products, with two further procedures for additional scrutiny of high-risk devices: the 'case-by-case' assessment and the 'Additional Assessment Procedure of Extraordinary Circumstances'.

EDMA considers that two similar procedures for implementing additional scrutiny measures of high-risk IVDs leads to unnecessary overlap and burdensome legislation. EDMA further believes that the 'Additional Assessment Procedure of Extraordinary Circumstances' is the right approach and the most appropriate for IVD products.

#### ***Why is the 'Additional Assessment Procedure of Extraordinary Circumstances' appropriate?***

This procedure provides Member States' authorities the decision-making power on which files to review and to make the final assessment.

This proposal is more balanced and better adapted to the realities of the IVD regulations than the 'case-by-case' assessment as it directs additional appraisals to truly novel devices, in order to better evaluate the risk to patient safety. It does so by taking into account the additional assessment that IVDs with Common Technical Specifications (CTS) already undergo. Moreover, this proposal helps to capture the knowledge of the assessments in the further development of CTS. EDMA considers that the second proposal of a 'case-by-case' scrutiny procedure to be hugely difficult to implement due to the bureaucratic nature of the system.

#### **EDMA proposal to Council:**

**The 'Additional Assessment Procedure of Extraordinary Circumstances' ensures a balanced approach to patient safety that is appropriate and sufficient for the realities of the sector.**

### ***IX. Definition of an IVD (Article 2, sub-point 2)***

The proposal of the Commission on the definition of an IVD was expanded by the European Parliament to include the concept of 'providing information concerning direct or indirect impacts on health'. This substantially broadens both the definition of an IVD and the scope of the Regulation as it would include devices such as mobile phones, general software packages or general laboratory equipment. However, in vitro diagnostic products run tests on a sample from the body in an artificial environment, most often a laboratory. They rely on samples – such as blood, tissue or urine – to conduct diagnosis, predictive testing, screening, and monitor conditions, from mild conditions to life-threatening cancers. Therefore, the European Parliament amendment to the scope of an IVD, i.e. to include software devices and laboratory equipment, is not appropriate for IVDs as these products do not satisfy the criteria normally used for the designation of what constitutes an IVD.

#### **EDMA proposal to Council:**

**Maintain the European Commission text and omit the European Parliament amendment to increase the scope of the IVD definition.**

**For further questions please contact:**

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