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EUCOPE Position

On the Commission Proposal COM(2012) 541

'*In vitro* diagnostic medical devices'

Summary

EUCOPE welcomes the Commission's aim to ensure high standards of quality and safety for *in vitro* diagnostic medical devices (IVDs) providing a high level of protection to patients. EUCOPE also supports the Commission's effort to guarantee the functioning of the internal market as regards these goods as well as innovation and competitiveness of the *in vitro* diagnostic medical devices industry.

The European Union supports the development of personalized medicines with extensive funding programs (€ 900 million for 2007-2013 in FP7). **This shows that personalized medicine plays an important role in the European Union's future healthcare policy**. **This should also be reflected in the regulatory framework for IVDs.** EUCOPE welcomes the funding of diagnostic methods as an important tool to foster innovation in this market. Equally - if not more important - is the fact that these diagnostic innovations need to be regulated in an adequate manner to safeguard quality, safety and the functioning of those diagnostics. The European Parliament should put particular emphasis on the need to proof the functioning of diagnostics but should allow for enough flexibility to enable especially small and medium-sized manufacturers to bring their products to the market. Otherwise, the Union's FP 7 policy which clearly intends to strengthen companion diagnostics and personalized medicine would be put at risk.

The new legislative framework has to take particular account of the fact that IVDs have by nature in most cases no immediate effect on the human body. Thus IVDs have to be assessed in relation to their performance since their reliability (sensitivity, specificity, reproducibility of the assay) is the crucial criterion for the risk evaluation. **Therefore, it would not be appropriate to simply transfer classification and vigilance rules for the medicinal product and the medical devices sector to IVDs.**

We particularly see the need for amendments on the following aspects:

1. The proposed safety and vigilance obligations imposed on manufacturers of IVDs are not appropriate as these products are generally not applied to the human body. Their main risk lies in a lack of reliability which can lead to misinterpretations of test results and subsequent treatment errors. **Assessment and vigilance obligations that have been designed for the evaluation of medicinal products are not suitable for IVDs and should therefore not be applied to them.** IVDs are not applied to the human body so safety risks are very low. In addition, pharmacovigilance rules are applicable anyway for the medicinal product.

2. **An automatic classification of companion diagnostics in class C is not justified, considering the low risk profile of many of these products.** Therefore, a classification should depend on a **case-by-case analysis.**

3. It should be clarified that **where clinical data is already available**, e.g. from literature, **it is not required to carry out additional clinical investigations**. Where a new IVD serves the same purpose as another diagnostic which is already on the market clinical evidence should be limited to the verification of equivalence of the new and the established IVD.

4. Once a companion diagnostic has been subject to a **procedure where the Notified Body consults the national competent authority (NCA) or the EMA, an assessment of an alternative use of the device by the Notified Body should not have to involve the NCA or EMA again.**

5. To prevent double testing and facilitate the market access for IVDs in several Member States and thus the functioning of the Internal Market, the new Regulation should provide for mandatory **cross-border recognition of laboratory test results**.

6. To ensure highest standards concerning the reliability of tests and thus minimize risks of misinterpretation of their results it is crucial to **harmonize and improve the quality of assessment and the monitoring of the market** by the Notified Bodies and the responsible Member State authorities.

1. Limitation of safety and vigilance obligations to a reasonable level

Currently the Commission Proposal on IVD foresees **extensive obligations** for manufacturers of companion diagnostics to **evaluate the safety of their products through clinical studies** (Art. 40, Annexes VIII-X) and to **ensure a post-market surveillance** (Art. 8(6), Annex XII Part B). In this regard, the Commission proposal **largely adopts the safety and vigilance system for medicinal products**. This, however, **does not sufficiently take the specific characteristics of IVDs into account**. IVDs are typically not directly applied to the human body and do not bear any considerable risk for patient safety. Additionally the documentation of adverse events that occur in a therapeutic treatment does not add to the reliability of tests. Adverse events are no direct results of the usage of an IVD but occur in the course of the medical therapy which is, primarily based on the physicians' therapeutic decision. In this regard, it has to be observed that, generally, physicians do not rely on the result of a single test when they take a decision on a specific therapy. Therefore, though a diagnostic may indicate the treatment which leads to the adverse event the diagnostic is not the direct cause of the event. **Consequently, it is the accurate performance of the diagnostic that is the crucial factor in the field of IVDs rather than immanent safety risks**. A vigilance system which has been designed for medicinal products does not improve the quality or reliability of tests. Furthermore, there is no need to implement a similar vigilance system into the IVD legislation **since the pharmacovigilance system for medicinal products (i.e. Regulation (EC) No 726/2004 and Directive 2001/83/EC) is applicable wherever a medicinal product interacts with a diagnostic test**. There is no added value in terms of patient safety in generally imposing these vigilance obligations on IVDs. **This is different for medical device as medical devices are generally applied to the human body (COM(2012) 542).**

Furthermore, the extensive requirements that are currently included in the Commission proposal seriously **hamper competition in the market**. The cited provisions **favor large companies** that develop companion diagnostics together with the treatments they are intended for. For these companies it is comparably easy to submit the required data as they can rely on studies and vigilance activities that have to be conducted in the course of the development of the medicinal product. This leaves little or no room for small and mid-sized competitors which independently develop diagnostics, e.g. companion diagnostics.

2. Automatic classification of companion diagnostics in class C

According to Annex VII Rule 3 f companion diagnostics are generally classified as class C devices. The Commission's aim to ensure a high level of product safety is highly appreciated. However, companion diagnostics have a low risk profile and have not been subject to serious safety concerns in the past. **In this context it is important to emphasize that the major risk in the use of IVDs lies with the misinterpretation of test results rather than immediate dangers emanating from the respective IVD itself.** Test results are generally interpreted in accordance with the labeling/the instructions of use of an IVD especially with regard to the statistic reliability of the diagnostic. **Therefore, the classification can only be based on the reliability of the test considering the highest available standards rather than danger emanating from the medical treatment.** The classification of companion diagnostics should therefore be assessed individually on a case-by-case basis, taking into account established classification criteria, namely the potential risks associated with the technical design and manufacture.

EUCOPE suggests that only those products are classified as class C where the intended use of the information resulting from the test and a case-by-case analysis justifies such a classification. Therefore, Rule 3 of Annex VII should be amended in the following way:

> "Devices are classified as class C if they are intended for:
>
> [...]
>
> (f) selection of patients, i.e.
> (i) Devices intended to be used as companion diagnostics; or
> (ii) Devices intended to be used for disease staging; or
> (iii) Devices intended to be used in screening for or in the diagnosis of cancer,
> **provided that an individual analysis of the device justifies an inclusion in this risk class."**

3. Clinical evidence

In Recital 42 of the proposal it is stipulated that:

"To ensure a high level of safety and performance, demonstration of compliance with the general safety and performance requirements should be based on clinical evidence. It is necessary to clarify the requirements for such clinical evidence. As a general rule, clinical evidence should be sourced from clinical performance studies to be carried out under the responsibility of a sponsor who can be the manufacturer or another legal or natural person taking responsibility for the clinical performance study."

Additionally, Article 4(3) and Article 47(1) stipulate that the demonstration of conformity shall be based on clinical evidence. Article 47(4) clarifies that where demonstration of conformity based on clinical performance data is not deemed appropriate, adequate justification for such an exception shall be given. **It follows that (a) the proposal does not provide for an obligation of the manufacturer to conduct a clinical performance in respect to his device, and (b) that exemptions to this rule are possible.** Furthermore, Annex XII ("Clinical evidence and post-market follow-up"), *inter alia*, states in Part A section 1.1.2 that for a new analyte and/or a new intended purpose, **the scientific validity shall be demonstrated based on literature or a combination of literature and other sources**. Therefore, it should be clarified that **where sufficient clinical evidence of the conformity of the device with the general safety and performance requirements is available through literature, conducting further clinical trials on humans and animals**

is unnecessary since the conformity has previously been well tested. This should be explicitly included into the wording of Article 47(1):

> "The demonstration of conformity with the general safety and performance requirements set out in Annex I, under normal conditions of use, shall be based on clinical evidence. **If clinical data proving clinical evidence is already available at the disposition of the manufacturer, e.g. from literature, it is not required to carry out additional clinical investigations.**"

In the case of a new IVD that serves the same purpose as another diagnostic which is already on the market there would be no additional value in performing new clinical studies on the linkage between the test and its **therapeutic performance**. In this particular situation analytical or clinical studies **should be limited to a comparison** between the new and the established IVD to verify the equivalence of the performance.

4. Alternative use of companion diagnostics

For companion diagnostics intended to be used to assess the patient eligibility to a treatment with a specific medicinal product the proposal imposes an obligation on the Notified Body to consult one of the national competent authorities (NCA) or the EMA (c.f. Art. 40(3)). The NCA/EMA may issue a statement within 60 days; the period can be extended once for another 60 days (in total 120 days).

In practice **this consultation requirement could lead to serious delays in the market entry** of companion diagnostics and to an unnecessary double notification/approval procedure if each intended purpose of a companion diagnostic has to be subject to such proceedings. Additionally, the consultation requirement would **not add to patient safety as any intended use of the product requires prior notification and examination by the responsible Notified Body**. A second involvement of the NCA/EMA is not necessary as they **already assessed the suitability of the device in the context of the medicinal product**.

For these reasons we suggest **to insert the following clarification into Art. 40(3) subparagraph 3**:

> "For companion diagnostics intended to be used to assess the patient eligibility to a treatment with a specific medicinal product, the Notified Body shall consult one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or the European Medicines Agency (EMA) in accordance with the procedures set out in Section 6.2 of Annex VIII and in Section 3.6 of Annex IX. **No consultation of the competent authorities or the EMA is required if the respective companion diagnostic has already been subject to a consultation procedure as outlined in the previous sentence**."

5. Recognition of laboratory testing

The Proposal foresees the appointment of EU Reference Laboratories (Art. 78) that shall, *inter alia*, verify the compliance of devices with the Regulation. However no provisions are foreseen to harmonize the cross-border recognition of laboratory test results. This leads to **legal uncertainties and potential double-testing** of devices when a product shall be launched in several Member States. Therefore the Proposal should provide for a **mandatory recognition of laboratory tests** that have been conducted in compliance with the regulation in another Member State. This could be introduced by adding a new Article 78a:

> "*If a Member State confirms the compliance of laboratory test results with the provisions of this Regulation, this confirmation shall be recognized as binding by any other Member State concerned.*"

6. Harmonization of standards for Notified Bodies

As the reliability of test results is the most significant factor for the safety profile of IVDs it is of vital importance that this aspect is thoroughly assessed and monitored. In order to minimize risks of misinterpretation of test results and ensure highest standards throughout the EU it is crucial to harmonize and improve the quality of assessment and the monitoring of the market by the Notified Bodies and the responsible Member State authorities.

Currently, **there are significant differences as regards the designation and monitoring of Notified Bodies** and the quality and depth of the conformity assessment performed by them. The **requirements for the designation of Notified Bodies should be strengthened further and should be harmonized to the largest possible extent** to ensure identical levels of quality of the Notified Bodies in all Member States and leave no room for Member States' discretion. Furthermore the **requirements concerning the establishment, organization and operation of national authorities responsible for Notified Bodies** should be harmonized **as far as possible**, including the rules for the monitoring of the Notified Bodies in order to safeguard that Notified Bodies are designated and monitored according to consistent standards throughout the EU.

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