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Enhancing the health of the public European wide and world wide and
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Amendment to a Definition and annotations on the term "medical diagnosis"

In the Borderline & Classification Working Group (BCWG) meeting, dated of March 13th, 2013, a task force represented by the German delegate presented a first draft proposal (PROPOSAL) concerning the definition and annotations on the term "medical diagnosis".

EUROM VI welcomes the initiative and thanks the task force for the PROPOSAL as the term medical diagnosis is not yet legally defined. Based on the cases Triamcinolone Acetonide and AFL-HSA, which have been discussed in detail in the recent BCWG meetings (for details see ANNEX 1), the demarcation of the terms **medical diagnosis** and **intra surgical visualization** has a relevant impact on the availability of improved surgical treatment options. Even a pure **visualization** as discussed for paramagnetic nanoparticles used for the localisation of lymph nodes might be distinguished from a medical diagnosis.

Due to **historical reasons** substances and combination of substances, which may be used in or administered to human beings to making a **medical diagnosis** are classified as medicinal products. In 1965 no regulatory framework for medical devices has been available and the respective products have been regulated within the former medicinal product directive 65/65/EEC. For any reason the provision was taken over into the directive 2001/83/EC (MPD), irrespective of the underlying mode of action, which in turn was implemented as the major demarcation criterion between medical devices and (functional) medicinal products. In fact the majority of substances for medical diagnosis *in vivo* have no pharmacological, no immunological or no metabolic mode of action and might be well regulated and controlled under the provisions of directive 93/42/EEC on medical devices (MDD), which itself includes the diagnosis of diseases, injuries or handicaps in its definition according to Art. 1, Para 2a) MDD. **EUROM VI** would appreciate a respective amendment of the MPD.

In any case **EUROM VI** applies for a definition of the term **medical diagnosis**, which does not lead to a similar coincidence between the MPD and the MDD for substances and combination of substances that are intended only for the **intra surgical visualization** or the pure **visualization**. The BCWG is authorized to amend the MEDDEV Documents, which should provide comprehensible guidance to the authorities, notified bodies and stakeholders. The MEDDEV document 2.1/3 already includes definitions on pharmacological, immunological and metabolic means and might be amended with new definitions on **medical diagnosis**, **intra surgical visualization** or the pure **visualization**.

Taking into account the goals of the Commission with respect to the new regulation on medical devices (e.g. support of innovations and SMEs, faster market access) and considering all the measures that are currently under discussion in terms of patient safety, **the BCWG also bears the responsibility not to impede relevant treatment options for the patients**, which would not be developed as medicinal products due to the missing interest of the pharmaceutical industry.

25.000 patients in Europe suffer from glioblastoma and might benefit from an improved surgical procedure based on AFL-HSA; the radicalness of the surgical procedure is relevant because a) if the



tumor resection is not radical enough remaining tumor cells might lead to a relapse or b) if the tumor resection is too radical this might lead to undesired loss of body functions).

Moreover, based on the discussion on paramagnetic nanoparticles used for the localisation of lymph nodes during the BCWG meeting dated of March 13th 2014, the BCWG might also decide on a separate definition for the pure visualization of organs and part of the body respectively. In fact the identification of a lymph node prior to its removal from the body for an *in vitro* diagnosis, is definitely not a diagnosis on its own. Rather the likelihood to detect metastases within the *in vitro* diagnosis is simply higher by the removal of the lymph node next to the tumor.

Finally, in contrast to products for medical diagnosis, there are other *in vivo* medical tools (devices) which are used as neutral fiducial markers¹ / landmarks especially in conjunction with minimally invasive surgery, robotic devices, imaging guided therapy, and endoscopic instruments.

These are tools for markation and mapping of distinct anatomic positions as a reminder for repeated detection / inspection of this site (point of reference or measure) especially for detection by other methods like imaging procedures. Tools used for this purpose are Indian Ink, fluorescent dyes, metal clips, or tiny gold particles or other inert but visible materials, which can be recognized visually or by imaging techniques in order to find the marked position again by the operating surgeon. These products are also called Fiducials (= neutral placeholder, trustee).

The placeholder alone cannot provide any contribution for a diagnosis (identification of diseases) it has no power of detection in the sense of sensitivity and specificity. It is a neutral instrument of the surgeon to mark a special place in the body in order to repeatedly locate it again, especially to outbalance position movements of the patient during imaging (position verification).

The following sections include comments and concerns regarding the PROPOSAL presented by the task force, as well as a proposal of EUROM VI for the definition of **medical diagnosis** and **intra surgical visualization**:

Definition and annotations on the term “medical diagnosis“

Definition and annotations of the term “medical diagnosis“ within the meaning of the definition of medicinal products according to Article 1 (2)(b) of Directive 2001/83 of the European Parliament and of the Council of 6th November 2001 on the Community code relating to medicinal products for human use.

As mentioned above the definition should not only refer to the MPD but also consider the recent discussions on intra surgical visualization and on pure visualisation.

A medicinal product is defined in Article 1(2) of Directive 2001/83/EC (MPD), as follows:

“2. Medicinal product:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

*(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a **medical diagnosis**.” [emphasis added],*

¹ Lydia L.Handsfield,et al.J.Appl.Clin.Medical Physics,Vol13,No5 (2012): Determination of optimal fiducial marker image-guided radiation therapy (IGRT) modalities: visibility of gold,carbon, and polymer fiducial markers.



It appears from this legal definition that a substance shall be considered to be a medicinal product when having the purpose to making a “medical diagnosis”. It is therefore important to understand and clarify the meaning of what a “medical diagnosis” is. Based on the existing definitions,

A legal definition is neither available in the MPD nor in the MDD. According to the German clinical dictionary² the term medical diagnosis is precisely defined as “identification of a disease”.

The English definition of diagnosis from the Oxford English dictionary³ is 1) the identification of the nature of an illness or other problem by examination of the symptoms and 2) the distinctive characterization in precise terms of a genus, species, or phenomenon.

and in particular the definition of an in vitro medical device according to Directive 98/78/EC,

Art. 1, Para 2b) of the **directive 98/79/EC on in vitro diagnostics does not include a definition of the term medical diagnosis** itself, **but refers to the examination of specimens** ... derived from the human body ... for the purpose of providing information *inter alia* concerning a physiological or pathological state

it could be said that a “medical diagnosis” is the demonstration or visualisation of the anatomy/morphology, the condition or the functions of the human body irrespective if these are physiological or pathological.

This conclusion may be regarded as one opinion, also it is not deducible from any given definition.

It could also be said that

A “medical diagnosis” is intended for the identification of a disease and the subsequent decision on the suitable therapeutic measurement.

Beside that

The intra surgical visualization as well as the pure visualization might be understood as a therapeutic measurement for a facilitated surgical procedure after a medical diagnosis and followed by an additional medical diagnosis for the assessment of the success of the surgical procedure and the decision on the follow up treatment.

Hence substances like x-ray contrast media, NMR enhancing agents, SPECT- and PET-radiopharmaceuticals are medicinal products.

Due to the unfavorable coincidence between the MPD and the MDD substances intended for a medical diagnosis will remain medicinal products unless an amendment of the MPD would solve that issue. However, substances intended for intra surgical visualization might be classified as medical devices.

Considering this it might be agreed that substances and combination of substances, which may be used for both **medical diagnosis** and **intra surgical visualization** (e.g. substances used for magnetic resonance tomography prior to and within a surgical procedure) would fall into the regiment of the MPD.

It should also be emphasised that a diagnostic medicinal product is to be composed of substances or combination thereof and used in vivo and not consist of instruments, apparatus, appliances, software, materials or other articles so to differentiate it from a medical device.

This assessment ignores the fact, that the term material must be regarded as an umbrella term, which *inter alia* includes substances and combination of substances. The German translation of the MDD

² Pschyrembel by W.de Gruyter

³ <http://www.oxforddictionaries.com/definition/english/diagnosis>



uses the terms “Stoffe und Zubereitungen aus Stoffen (= substances and combination of substances) instead of material.

Finally, the mode of action is not a criterion in this case.

This is correct. However, it does also not except the possible differentiation between the medical diagnosis, intra surgical visualization and visualization and the uptake of respective definitions into the MEDDEV document 2.1/3.

Concluding remark

The final decision on the definitions for **medical diagnosis**, **intra surgical visualization** and **visualization** requires the political intention of the parties to enable the availability of the best treatment options for the patients. The MDD provides an adequate legal framework to secure the safety and efficacy of substances and combination of substances for the purpose of an **intra surgical visualization** or a pure **visualization**. In the case of AFL-HSA, which would be classified as a class III medical device according to Annex IX, Rule 6 MDD the medical device route is the only realistic option for a product launch.