



EUROM VI "Medical Technology"

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Enhancing the health of the public European wide and world wide and
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Berlin, Apr. 2014

Amendment to PROPOSAL 2 concerning the definitions of pharmacological, immunological and metabolic means as reported in the MEDDEV 2.1/3 Rev.3

In the Borderline & Classification Working Group (BCWG) meeting, dated of March 13th, 2013, the task force (DE, IT, NL and EMA) presented the second draft proposal (PROPOSAL 2) concerning the definitions of pharmacological, immunological and metabolic mode of action as reported in the MEDDEV 2.1/3 Rev.3 Section A.2.1.

Again **EUROM VI** welcomes the initiative and thanks the task force for the PROPOSAL 2 as the current definitions of MEDDEV 2.1/3 Rev.3 are partly scientifically not reasonable and lead to confusion in terms of the demarcation of medical devices according to directive 93/42/EEC (MDD) and medicinal products according to directive 2001/83/EC (MPD).

The following sections include the PROPOSAL 2 and the amendments of **EUROM VI** considering the recent discussions of the BCWG and the amendment referring to the first draft proposal (PROPOSAL 1) submitted by **EUROM VI** in November 2012 (see Annex 1).

***"Pharmacological means"** is understood as an interaction between, ~~or an indirect effect of, the molecules of the~~ a substance in question or its active metabolites and a constituent of the human body (including any of its parts, or an organism or other pathogens like bacteria, fungi or viruses within or on the body) through any type of chemical binding- a specific target at a cell surface or at an intra-cellular level, which results in a significant initiation, enhancement, mitigation or blockade of physiological or pathological ~~characteristics~~ processes associated with that interaction.*

Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.

Examples of constituents of the human body may include: cells, receptors, membrane proteins, ion channels, enzymes and intracellular structures.

EUROM VI welcomes to include the term **active metabolites** into the definition of pharmacological means, as it emphasizes the concept, that immunological means and metabolic means are a subset of pharmacological means, as presented by the task force in the BCWG meeting in Oct. 2012. Immunological means and metabolic means are based on pharmacological principles in terms of the interaction between the molecules of the substance in question and a constituent of a biological system.

In contrast the terms **indirect effect** and **any type of chemical binding** should be avoided in the definition as they would lead to uncertainties and misinterpretation again. According to its legal



definition medical devices are beside others intended for the purpose of prevention, ..., treatment or alleviation of a disease. Such a therapeutic effect can be achieved directly or indirectly and may be *inter alia* based on Van der Waals forces, H-bonds, hydrophobic or electromagnetic effects, including electrostatic interactions.

For instance the reduction of the bioavailability of fat and external cholesterol derived from nutrition by binding to chitosan in the gastrointestinal tract will indirectly influence the physiological processes of fat absorption and the cholesterol plasma level.

However, the binding of fat to chitosan is not a pharmacological but a physico-chemical process.

“Immunological means” is understood as an action mediated or exerted (including e.g. stimulation, modulation, replacement) by immune-competent cells (e.g. lymphocytes, phagocytes, macrophages, dendritic cells) and/or by molecules involved in overall immunological response (e.g. toll-like receptors, complement factors, cytokines, antibodies).

A means of action can be considered “immunological” only if the induction or blocking of the immune response is the principal intended consequence of the administration of a substance.

Examples: vaccines, antibodies, antivenoms and certain therapies which depend on an immunological means to target therapy.

EUROM VI has no concerns with respect to the current proposal for the definition of immunological means and welcomes the linkage to the principal intended consequence. In analogy, this linkage would also be relevant for the definitions of pharmacological and metabolic means, as well as for the correct interpretation of Annex IX, Rule 13 of the Directive 93/42/EEC on medical devices (see section 2.2 of Annex 1).

“Metabolic means” is understood as an action induced by active metabolites for the claimed intended use, which involves an alteration, including stopping, starting or changing the rate, extent or nature of the chemical-systemic physiological processes (whether normal or pathological) participating in, and available for, function of the human body or an organism or pathogen within or on the body.

The active metabolites result from Metabolism, which is the set of chemical-physiological reactions that happen in living organisms. It includes processes for growth, reproduction, response to environment, survival mechanisms, sustenance, and maintenance of body structure and integrity.

With regard to the concept of chemical process the binding between molecules which does not mediate, directly or indirectly, a response within or on the human body is considered a chemical, not a metabolic mode of action.

A typical chemical mode of action is the local pH modification or the sequestering action of a molecule. The chemical mode of action should be reproducible in vitro in a closed not biological inert system.



In principal it should be noted that the current definition of metabolic means is not restricted to substances and combination of substances. The current definition of metabolic means, as well as the description of metabolism according to MEDDEV 2.1/3 and PROPOSAL 2 applies for almost every interaction of any entity with human cells and tissues! As a result the definitions are in direct conflict with several medical devices, as per definition medical devices shall not achieve their intended purpose by metabolic means (e.g. defibrillator).

According to the concept that immunological means and metabolic means are a subset of pharmacological means and in order to be consistent with the usage of the term **active metabolites** (see above *pharmacological means*) this term should also be considered in the definition of metabolic means.

Moreover **EUROM VI** would welcome to readopt the **concept of the chemical process** as suggested by the sub working group in PROPOSAL1, which is completely in line with the arguments against the usage of the terms **indirect effect** and **any type of chemical binding as described above**.

The difference between a pharmacological and metabolic mean of a given substance might be the fact, whether or not these substances have to be metabolized prior to achieve their activity. A substance with a metabolic mode of action might be understood as a pro-drug, which is activated in the human body by an anabolic or catabolic metabolism of the cells and tissues.

Annex 1:

Amendment to the definitions of pharmacological, immunological and metabolic means as reported in the MEDDEV 2.1/3 Rev.3, EUROM VI, Nov. 2012