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**ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC-PUBLIC CONSULTATION PAPER as published in http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf**

Dear Sir or Madam,

the European Association of Nuclear Medicine (EANM) very much appreciates the European Commission's initiative to consult all relevant stakeholders and to launch a broad public debate on the assessment of the functioning of the "Clinical Trials Directive". In this regard, we welcome the opportunity to address the specific issues related to the use of radiopharmaceuticals in Clinical Trials, which is of utmost importance for researchers and health professionals in nuclear medicine.

The comments given below address the consultation items of the "ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC-PUBLIC CONSULTATION PAPER" as published in http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf

**KEY ISSUE N°1 TO BE ADDRESSED: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS**

**Consultation items n°2 and 3:**

The description of the situation is quite accurate, but consequences may differ depending on the country.

When dealing with clinical trials involving diagnostic radiopharmaceuticals (mainly positron emission tomography (PET) RP) used in microdose amounts, competent authorities in some countries are asking for details neither included in the Clinical Trials Directive nor in the national legislation derived from its transposition. This is mainly derived from their lack of expertise in the specific kind of products they have to evaluate. This leads not only to longer delays before "first patient in" but also to increased costs or even to negative outcomes of the request as compared to similar CT in other countries. In countries more used to deal with this kind of trials, more reasonable criteria are applied. In this sense, the possibility of community-wide streamlining of the NCA-authorization process might be very positive with regard to certain product categories (such as radiopharmaceuticals).

For clinical trials sponsored by the academia (usually CT not intended to get a marketing authorization for the studied product), the problem is even greater. Many academic CT are funded from grants that commonly require previous approval of the CT to apply for them. If the delay is so long, the grant application might either not be possible to be filed or the time frame to conclude the grant might be finished even before the final approval of the CT.

**KEY ISSUE N°2 TO BE ADDRESSED: INCONSISTENT IMPLEMENTATION OF CLINICAL TRIALS DIRECTIVE**

**Consultation item n°6:**

Another example in scope of the Clinical Trials Directive is the difference among the Member States on how to proceed with “not-interventional” trials when the product used is a medicinal product prescribed in the usual manner but it does not have marketing authorization. In some countries, a clearly "non-interventional" study can be considered as an interventional CT. In these cases, it concerns radiopharmaceuticals used in micro-dose amounts labeled with short lived radionuclides exclusively intended to be used as surrogate diagnostic imaging agents and not aiming to achieve a marketing authorization. The fact that the procedure to authorize a clinical trial with these types of products is identical with that for one product intended to get a marketing authorization makes the research with these types radiopharmaceutical commonly unaffordable for academic and not commercial sponsors. These Clinical Trials should be reviewed under a different procedure than the ones in which the final intention is to ask for a marketing authorization. Otherwise the academic studies will be impossible to be carried out in practice.

**Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?**

As it is described in consultation nº2, the increase in administrative costs, particularly for academic and non-commercial sponsors, has made it very difficult to continue with this type of research since there is not a commercial interest behind it.

One example is the fees that have to be paid for a clinical trial submission when the medicinal product is not a commercial one. When there is no commercial intention in the trial, it could be very helpful to have a centralized data base with all the approved IMPs what could help a lot the academic studies with not commercial products, and it might also help the NCA to evaluate much faster and objectively a CT, avoiding the need to request additional safety/toxicity studies for an already approved IMP.

**Consultation item n°8:**

The adoption of the text of the Clinical Trial Directive as a Regulation might help to harmonize requirements, albeit the process for such commitment might be extremely long. Anyhow, the divergent applications are due rather to the concrete application on a case-by-case basis than to the consequence of transposing the directive to national laws. Once more, differences in expertise and interpretation of the CT Directive principles by evaluating organisms are the key.

**KEY ISSUE N°3 TO BE ADDRESSED: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS**

**Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?**

A clear example of insufficient risk-differentiation are CT with diagnostic radiopharmaceuticals, (specially PET radiopharmaceuticals). As a whole, radiopharmaceuticals are probably the safest medicinal products of all because:

- they are used only once or a few times at most in a patient's lifetime;
- they contain minute amounts of active ingredients (mostly in the microdose range);
- the number of reported adverse reactions to diagnostic radiopharmaceuticals is probably the smallest of all medicines, and the number of SUSARS in CT involving radiopharmaceuticals is negligible;
- radiopharmaceuticals are applied in a controlled environment under the control and supervision of expert personnel;
- the risk related to radiation is not only extremely low, but also calculable.

A risk differentiation could be addressed in a revision of the CT directive, and should allow easier implementation of Clinical Trial especially in academic environments regarding reduced amount of documentation and pre-clinical data requirements as to be discussed in detail with relevant parties concerned.

**Consultation item n° 10: Do you agree with this description? Can you give other examples?**

Another example of "requirements not adapted to the practical circumstances" is the specific case of radiopharmaceuticals used in clinical trials, specifically for those diagnostic radiopharmaceuticals used for surrogate imaging of the consequences or effects of the treatment of the medicinal product used in the clinical trial.

**Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?**

Some of the guidelines that would need revision in order to address this problem are:

- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004)
- Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial

**Consultation item n° 12: In what areas would an amendment of the CT Directive be required in order to address the issue? If this was addressed, can the impacts be described as quantified?**

In our opinion, there would be two main areas needing amendments:

1. CT with diagnostic radiopharmaceuticals used in micro-dose amounts.
2. A clear differentiation between the requirements for a commercial and an academic (non-commercial) sponsor would adapt the requirements of the CT Directive to the practical necessities (see below).

**Consultation item n°13: Would you agree to this option and if so what would be the impact?**

An outright exclusion of the academic sponsors from the CT Directive would be preferable, but another kind of regulation would hence be needed to try to harmonize requirements among different countries. As this might take to much time, a specific regulation of CT carried out by academia inside the CT Directive might probably be the most straightforward way to proceed.

We are at your disposal for any further information.

Yours sincerely,

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EANM President

Clemens Decristoforo
Chair, EANM Radiopharmacy Committee

**About the European Association of Nuclear Medicine**

**Umbrella Organization**

The European Association of Nuclear Medicine (EANM) is the umbrella organization of Nuclear Medicine in Europe and represents the sector towards the European Institutions. It was founded in 1985 as a professional non profit medical association, serving as a communication platform for clinical and research excellence in Nuclear Medicine. There are two membership branches of the society: one being 38 national societies (member states of the Council of Europe), the other being individual members (3.863 members), comprising physicians, radiologists, chemists, radiopharmacists, physicists and technologists.

**Scientific Strength**

Presently there are 11 committees representing the most important sub-specialties of Nuclear Medicine: Cardiology, Dosimetry, Drug Development, Molecular Imaging, Neurology, Oncology, Pediatrics, Physics, Radionuclide Therapy, Radiopharmacy and Technologists. These committees are furthermore the scientific pillars of the association and important cooperation partners for related fields such as Oncology, Radiology, Cardiology, Neurology, Pediatrics and Molecular Imaging. The official journal of the EANM, the “European Journal of Nuclear Medicine & Molecular Imaging” (journal impact factor in 2008: 4.532 ), is known for its scientific quality and serves as a communication tool for the cutting-edge research findings and Guidelines written by the EANM Committees.

**Professional Infrastructure ensuring Continuity**

Since 2001 there is an Executive Secretariat and Educational Facility in Vienna, which ensure the administrative workflow of the whole association and of the educational branch in particular: The European School of Nuclear Medicine (14 teaching courses per year at the Educational Facility in Vienna, 3 seminars per year in Central and Eastern Europe) is an integral part of the EANM. Moreover, the congress management department is a core unit of the Executive Secretariat, which is in charge of the organization of the annual scientific congress (EANM'10 Vienna: October 9 - 13, 2010) usually gathering around 5,500 participants for a complete spectrum of state-of-the-art scientific sessions in Nuclear Medicine.

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