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Quality Requirements of Tracers for Drug Development

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The tracer approach used in PET and SPECT is especially valuable in early stages of drug research, where researchers can directly label a drug lead to see where it goes. In addition, in early preclinical evaluations in humans, PET and SPECT tracers can reveal molecular changes brought about by the drug. This is an extremely important capability for evaluation of new drugs for treating diseases where changes on the molecular level occur long before becoming visible in anatomic imaging.

The tracers agents used in humans in the developmental stage of new drugs and the precursor materials used in their production have to meet high quality standards to ensure the highest possible safety for the patients or volunteers and to guarantee the reliability of the results of the imaging studies. Moreover, In Europe, a specific legislation with respect to investigational new drugs, including tracer agents, has evolved.

On May 1st 2004, the EU Directive 2001/20/EC (1) came into force in the European countries laying down the principles of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use. The provisions of this Directive have been transposed into national laws in most of the European member states. In addition, EU Directive 2005/28/EC (2) defines the principles and detailed guidelines for GCP regarding investigational medicinal products for human use.

As a consequence of the new legislation, documentation on the quality and preclinical (i.e. toxicological) data of investigational medicinal products, including radiopharmaceuticals, needs to be submitted to obtain approval from the national health authorities in the member states prior to initiating a clinical study in humans. Approval for the quality, safety and efficacy of the investigational drug product, including the used tracer agents, should be sought in every country involved in multicentre clinical trials.

The quality requirements for medicinal products such as radiopharmaceuticals used in clinical studies often differ to a certain extent from one country to another. The same holds true for the current legislation regarding preparation, dispensing and use of radiopharmaceuticals, that are routinely used in hospitals for diagnostic or therapeutic purposes. In addition, the scope of the national legislation which is based on the definition of an investigational medicinal product, may also differ from the scope of the corresponding EU legislation and therefore may have substantial impact on the clinical research in each member state.

The current chemical-pharmaceutical quality requirements for investigational radiopharmaceutical products are covered by a general EMEA draft guideline regarding investigational medicinal products in clinical trials (3), which provides only a limited level of detailed guidance for ready-to-use compounds (e.g. ^{123}I-Ioflupane, ^{18}F-FDG), kit based radiopharmaceuticals (e.g. ^{99m}Tc-exametazime), or in house made non-licensed new tracer agents (e.g. ^{11}C-raclopride).

Another point of concern relates to the impact of the new legislation on clinical trials performed by non-commercial research centres. Many academic research centres developing new radiopharmaceuticals often do not have the facilities or budget to produce small batches of radioligands for clinical use under GMP conditions, which is a requirement for production of new investigational drugs for use in clinical studies. However, in some countries magisterial and officinal preparations (to which some radiopharmaceuticals can belong) are excluded from this requirement.

In conclusion, it is clear that the continuously changing European pharmaceutical legislation regarding clinical trials and quality requirements for new investigational drugs, including tracer agents, has an increasing impact on radiopharmaceutical research both at academic and industry level.

References

(1) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. (http://pharmacos.eudra.org/F2/eudralex/vol-1/DIR_2001_20/DIR_2001_20_EN.pdf)

(2) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. (http://pharmacos.eudra.org/F2/eudralex/vol-1/DIR_2005_28/DIR_2005_28_EN.pdf)

(3) CPMP/CHMP/QWP185401 Draft guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. (http://www.emea.eu.int/Inspections/docs/18540104en.pdf)