Regulations for Human Application

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Clinical trials in the European Union (EU) are defined as "investigations in humans intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of investigational medicinal products (IMP), and/or to identify any adverse reactions to IMPs and/or to study absorption, distribution, metabolism and excretion of IMPs with the object of ascertaining their safety and/or efficacy". Consequently, clinical trials can be considered an indispensable part of clinical research which, in turn, is essential to develop medicinal products, and to develop and improve medical diagnosis and treatment.

The rules governing medicinal products in the European Union are complex, and they can be found in Eudralex, published by the Directorate General for Health and Consumers, and in some papers documents published by the European Medicines Agency (EMA).

Volume 1 of Eudralex (1) "The rules governing medicinal products in the European Union" compiles the body of EU legislation in the pharmaceutical sector for medicinal products for human use, including the basic Directive 2001/83/EC ("Community code relating to medicinal products for human use"). Volume 10 (2) contains legislation and guidance documents specifically applying to clinical trials and is organized in 6 chapters, dealing with (I) Application and Application Form, (II) Monitoring and Pharmacovigilance (III) Quality of the IMP, (IV) Inspections, (V) Additional Information and (VI) Legislation. The current complex legal situation concerning clinical trials and radiotherapeutics has been summarized by the Drug Development Committee of the EANM (3), while a summary of the differences among the regulatory frameworks of different European countries has been recently been reviewed (4)

A major challenge for clinical research in Europe has been set by the change of how clinical trials have to be conducted. This was started with the so called "Clinical Trial Directive" (Dir 2001/20/EC) that considering that he basis for the conduct of clinical trials in humans is the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, established the basis for normalized procedures for approval by National Competent Authorities (NCA) and conduct of clinical trials.

The Directive introduced a number of general requirements such as standardized documentation including pharmaceutical requirements, and compliance with Good Clinical Practice (GCP) as a way to provide assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible. The Clinical Trials Directive was concretized further by Directive 2005/28/EC (the "GCP Directive") laying down principles and detailed guidelines for GCP as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

Directive 2003/94/EC (the "Good Manufacturing Practice Directive") introduced the general requirement for preparation of Investigational Medicinal Products (IMP) according to GMP, forming the basis for issuing a new annex 13 to European GMP for these preparations.

A number of additional guidelines have followed including guidelines for the first use of a new pharmaceutical in man (first in human clinical trial guideline), the chemical and pharmaceutical documentation, the so-called Investigational Medicinal Product Dossier (IMPD), etc.

The overall complexity of clinical research with IMPs is even increased with the possibility to use in clinical research Non Investigational Medicinal Products (NIMPs), that are medicinal products that do not fall within the definition of IMP as defined in the Clinical Trial Directive. In many cases, PET tracers used in clinical research could be considered NIMPs. As a general rule, the documentation requirements for the application dossier for IMPs also apply to NIMPs, albeit a simplified dossier for a NIMPs could be used depending on the extent of the knowledge on the NIMP. As NCA from different EU countries often have discrepancies on what to consider an IMP or a NIMP, a Guidance on IMPs and NIMPs has recently been published (5) by the European Commission that supersedes the existing document from 2007.

In some European countries these problems may be circumvented when RP are not used for a clinical diagnosis, but within a basic research project, where the radiotherapeutic then is not considered as an IMP. Some authorities accept applications if they are prepared within the framework of pharmacy practice or within marketing authorization exemptions, however this again is very variable between individual countries. In any case, the latest EU legislation derived from Directive 2005/28 (and its implementation in the different EU member states) has in practice made it extremely difficult for the academia or non-profit organizations to carry out their own clinical trials.

The legislative corps for CT was designed almost exclusively having in mind the pharmaceutical industry, and by maximizing some requirements (probably to non-reasonable limits) has posed excessive hurdles to the development of CT. After several years and many complaints from scientific societies, academic institutions and patients associations, it has been acknowledged that the number of clinical trials in the EU has been significantly reduced in favor of either the US or developing countries. At the end, also funding for research associated with the development of new medicinal products has also been reduced.

One major exemption from the tight legal framework in clinical trials is the so called microdosing concept, reducing the requirements for preclinical safety testing when "less than 1/100 of the dose calculated to yield a pharmacological effect of
the test ...and at a maximum dose of < 100 µg” is administered.

Apart from the regulatory framework related to clinical trials as defined above, the European Medicines Agency (EMA) whose main responsibility is the protection and promotion of public health, through the evaluation and supervision of medicines for human (and veterinary) use, publishes Guidances and other documents related to topics related to clinical trials as they are a key part of the overall authorization process of a new medicinal product.

Some of the more relevant of such documents related to clinical trials are the "Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (CPMP/ICH/286/95)" approved in December 2009 and the "Position Paper on Non-clinical safety studies to support clinical trials with a single microdose". PET tracers are specifically cited in these documents, thus recognizing the important role that PET tracers can play in the very early stages of clinical research.

Notwithstanding the importance of safety for the participating subjects in any clinical trial, the EU authorities are aware of the aforementioned shortcomings and unintended negative consequences of the CT Directive and the derived legislation, and published last year a public consultation paper aiming to consider various options for further improving the functioning of the Clinical Trials Directive.

References