Role and competence of the Ethical Committee for the human clinical investigations in orphan drugs development: procedures for pre-licencing access to the cure of rare diseases

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Orphan drugs are medicines or vaccines intended to treat, prevent or diagnose a rare disease. Examples of rare diseases include genetic diseases, rare cancers, infectious tropic diseases and degenerative diseases. Orphan designations are often based upon: severity (life- threatening or chronically debilitating conditions) and unmet need (no therapeutic alternative or the new product provides significant clinical benefit). Orphan drug designation may also allow drugs for non-orphan diseases to gain market access. Oncology products account for the greatest number of orphan drug designations in the US (32.5% of all orphan designations); similarly, in, Europe, Japan and Australia. Pre-licensing access in the form of Expanded Access program also known as Compassionate Use (art. 83 of Regulation EC No 726/2004, Italian DL 8 Maggio 2003) and off-label use to orphan drugs is common (17 of 35 countries) and allows the importation of unauthorized medicines on a named patient or patient group basis. However, when it exists, pre-licensing access is rarely reimbursed by public health insurance but in such cases, it promotes both the availability of, and access to these medicines regardless of positive marketing authorization or inclusion on a national reimbursement list. The role and competence of the Ethical Committee for the human clinical trial investigations are regulated by the EU and the National law. The scientific board of the CE accepts the proposal for clinical investigations activating all procedures to evaluate the scientific protocol, approves or modify the informed consent, evaluate the risk / benefit balance submitted by the sponsor/promoter of the study drug through the analysis of the investigators brochure (I.B.) and the safety documents such as the periodic safety report (PSUR), may approve or refuse the amendments related to the study drug, and evaluates the capability of the investigator site to perform the requested clinical study. It also evaluates protocols related with medical device, nutritional based therapy, chirurgical procedures other than drugs. The clinical trials and Expanded Access program ongoing and monitored by the CE of Area 2 Puglia are related with orphan drugs under investigation in emato-oncology, neurological diseases including epilepsy, haemophilia and autoimmune diseases. Accelerated online procedure has been implemented for the evaluation and approval of the compassionate use of orphan drugs for rare diseases. Other than specifically designed clinical trials, the Expanded Access program remain the most powerful and used regulatory procedure to provide orphan drugs to patients not eligible for any clinical trials affected by a severe disease. It is addressed to a single patient or group of patients with no therapeutic alternative, for a drug under investigation in the same indication in concluded or ongoing Phase III or concluded phase II trials showing a favourable risk / benefit balance. Taking into account the fact that there is often a lack of quantity and quality of clinical evidence for orphan drugs, due to a limited number of patients and the fact that the rare patients

are not eligible for clinical trials, an accurate risk/benefit balance evaluation is a concern for this class of drugs as well as High Technology Assessment evaluation. The current guide line related with the evaluation of risk / benefit balance of the study drug are designed for the evaluation of non-orphan drugs. Novel principles and algorithms are needed in the evaluation of orphan drugs in the national and regional committee to accelerate the access to the cure of rare diseases.