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Orphan Drugs for Rare Cancers: Proposals for Action at the European Level

Hosted by MEP Frieda Brepoels
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Abstracts

What can the EU do to improve how we measure efficacy of orphan drugs in rare cancers?

Paolo G Casali, *European Society for Medical Oncology (ESMO)*

By definition, the problem of rare cancers is their number. Among others, this limits the marketing potential of new drugs as well as the statistical power, and even the feasibility, of clinical trials. These are the gold standard for measuring efficacy of new treatments in medicine.

Financial incentives to pharma companies due to develop these drugs in rare cancers, and supports during the regulatory approval process, are at the core of orphan drug regulations which are in place worldwide, including the EU. These regulations are unanimously regarded as a success.

A limitation is that a company may nonetheless decide not to develop an orphan drug in a rare indication inasmuch as it perceives that the non-approval risk is high, due to the limited evidence of efficacy likely to be generated given the low number of patients. In medical oncology, the end result will be the need to use the drug off-label if it is already on the market for another indication, or even that the drug will not be available at all. Thus, there is an acute need for innovative methodologies in clinical trials on rare diseases. Bayesian approaches to clinical research may be more appropriate than conventional frequentist methodologies to help the clinical decision-making process in conditions of uncertainty. All available information should be best exploited to build new knowledge, whether it derives from clinical trials or anecdotal reports or population registries. However, an inevitably higher degree of residual uncertainty may be easier to accommodate at the bedside, through a shared decision-making process with the patient, but more difficult to handle under a regulatory perspective. Since the approval of a new drug generates costs for the society, especially in the welfare systems of EU countries, an effort should be made to deal with this issue thoroughly. Currently, the divide between the regulatory process, based on risk/benefit considerations, and the reimbursement process, based on cost/efficacy considerations, may not help to overcome problems posed by rare cancers, where the uncertainty on efficacy (benefit) may be inherently higher even after good clinical research. The academy, the industry, patients and politicians should make an effort to work together to generate innovative scenarios for the development of new drugs in rare cancers, and rare diseases.

Then, clinical trials need to be done, and organizational difficulties are most challenging when the numbers are low. Regulatory requirements for clinical trials should be kept to the minimum which is actually requested for them to generate reliable knowledge, eliminating any useless red tape. There is a strong feeling in the community of researchers that this is not the case today, and the EU regulations on clinical trials may be crucial to this. In the end, it is a matter of money, so that academic trials, and industry-sponsored trials with budget limitations, are obviously at stake.

In addition to regulations, the existence of collaborative clinical networks devoted to rare cancers is crucial to enable clinical trials. These should be wide enough to enrol a high number of "rare" patients, but they should also be done by centres with clinical expertise in the specific cancers. Networks imply an amount of medical extra-time, which needs to be financed. All too often, funded projects are limited in time and artificially separate clinical research from health care. Especially in rare cancers, and rare diseases, care and research inevitably fade into each other, and, in a sense, should never be split.

Importance of cancer registries and e-health for development of and access to orphan drugs

Dr Michael Callens, *President, Belgian Cancer Registry*

Registration of cancer and rare diseases enables caregivers, scientists and researchers, authorities and the general public to access a wealth of information. These data - combined with mortality, treatment and prevention data – permit to gain insight into the characteristics of various forms of cancer, temporospatial changes, possible causes, the results of treatment and effects of primary or secondary prevention. Registration results can be used for patient care, screening, epidemiological research, research on cancer incidence, prevalence, survival, health-care planning and monitoring.

Experience with diagnosis, staging and treatment is often limited - even in major cancer centers - because of the small numbers of rare cancers. Registration of all useful information on a European level is needed to obtain good statistical power. This registration must include data that permits measuring efficacy and adverse effects of new treatment modalities (e.g., orphan drugs). An international approved dataset of relevant information (cfr Rarecare project, Eurochip) should be created for each rare cancer. Special emphasis is needed with respect to common medical semantics, message formats, standard rules of coding, classification, quality checks and follow up and update frequency. Experience in Belgium with cancer registration permits to conclude that the participation should be mandatory and a condition for reimbursement of orphan drugs. Patients should be informed that registration- without individual informed consent - is beneficial for their personal and public health. A unique identifier should be used. This enables to obtain additional information, linkage with other databases and follow up in time. For scientific analysis and reporting coded or anonymized data (= Belgian eHealth service) should be used. Registration should be done in first instance on a national level to optimize quality control, linkage with other sources, initial data processing and analysis. This leads to nationwide registers. Subsequently, data will be pooled in a European register. Interpretation and scientific analysis of European data must be executed by a multidisciplinary group of experts.

Experience in Belgium with cancer registration demonstrates that an electronic registration is most efficient. The Belgian 'eHealth' platform provides secure electronic exchange of information between all actors in the health care sector through:

- preventive access control = user and access management: who can fill in or read what, when, of who, how long', using validated authentic sources and respecting the 'privacy law'
- an information exchange platform for the accessibility of 'services of added value' (e.g., common data files),
- eHealth basic services as time stamping, encryption for secure electronic data transfer, logging (who, when, what, about who – no content).

The role of the European Union is to remove linguistic, administrative, legal and technical barriers within the EU by creating a regulatory and legal frame work. The national solutions must be interoperable ('talk to each other') at EU level, user-friendly and trusted by both patients and health care professionals. Appropriate data protection, system security and performance criteria need to be included in any cross border application. We welcome the commitment of the member states and the EU commission to achieve full interoperablility of eHealth services which will be of major importance for a better approach towards rare cancers (diseases) and orphan drugs.

Sustainable and improved access to orphan drugs: Why and how Member States should collaborate in the European Union

Yann Le Cam, *Chief Executive Officer, European Organisation for Rare Diseases (EURORDIS)*

The regulatory framework established with the Orphan Drug Regulation has proven to be successful in terms of drug development *stricto sensu*. Nevertheless, as shown by EURORDIS Surveys on Availability of ODs across all EU Member States (2001, 2003, 2005, 2007), rare diseases patients do not have equitable and timely access to the approved Orphan Drugs they need. There are major inequalities in patient access between MS, between regions and between hospitals.

Currently, we can benefit from a new Policy base aimed at improving availability of ODs. The main reference documents of this new base are:

- The guiding Principles of the EU Pharma Forum on "Improving Access to orphan medicines for all affected EU citizens" (November 2008);
- The Commission Communication on RDs, Chapter 5.3 "Access to ODs" (December 2008);
- Council Recommendation on RDs, Chapter 5 "Gathering the expertise on RDs at the European level" 5.5 "therapeutic or clinical added value of ODs" (June 2009).

Slow placing on the market or even no placing on the market is not linked with the value of the drug. There are responsibilities for delays on the side of Member States not having the required expertise or wanting to save money and on the side of the pharma companies, which don't have resources to apply 27 different procedures or are not interested in small national markets.

In this context, EURORDIS and other stakeholders are proposing to make the best use of the existing scarce expertise in order to allow for a European Common Scientific Assessment of the Clinical Added Value of Orphan Drugs (CAVOD).
EURORDIS strongly believes that the answer is at the European level: time is mature to make the step from "agreed principles" to "real action implementing new good practices".

The advent of tissue products and vaccines in cancer treatment: All cancers, rare cancers?

André Lhoir, *COMP member, FAMPH*

Human tissue and cell derived products are increasing as orphan medicinal products. They represent a wide range of promising novelties. The current development will hopefully be translated in significant innovation: new products based on biomarkers and personalized medicines will appear representing new hopes for patients.

Due to the specific nature of tissue treatments and cell derived products, there is a need for specific expertise at each stage of the development process: both for regulators and for investigators. The balance between a possible benefit for the patient and a risk of using a new treatment needs to be carefully examined and monitored. Collaboration by networking through reference centers can be an important factor in this particular domain. The further development of biobanks will help research.

All new antineoplastic & immunomodulating medicinal products, including advanced therapies, orphan or not, for adults and for children, are mandatory assessed centrally before marketing authorization can be granted for the entire European Union. They represent a leading therapy area for the EMA (during the development phase as sponsors are seeking scientific advice or protocol assistance) and for the national agencies and ethics committees (responsible for the clinical trials at their territory).

Tissues and cells from human origin have a double impact in the field of solidarity; firstly at the time of the altruist donation for allogenic applications, and secondly at the time of marketing when reimbursement will be requested.