EXPANDED ACCESS PROGRAMS (COMPASSIONATE USE): UNDERSTANDING REGULATORY REQUIREMENTS

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The regulatory-defined purpose of Early or Expanded Access Programs (EAPs) also called Compassionate Use Programs (CUPs) or Managed Access Programs (MAPs) is to provide access to an unauthorized medicinal product or a medicinal product that is authorized but not yet available on the market and that satisfies an unmet medical need.

Where research is the primary intent of using an investigational drug in a clinical trial setting, in an EAP, the intent is treatment.

One should therefore keep in mind that such a program is managed completely differently than a clinical trial, both in terms of documentation and approval processes, and typical clinical trial activities like monitoring are not expected to be performed. Safety data collection and reporting, however, is generally required.

In many countries, Health Authorities have created regulatory frameworks for granting access to unauthorized medicinal products for patients who do not have alternative treatment options or do not meet eligibility criteria for entering into a clinical trial. The most advanced regulatory framework for EAPs can be found in the US and the EU and its Member States (MSs).

In the US, FDA has put in place EAPs that set the conditions under which patients with serious or life-threatening diseases that have no comparable or satisfactory treatments alternatives and for which the potential benefit justifies the potential risks of the treatment (risks are not unreasonable in the context of the disease / condition being treated) can get temporary access to investigational drugs outside of a clinical trial. It is also requested that providing the drug will not compromise product development.

There are 3 categories of EAPs, one for individual patients, one for intermediate-size patient populations, intended for situations where multiple patients with the same condition might benefit from a particular investigational product; and one for large patient populations. The latter is called a treatment IND or protocol and it is expected that the drug is being investigated in clinical trial designed to support marketing, or trials are complete and the sponsor is actively pursuing approval and there is sufficient evidence of safety and effectiveness.

Each one of these 3 categories of expanded access can be submitted as an Access Protocol as an amendment to an existing IND, which is typically used when an IND is in place, or as an Access IND, as a new IND, which is typically done when there is no IND in place or the sponsor of an existing IND for the drug declines to be the sponsor of the access use (this may happen when for individual patient use, the sponsor prefers that the treating physician submits an individual patient IND).

If an existing IND is in place, the FDA prefers an Access Protocol as it is a less burdensome administrative process for both the FDA and sponsor and all data from both the access program and clinical trials is consolidated in one IND, facilitating earlier detection of safety concerns.

In order to start an EAP in the US, the FDA needs to be notified. For a new IND, a 30-day waiting period has to be allowed for and IRB approval obtained, while for an existing IND, the treatment under the Access Protocol can start once the Access Protocol has been submitted to FDA and approval from IRB has been obtained.

For emergency use, there is an exemption from written submission, prior review and approval from IRB and submission to FDA. This is when a patient needs to be treated in emergency cases and there is no time for a written IND submission to the FDA. Such requests are mostly made by the physician by phone. Verbal approval authorization is obtained. However IRB notification must follow in 5 working days of initial treatment and submission to FDA in 15 working days.

In the European Union and its MSs, Early Access Programs (EAPs) are called Compassionate Use Programs (CUPs) and are governed by the individual Member States (MSs) and regulations differ widely among the EU MSs with some MSs handling more tightly regulated rules for access than others. On a community level, however, the European Medicines Agency (EMA) through its Committee for Medicinal Products for Human Use (CHMP) may, at the request of a MS, issue an opinion regarding the conditions for compassionate use for a specific medicinal product. Article 83 of Regulation 726/2004 (Regulation No 726/2004 of the European Parliament and of the Counsel - laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing European Medicines Agency (EMA)) allows for medicinal products without a Marketing Authorization (MA) to be made available for compassionate reasons to a group of patients (cohorts) with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. The medicinal product concerned must either be the subject of an application for a MA or must be undergoing clinical trials.

The CHMP's opinion includes the conditions for use (recommendations for health professionals on how to administer and use the medicinal product safely and effectively), the conditions for distribution (e.g. subject to a prescription or special or restricted prescription) and patients targeted (restricted population as identified by the CHMP, that would benefit from the treatment for CU) and the conditions for safety monitoring.

The CHMP opinions are not binding on MSs but the European Regulation requires nevertheless that MSs take any available opinion into account. While this procedure is still seldom used, one should take into consideration that each EU MS where an EAP/CUP is planned to be conducted, may request the CHMP opinion and consequently it can be assumed that other involved MSs will implement the opinion. Information on CHMP opinions is published on the EMA website.

An EAP to investigational drugs program was a recently introduced by the Ministry of Health, Labour and Welfare (MHLW) in Japan in January 2016. The program has similar features as the program known as EAP in the US or CUPin the EU.

Looking further to other countries across the globe, a wide divergence can be seen in the way EAPs or CUPs are regulated, with some countries allowing for a cohort approach while in other countries, the regulations are restricted to an individual patient approach. In some countries, the only regulatory approval needed for access to the unauthorized drug is an import license.

Conclusion

EAPs are not clinical trials and are regulated in a very different way.

Many countries, including the US, the EU (both on a Community and national level), Japan, Canada, Australia, etc. have developed a regulatory framework for regulating access to unapproved medicines which is country/region specific.

It is clear that from a regulatory perspective, it is pivotal to have a good understanding of the local requirements for EAPs/CUPs in order to be able to ensure a smooth transition from the clinical research program to the EAP. With a collectively large regulatory intelligence and understanding of the scope and conduct of EAPs, Covance is a key partner for the successful execution of such programs.

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