



21. Emergency Use, Expanded Access, Compassionate Use, and Off-Label Use of Medicines

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Faced with the COVID-19 pandemic, several drug regulatory agencies implemented new concepts of rapid access programs, accepting the exceptional use of medicines even in the absence of the usual evidence of efficacy required for marketing approval. Amid heated discussions on the use of medicines “outside the label” (off-label), the terms emergency use, compassionate use, and expanded access have gained prominence. These terms deserve closer examination, as they are not widely known in our setting and there are important differences in how they are defined and applied by regulatory agencies in different countries.

The concept of patient access to experimental treatments prior to any approval by a regulatory agency was first regulated by the FDA in 1987, in response to the crisis caused by the emergence of AIDS. This allowed more than 4,000 patients to be treated with zidovudine (AZT) at least six months before its definitive approval (Young et al., 1988).

In the United States of America, the FDA authorized the use of several drugs for the treatment of COVID-19 through the [Emergency Use Authorization](#) (EUA) program (Rizk et al., 2021). The most famous authorization was granted for chloroquine and hydroxychloroquine on March 28, 2020, later revoked on June 15, 2020, but EUAs were also issued for remdesivir and for the combination of casirivimab and imdevimab, among others. It should be noted that emergency use of medicines is intended for public health emergencies arising from threats posed by infectious diseases or by other causes such as chemical, biological, or radiological agents. In such cases, the medicine immediately becomes part of medical practice and may be prescribed by any physician, provided that a signed informed consent form is obtained from the patient, without even requiring the submission of a clinical trial application for the medicine in question.

In Brazil, a similar program was adopted for COVID-19 with the publication of RDC No. 475 of March 10, 2021, which established procedures for temporary authorization of emergency use of medicines and vaccines, at the request of the pharmaceutical company. Within this framework, remdesivir, the combination of monoclonal antibodies casirivimab and imdevimab, and more recently the combination of bamlanivimab and etesevimab were approved.

It is noteworthy that the FDA has another program that enables patient access to unapproved medicines even outside a public health emergency. This procedure, called [expanded access](#), is more bureaucratic, restricted, and demanding. In fact, it is limited to qualified physicians registered at specific sites, and it requires, among other aspects,



authorization to initiate clinical trials. This program was designed to serve patients with life-threatening conditions or serious diseases for which no satisfactory therapeutic alternatives exist and who are unable to participate in clinical trials with the experimental medicine (Rizk et al., 2021). It is also worth noting that the European Medicines Agency (EMA) has a similar program, known as [compassionate use](#), a term that is sometimes also used by the FDA.

In Brazil, however, Anvisa distinguishes these two terms according to [Resolution RDC No. 38 of August 12, 2013](#) (amended by [RDC No. 311 of October 10, 2019](#)), which defines two programs with somewhat different characteristics:

- **Expanded Access Program** allows the “*availability of a new, promising medicine, not yet registered with Anvisa or not commercially available in the country, that is undergoing or has completed Phase III clinical development, intended for a group of patients with serious debilitating and/or life-threatening diseases and without satisfactory therapeutic alternatives using registered products”*. This program allows treatment of patients who could not enter the clinical trial due to lack of access or failure to meet inclusion and/or exclusion criteria, and for whom access to treatment is deemed necessary by a physician.

- **Compassionate Use Program** aims at the “*availability of a new promising medicine for personal use by patients who are not participants in an expanded access program or a clinical research study, not yet registered with Anvisa, that is in the process of clinical development, intended for patients with serious debilitating and/or life-threatening diseases and without satisfactory therapeutic alternatives using products registered in the country”*. The main difference here is that Anvisa’s authorization is personal and non-transferable, and it is not limited to medicines already in advanced clinical phases (Phase III), provided that the initial clinical data observed are promising.

For both programs, Anvisa assesses the following criteria before granting authorization: disease severity and stage, absence of satisfactory therapeutic alternatives in the country, severity of the clinical condition and presence of comorbidities, and the risk–benefit relationship of the requested medicine.

It is worth drawing attention to the current trend of considering expanded access programs as sources of real-world data, another term that is now widely used in the evaluation of [effectiveness rather than efficacy](#), including for COVID-19 vaccines (Polak et al., 2020). Indeed, data from expanded access programs are increasingly accepted as evidence by regulatory agencies when it is not possible to obtain data from standard clinical trials, such as [randomized controlled trials](#). This situation occurs mainly in cases of rare diseases or medical conditions not addressed by currently available therapies. Polak and colleagues (2020) conducted a systematic study of the role of data derived from expanded access programs in the regulatory approval process at the FDA and EMA. They found that 39 approvals relied on this type of data to consolidate the



efficacy profile of a treatment. In four cases, these data constituted the sole source of evidence of clinical efficacy (Polak et al., 2020).

On the other hand, what is meant by off-label use of a medicine? In the United States of America, the term off-label is commonly used to mean “*unapproved use of an FDA-approved drug*”. According to a technical note from Anvisa’s Office of New Drugs, Research and Clinical Trials, a medicine is considered to be used off label when it is prescribed for an indication that is not included in the package insert of the medicine duly registered with the country’s regulatory agency. Thus, off-label use is, by definition, not authorized by a regulatory agency, but this does not imply that it is incorrect or illegal, as highlighted by Meadows and Hollowell (2008), who argue that physicians do not need to inform patients that their prescription is off label, let alone ask them to sign an informed consent form. In certain cases, off-label use may be rational and appropriate, as it may represent a treatment widely reported in the medical literature. In fact, according to a 1994 reference cited by these authors, 40-60% of all prescribed medicines were for off-label use, at least in the United States at that time. On the other hand, it is important to emphasize that such use is at the physician’s own risk and may eventually be characterized as medical malpractice, exposing the physician to legal action if a patient files a lawsuit. In this case, there is no need for the physician to request authorization from the regulatory agency or from the pharmaceutical company, since the medicine is commercially available for the use(s) listed in the package insert. This situation may occur when a physician believes that a given medicine may benefit a patient based on preliminary evidence or by analogy with another disease, for example, as occurred, justifiably at first, during the COVID-19 pandemic.

References

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