ITALY APPROVES A NEW REGULATION ON COMPASSIONATE USE OF MEDICINAL PRODUCTS

By decree of Ministry of Health dated September 7th 2017, published on the Official Gazette on November 2nd 2017, Italy has finally approved a long waited regulation on compassionate use (CU) programs, which will enter into force on December 2nd 2017. Starting from that date, the new law will entirely replace the Ministerial Decree 8th May 2003 which, since the Italian Medicinal Code was approved in 2006, was intended to be a merely transitional provision (article 158.10 of legislative decree 219/2006) and yet has remained effective for more than a decade. Expectations on the upcoming regulation were quite high especially with reference to the need to fill the gap between the Italian situation – where CU programs can typically only be initiated upon physician’s request, while the company maintains a mere reactive role - and the relevant European regulation on company CU programs (Whereas 33 and article 83 Reg 726/2004; EMA Guidelines on compassionate use, 2007); yet it looks like an occasion has been partially missed, while a number of new critical issues have arisen.

The main worth-mentioning change is the definition itself of compassionate use, which has been broadened so to include a number of cases which, as of today, do not fall from a legal standpoint in the scope of the CU regulation (although often included in practice).

In particular, under the new regulation, compassionate use will no longer only bear the traditional meaning of “use of investigational products outside trial settings”, but it will also significantly include:

(i) off label use of a licensed product;
(ii) in label use of licensed products which are not available yet on the Italian territory.

As to off label use, it will be interesting to see how this new regulation will coordinate with the existing laws on off label use in Italy (law n. 94/1998, so called “Di Bella” law). This is not only a procedural matter, e.g., which authorization or approval is required, by which competent authority etc., but it triggers a number of substantial issues as well. These include, among the others, whether in the future the pharma company will be allowed to legitimately charge for the product (as it has been done until today) or the product will have to be supplied free of charge, as required by the CU regulation. In the latter case, being the free supply a typical, essential feature of CU programs, will the company retain the right to refuse the supply? What should be deemed as an acceptable ground of such refusal?

In addition, it shall be investigated whether the CU regulation will have the ultimate effect of legitimating off label use beyond the mandatory limit of the named patient basis, considering that CU typically includes not only uses on a named patient basis but also uses on cohorts of patients. From a strictly legal standpoint, such a consequence should be ruled out in consideration of the fact that off label use on “systematic basis” is prohibited by the primary laws concerning off-label (article 1.796(z), Law n. 296/2006), which are hierarchically superior to the Ministerial Decree on CU. However, it is not possible to exclude any surprising twist in its implementation.

As a final consideration, it must be recalled that, according to the EU laws, off label use is expressly excluded from the compassionate use definition (see EMA Guidelines on compassionate use, 2007, section “Compassionate use vs off label use”): on this point, the new Italian regulation is evidently inconsistent with the EU principles.

The second addition - i.e. in label use of licensed products - seems to implicitly refer to the case of centrally authorized products while their price and reimbursement negotiation is ongoing. Ensuring a timely access to new medicines without letting the delays of a difficult price negotiation getting in the way has been one of the regulators’ priorities in the recent years; unfortunately, the measures introduced in 2012 have proved little effectiveness, mainly for financial reasons. Indeed, since 2012, centrally approved medicinal products intended for life threatening disease or for rare disease should be “automatically” classified by the Italian Medicine Agency (AIFA) as products which can be marketed at a price freely set by the marketing authorization holder until the national P&R procedure is concluded (so called “not negotiated class”, C-nn).
However, the high costs of those medicines, which without the NHS funding would entirely remain on local hospital’s budgets, have been an impediment to their use in the clinical practice, to the prejudice of effective access to the same by patients. As a consequence, what happened in the practice was an intentional stretching of the existing laws on compassionate use so to allow (free) supply of highly costly, centrally approved medicines until the conclusion of the P&R negotiation. Although clearly against the literal wording of the previous law, which as mentioned only applied to investigational products, such practical solution has been formally backed by the Council of State in an opinion issued in 2016. Today, the new regulation goes in the same very direction and provides the legal basis for a practice that, although intended to ensure the full implementation of the health right, may raise many regulatory and compliance issues, especially considering the stretched timelines of P&R negotiations in Italy.

Passing now to the main features of the new regulation, the requirements of CU programs are essentially in line with the already existing ones:

- The scope of compassionate use remains the treatment of life-threatening or seriously debilitating conditions, including rare diseases, when an appropriate therapeutic alternative lacks and the patient cannot be enrolled in any ongoing clinical trial. In addition, it covers the therapeutic continuity of those patients who have participated in a clinical trial with a positive, beneficial outcome. The law does not apply to ATMPs, being the hospital exemption regulated by an ad hoc piece of law, namely Ministerial Decree 16 January 2015;

- Essential pre-requirement is that the efficacy and safety profiles must be reasonably supported by phase III clinical trials results on the intended indication or phase II in case of life threatening conditions. A significant exception has been introduced for rare diseases: it is in fact possible to rely on trial results of phase I, even regarding a different indication but for the same dose and way of administration, as long as the safety profile is reasonably proved and a clinical benefit can be expected based on the mode of action and the pharmacodynamics of the molecule;

- The compassionate use can be either on a name patient basis or in the form of a program based on a standard protocol and open to cohorts of patients;

- From a procedural standpoint, the request is made by a physician or group of physicians. The request must be approved by the Ethic Committee and the protocol/therapy plan submitted within 3 days to AIFA, which retains a vetting power. The physician shall take personal and direct responsibility for the use and shall obtain the patient’s informed consent;

- Pharma companies must notify within certain timelines the Italian Medicine Agency (AIFA) with their intention to set up and/or close down a CU program;

- Finally, the data collected with CU programs can be used by pharma companies for registration purposes, as a support for the main data collected by the company through its own registration trials.

In conclusion, while the procedural aspects remain substantially unaltered, the new regulation raises a number of critical issues connected to its broader scope of application and the (lack of) coordination with the European and Italian laws regulating, on one hand, off label use, and, on the other, the Cnn class. The practical effects and the potential distortions of the new system will be soon tested. In these recent times of financial constraints, it is in fact easy to foresee an extensive use of the new provisions in order to obtain free supply of highly cost medicines for the longest period permitted by the law. The inherent risk is that it may call into question some basic principles regulating medicinal products, above all the “MA principle” under article 6 of the Directive.