Off-label use of medicines: an agenda for post-Covid-19

09 APR - *Dear Director,*
In order to deal with the Covid-19 pandemic, AIFA has taken some decisions concerning the “648 list”, the list of medicines established by Law no. 648/1996, which includes, among others, off-label medicines, i.e. medicines that may be used outside their authorised indications. The decision of March 17 added interferon beta-1 (indicated for multiple sclerosis) to the list, only for it to be removed shortly afterwards (decision of March 25) on account of formulation problems. Through the decision of 17 March, AIFA authorised the use of other medicines (chloroquine, hydroxychloroquine and other anti-malarial drugs) at the cost of NHS for patients affected by Covid-19 "exclusively in consideration of the health emergency posed by the pandemic in Italy". They were not added to 648 list, however, as the AIFA found that the law no. 648/1996 was not a legal basis for it.

We do not know exactly why the interferon was considered for inclusion in 648 list, while it was established for the other medicines that the law was not applicable.

What is certain is that the authorisation of the off-label use of antimalarials and antivirals at the cost of the NHS constitutes an exception to Law 94/1998 (called the "Di Bella" law) which, specifying the conditions for prescribing off-label medicines, adds that "under no circumstances" could the prescription give the right to supply medicines not present on 648 list at NHS’ cost. The widespread reimbursed use of off-label medicines is also prohibited or restricted by Law 296/2006 and Law 244/2007. It is true that the Constitutional Court (judgment no. 185/1998) declared the unconstitutionality of the prohibition contained in the “Di Bella” law in the part where it does not provide for the supply free of charge of anticancer medicines, subjected to trials of the “Di Bella method”, in favour of the poors, but within defined limits and expressly excluding any other aspect of unconstitutionality; this condition of the law therefore does not indicate any possibility of derogation legitimising the recent AIFA measure, as laid down in the applicable legislation.

Let us be clear, the legal framework of “*Senatus Consultum Ultimum*” determined by Covid-19 certainly justifies and makes perhaps inappropriate – as the pandemic continues – what may appear to be the fruit of subtle casuistic reasoning and much will probably be modified in the legislative framework being established.

However, the opportunity is to consider whether, in the post-Covid period, it would be appropriate to review the discipline of therapeutic use of unauthorised medicinal products and off-label use of authorised medicinal products, in an organic and rational way.

Law 648/1996 was originally an "emergency" law, approved at a significantly turbulent time in the

pharmaceutical sector, which began in 1992-1993 which also caused considerable delays in the procedures for making innovative medicines available to the NHS: a "spending" law, inspired by the aim of anticipating the standard procedures.

When initially drawn up, the 648 list included medicines without a valid therapeutic alternative. In 2014 it was amended to extend the list to include medicines with a valid alternative, providing that the off-label indication is known, complies with research conducted by the medical-scientific community and is compatible with criteria of cost-effectiveness and appropriateness. The amendment (also handled as an "Emergency" in its own way) was approved to allow the NHS to provide Avastin, a cancer medicine, for ophthalmic uses for which other more expensive medicines are institutionally used. For this reason, Law 648/1996 also became a “savings law”.

Then there is the Ministerial Decree of 7 September 2017, which regulates the therapeutic use of medicines subjected to clinical trials, implementing Article 158 of Legislative Decree No. 219/2006.

There is also the Ministerial Decree of 11 February 1997, which regulates the methods for importing medicines authorised abroad but without marketing authorisations in Italy.

As can be seen, a set of laws of various kinds, largely originating from contingent or exceptional situations, starting from the “Di Bella Law” with overlapping technical and economic regulations, which create an inconsistent framework that is difficult to coordinate, for example between Law No. 648/1996 in its “savings” configuration and the technical and regulatory conditions for possible off-label use established by the “Di Bella” law (difficulties sometimes aggravated by interventions made at the regional level with constitutional problems: see Constitutional Court judgment nos. 8/2011 and 151/2014). A regulatory framework in which the Italian Medicines Agency could not find the legal basis for a measure made necessary by the gravity of the moment.

It seems increasingly essential to put ‘emergency’ pharmaceutical legislation and coordination of possible ordinary exceptions to the regulations of the sector on the post-Covid 19 agenda.

Carlo A. Piria
Lawyer in Milan