# Recent requests to the Ethic Committee of the University Hospital of Bologna of 'compassionate use' concerning forthcoming drugs: a real undelayable therapeutic need or Companies' pre-marketing promotional activity?

N. Montanaro[1,3], G. Chiabrando[2], S. Proni[2], M. Melis[3], D. Motola[3]

[1] President of the Ethic Committee of S.Orsola-Malpighi University Hospital, Bologna
[2] Scientific Secretariat of the Ethic Committee of S.Orsola-Malpighi University Hospital, Bologna
[3] Pharmacology Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna

**Introduction.** An increasing number of requests of compassionate use sent by doctors to our Ethic Committee regarded drugs quite near to the final marketing approval. According to the Italian Ministry Decree of 8 May 2003, the premarketing use of a new medicine is allowed only (a) when no other therapeutic options are available for a patient suffering from a serious or rare disease, and phase III studies on that specific condition are in course or completed (or, in presence of patient's life-threatening clinical conditions, phase studies have been already completed), and (b) available data from the studies in course allow a favorable opinion on the efficacy and safety of the requested medicine.

**Methods.** In the period 2010-2012, our Ethic Committee received 61 requests, concerning 22 different active principles and involving 122 patients. All the requests concerned medicines submitted to EMA, being at different stages of scrutiny.
Almost all the drugs requested for compassionate use were antineoplastic agents: abiraterone acetato, boceprevir, brentuximab, crizotinib, defibrotide, eculizumab, everolimus, ipilimumab, lidocaine, mepolizumab, midostaurin, nilotinib, ofatumumab, pasireotide, pazopanib, ponatinib, regorafenib, romidepsin, ruxolitinib, talidomide, teduglutide, vemurafenib.
In order to analyse the temporal pattern of the requested drugs in relation to their premarketing procedural steps, for each requested drug we paired the date of the first request to our Ethic Committee with the date(s) of (a) submission to EMA, (b) CHMP positive opinion, (c) EC marketing authorization (if issued).

**Results.** Results can be summarized as follows:

1. Almost all the requests concerned drugs already submitted to EMA, i.e. drugs having also completed their registrative phase III studies. The only exception was brentuximab, requested before being submitted to EMA.
2. On average, almost one half of the requests concerned drugs with an already issued CHMP positive opinion. The proportion of the requests concerning drugs already approved by CHMP followed a clear trend year by year. In 2010 the requests were 3 out of 13 (23%) in 2011 they were 7 out of 16 (44%), and in 2012 they were 12 out of 14 (86%). The remaining 18 requests concerned drugs with peculiar EMA procedural steps (e.g. withdrawal of the application, information not available, etc) They were eculizumab, lidocaine, mepolizumab, midostaurin, nilotinib, ponatinib, regorafenib, romidepsin.
3. The requests concerning drugs already authorized by the EC (but not yet marketed in Italy) followed a similar trend.

**Conclusion.** An increasing proportion of requests of compassionate use of drugs near to enter the market was seen along the period 2010-2012. From one point of view, this trend could suggest that doctors' are more and more aware of the potential benefits of the forthcoming drugs, paying an increasing attention to the therapeutic opportunities offered by the novelty of the clinical research. However, from another point of view, this trend seems to reveal an increasing promotional activity of the pharmaceutical industry, aimed at familiarizing doctors with the forthcoming medicines.. Moreover, this widespread use of drugs not yet marketed may mask the promotion of phase IIIb open trials in disregard of all the rules governing the submission of a clinical trial protocol.