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RESEARCH ARTICLE

OFF-LABEL USE IN ITALY: IS THERE SPACE FOR HARMONIZATION?

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ABSTRACT: With Law no. 96 and subsequent updates, in Italy the use of authorized medicinal products is allowed outside of the summary of product characteristics indications under the direct responsibility of the prescriber and in patients who cannot be treated satisfactorily with authorized standard treatments.
Considering that to date no guidelines on request and authorization procedures for off-label use have been established at a national, or at least regional level, an anonymous survey was conceived to outline the current framework on this topic.
The survey was structured with 10 multiple choice answers and checkboxes, and one comments section. The link to access the questionnaire was firstly sent by email to select Italian physicians and clinical research coordinator to test the tool. Corrections were made in line with observations and suggestions and it was then shared with a wider audience through the Italian Group of data Manager's mailing list.
The total number of completed surveys collected was 34. The off-label use requests are performed in most cases by the prescribing physicians alone (59%, n = 20) or with the help of a study coordinator (41%, n = 14). Moreover, most sites (64.5%, n = 22) have a multidisciplinary commission evaluating the off-label use requests, and in almost half (41%, n = 14) the health director is responsible for the final authorization. The latter is granted in less than a week in 38.2% (n = 13). 79.5% of respondents (n = 27) confirmed the evaluation can be expedited in urgent cases.
Despite a common approach in the majority of cases, there is still a notable variability in the request and authorization processes for off-label use among prescribing sites so there is an urgent need for an update in legislation on this topic to standardize the process.

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Impact statement: There is an urgent need for an update in legislation about off label use to standardize the process of request and authorization.

Key words: *off label use; multidisciplinary team; heterogeneity; authorization processes; standardization.*

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BACKGROUND

Off-label use consists in prescribing a drug outside the terms of the marketing authorization (MA) and therefore in indications not covered by the Summary of Product Characteristics (SmPC). It is difficult to identify a general off-label prescription model, as it may concern the use in specific patient populations (paediatric, oncological,

psychiatric, affected by rare diseases) and which differs from the SmPC for pharmaceutical form, dosage, different indication (1). An off-label prescription may also refer to the prescription of a drug for an authorized indication, where only the administration route differs from that covered by the SmPC.

Worldwide, approximately 20% of commonly prescribed drugs are off-label and the percentage is increasing in specific patient populations, such as children, pregnant women and cancer patients. Off-label use is especially prevalent in oncology for many reasons, including the wide variety of cancer subtypes, challenges associated with conducting clinical trials, rapid dissemination of preliminary results, and delays in new drug approvals by Competent Authorities (2, 3).

In Italy, off-label use was regulated for the first time by Law 94/98 (4), better known as the *Di Bella Law*. At the time, somatostatin was used to treat gastrointestinal disorders, such as bleeding ulcers. Already in 1977, Luigi Di Bella had introduced somatostatin in his multitherapy to treat solid tumors. In the following years the "Di Bella method" became a media case: according to the doctor, the combination of somatostatin with other drugs was able to prevent the formation of metastases. Despite the absence of scientific research supporting these assumptions, Law 94 was urgently issued to try to contain the possible economic repercussions on the National Health System of the extensive off-label use of somatostatin, an authorization which later was revealed to be wrong and ineffective.

Owing to the *Di Bella Law,* and subsequent updates, the use of industrially produced drugs is allowed for an indication/route of administration/method of administration or use other than that authorized. Such use is allowed under the direct responsibility of the prescriber and in patients who cannot be successfully treated with medicinal products for which that therapeutic indication or that route or method of administration is already approved, provided that at least favourable data from Phase II clinical trials are available for this use.

The direct responsibility of the doctor, despite it being a regulatory requirement, is a fundamental aspect of off-label prescription from an ethical standpoint. Off label use may in fact influence clinical practice, *i.e.* the general approach of the doctor towards the therapy that he prescribes to the patient. If off-label prescription of a drug, in some selected clinical situations, can represent a precious opportunity, in some others this is the only possible therapy for the patient. The widespread and indiscriminate use of the off-label drug, for which "efficacy" and/or "safety" has not been ascertained, could lead to possible unforeseeable harms for the patient. Often, damage can be avoided where authorized therapeutic alternatives that have been extensively tested for safety and efficacy are available.

In Italy, with Law 648/96, there is the possibility of prescribing off-label drugs at the expense of the National Health System (NHS). This applies only to those drugs for which the efficacy and safety of the off-label indication is known, supported by research conducted within the national and international medical-scientific community, based on parameters of cost-effectiveness and appropriateness, and are subject to approval by the technical commission (CTS) of the Italian Medicines Agency (AIFA) and inclusion in a special list published on the Agency's website "Drug List 648/96". The inclusion of a medicinal product in the list can be initiated by the CTS itself and or at the request of scientific societies, healthcare companies or by any scientific structure.

Before evaluating and approving the inclusion of a new drug in the off-label list, the CTS requires a set of documents that include information regarding:

1. the severity of the disease to be treated;
2. the absence of valid therapies;
3. the proposal of a different therapeutic treatment;
4. indicative costs;
5. the authorization of the medicinal product in Italy and abroad;
6. the scientific documentation with all the relative clinical data.

Medicines that acquire a favourable opinion from the CTS are included in the appropriate list following the publication in the Official Gazette of the relevant AIFA provision and can be prescribed at the total expense of the NHS for all subjects who are affected by the pathology identified within the national territory. The medicines remain on the list until the requirements that led to their inclusion persist and, in any case, until a new provision by the Italian Medicines Agency is issued.

Specifically, the Law (5) art. 1, paragraph 4 establishes that, if there is no valid therapeutic alterna-

tive, the following types of medicines can be supplied at the expense of the NHS, even outside the authorized indications:

1. innovative medicinal products whose marketing is authorized in other States but not on the national territory;
2. medicinal products not yet authorized but undergoing clinical trials;
3. medicines to be used for a therapeutic indication other than the authorized one.

With Law 296/2006 - "Financial law for the year 2007" (6), the Institutions asked the local health authorities, hospitals, university hospitals and Scientific Hospitalization and Care Institutes to identify by 28 February 2007 the responsible for the application procedures of the provisions of law 648, also in terms of administrative liability for tax damage. The law temporarily attributed this responsibility to the company health departments.

Despite this first attempt, to date no standard guidelines have been established at national, nor at regional, level on how to request and authorize off-label use. There is, therefore, variability regarding this process between the various institutions involved.

For this reason, the Italian Data Manager - Clinical Research Coordinators Group (GIDM) has decided to conduct a preliminary investigation aimed at outlining the current picture in Italy regarding the request and approval process for off-label uses and the figures involved in the process.

MATERIALS AND METHODS

The survey was conducted through the dissemination of an anonymous online questionnaire, consisting of 10 questions, some of which with multiple choice answers, and an open final section for comments. All questions had mandatory answers. A copy of the questionnaire is available in **Appendix 1**.

A first version of the survey was sent to a pool of 10 professionals (clinicians and clinical research coordinators) and the final version was drafted taking into account their comments and revisions. The questionnaire was sent in April 2022 to two distinct pools of professionals: a) a group of 20 clinicians, chosen by the project steering committee in order to guarantee geographical, pathological and type of origin heterogeneity; b) to participants in a GIDM course on the topic of "off-label use of drugs", open to any professional category involved in the world of clinical research (38 professionals). The link to access the electronic questionnaire was sent by e-mail and the recipients had 7 days to complete it. The data was analysed in May 2022.

Among the professionals to whom the questionnaire was sent, 34 completed the questionnaire (58.6%), with a majority of replies coming from Lombardy (27%, n = 9) and Piedmont (19%, n = 6), for a total of 12/20 regions represented (60%). The professionals who joined the project were mainly clinicians (50%; n = 17) and clinical research coordinators (41%; n = 14), with a clear

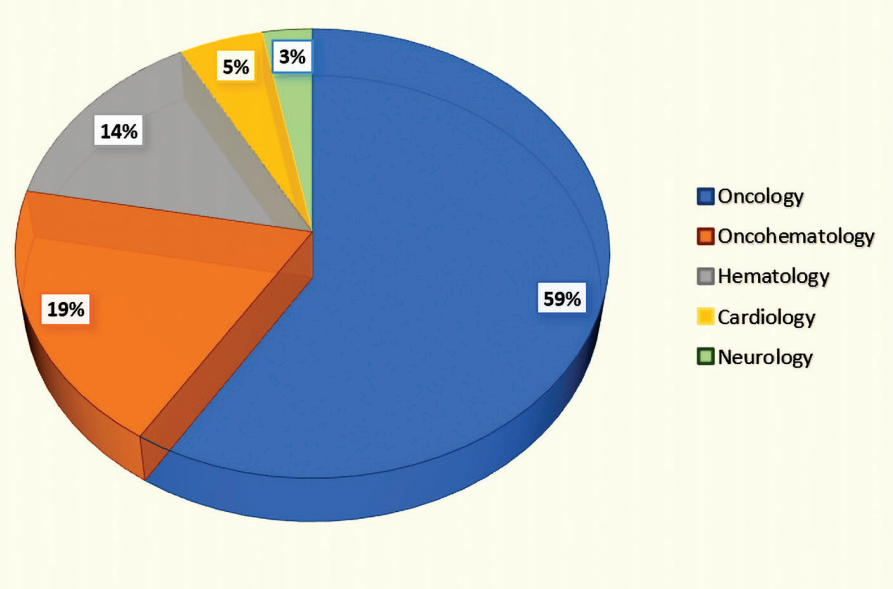

Figure 1. *Profession of the project participants.*

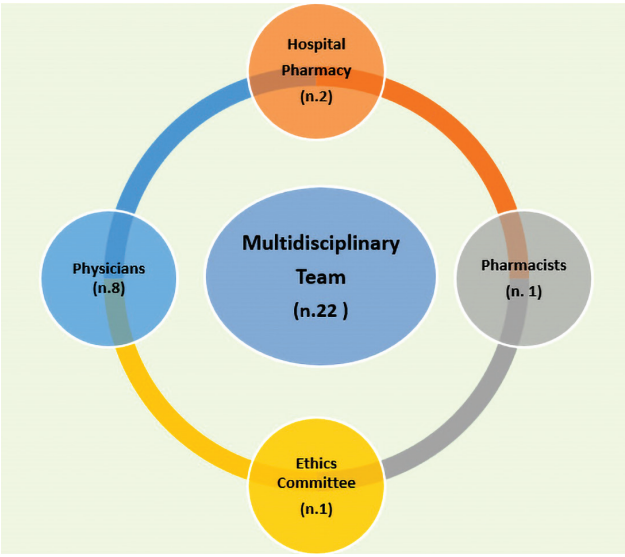

Figure 2. *Responsible for evaluating individual off-label use requests.*

prevalence of respondents working in the oncology field (59%; n = 20) (**Figure 1**).

With respect to the procedures necessary in the respective structures of origin for the management of requests for off-label use, the answers show that the activity is the responsibility of the clinician, who deals with it alone (59%; n = 20) or with the help from their Clinical Research Coordinator/Data Manager (41%; n = 14).

The evaluation of the individual off label requests is in most cases (64.5%; n = 22) entrusted to a multidisciplinary group (**Figure 2**) while the answers show extreme variability regarding the process of officially authorizing the individual off label uses within the structure: in half of the cases (n = 17) it is the same group that carried out the assessment, while in other structures it is a responsibility of the health management (41%; n = 14), the Ethics Committee (3%, n = 1) or other departments/commissions (**Figure 3**). In more than half of the cases (64.7%; n = 22), moreover, in some cases there is the possibility to request the off-label use of a drug for several patients with a specific indication (widespread and systematic use).

Assessment timelines also lack standardization across the Country, these range from less than a week (38.2%; n = 13) to over a month (5.88%; n = 2) (**Figure 4**); more than two thirds of the respondents (79.5%; n = 27), however, admit that therapeutic urgencies may trigger emergency procedures to expedite the assessment.

Just under half of the structures to which the respondents belong (47%; n = 16) organize and carry out information activities for the patient who is prescribed an off-label drug.

DISCUSSION

The possibility of prescribing off-label drugs certainly represents an important opportunity for patients. In addition to constituting a therapeutic option - sometimes the only one - it allows in fact to make drugs available to the patient in a phase prior to registration, on the basis of available scientific evidence and to have early access to treatments or uses considered "innovative". This is of greater importance in specific contexts, such as the treatment of rare pathologies or pathologies affecting segments of the population not normally included in clinical trials and certainly has a great impact from the point of view of the pre-

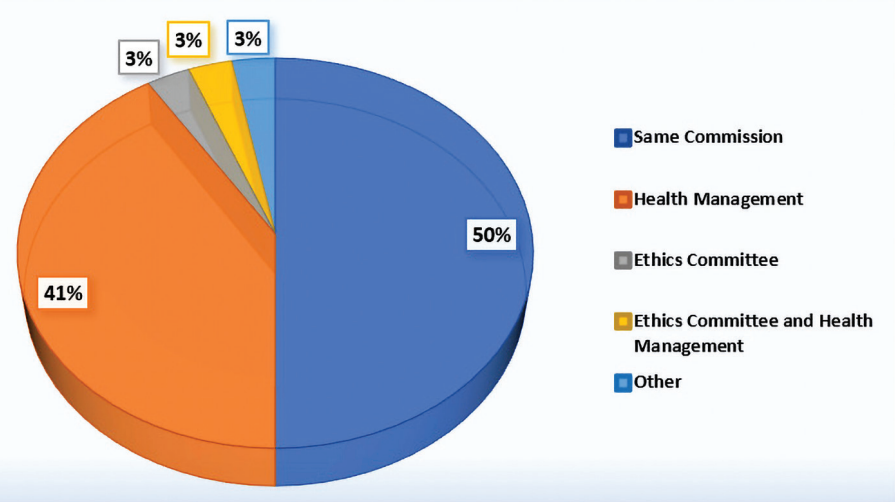

Figure 3. *Responsible for official authorization for off label use.*

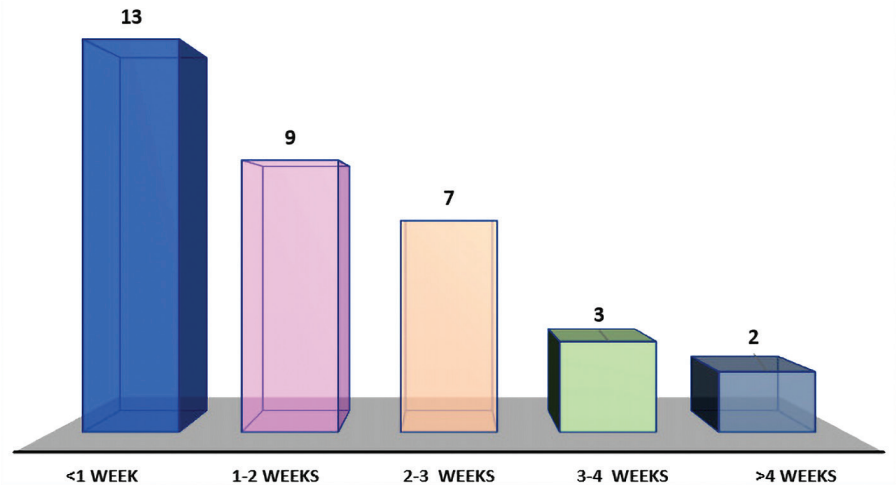

Figure 4. *Timing of evaluation and authorization.*

scriber's ethical and professional responsibility. Despite the relevance of the topic, as confirmed by our research, there are still several grey areas and procedural disparities which probably deserve a deeper reflection and discussion at different levels. By law, the responsibility for off-label prescription lies with the physician prescribing the treatment, however, the lack of national or at least regional guidelines, results in the lack of an official designated professional figure in charge of managing requests. In this regard, the data collected suggest that they are almost always clinicians, with or without the support of research coordinators. It appears clear that the evaluation of individual requests, however, requires the commitment of a multidisciplinary team, given the criticality of the topic.

Perhaps the most interesting data concerns the responsibility and burden of officially authorizing individual off-label uses; from the data collected, in fact, it appears that an "institutional" body (*i.e.* health management / ethics committee) is not required, given that in many centres the authorization comes from the same multidisciplinary group that performed the evaluation.

The differences in authorization procedures is reflected in an extreme variability with respect to evaluation timelines, for which there are no established deadlines. This being said, the desire to optimize procedures seems to be shared on a national level, given that the majority of respondents reported the possibility of requesting the off-label use of a drug for a specific indication (widespread and systematic use) for several patients and the possibility of establishing procedures for urgent cases.

Certainly, if uniform and clearer legislation existed regarding the use of off-label drugs, it would be much easier to optimize processes and perform adequate checks on compliance with approval times which, given the seriousness of the matter, certainly should not exceed 30 days as reported by some respondents. The use of shared paths would also make it possible to improve the collection of data in terms of safety, as envisaged, among other things, by the AIFA operating procedure relating to the management of reports in the new pharmacovigilance network (7). As regards off-label drugs, indeed, the reporting of suspected adverse reactions (ADRs) to AIFA, it being outside the strictly monitored context of clinical trials, may be subject to underreporting. On this issue we should probably also reflect on the lack of training and awareness programs dedicated to professionals, whether they are clinicians, healthcare professionals or even simply pharmaceutical sales representatives. More spontaneous reporting would be essential, also given the almost total absence of data from real life and considering the presence, in Italy, of deep grey areas concerning the legislation in the field of observational research.

Given the lack of training offered to stakeholders, it is not surprising that the data collected from the few institutions carrying out awareness and training activities for patients who are prescribed an off-label drug, is fairly limited. A greater involvement of patients would not only mean an alignment to the requirements set out by the European Union, but would also represent an opportunity to increase the awareness of the subjects with respect to the treatments they are prescribed.

It would also be interesting to provide for a meticulous traceability of off-label uses. Although AIFA periodically supplies the list of drugs that can be supplied at the total expense of the NHS in accordance

with law 648/96 and related therapeutic indications, it is currently not possible to know the annual number of off-label prescriptions, as these drugs in question are purchased through traditional channels. Undoubtedly the data collected, given the small number of respondents, should be acknowledged as an indicative picture of the Italian situation on this topic. Despite this, we trust that the choice of the initial sample ensures a certain reliability of the photograph resulting from our pilot investigation. A possible future development could be represented by the dissemination of the questionnaire to the 149 research centres recently surveyed by the Federation of Italian Cooperative Oncology Groups.

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COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of Interests

The Authors have declared no conflict of interests.

Authors' Contributions

CC, RC: conceived of the presented idea; CC: questionnaire; CC, RC, VF: wrote the paper; IF, FF: revised the final version of the paper.

Availability of data and materials

All data underlying are aviable in the article (and in its online supplementary material).

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

APPENDIX 1

Questionnaire

1) In which region do you work?
- Abruzzo
- Basilicata
- Calabria
- Campania
- Emilia Romagna
- Friuli Venezia Giulia
- Lazio
- Liguria
- Lombardia
- Marche
- Molise
- Piemonte
- Puglia
- Sardegna
- Sicilia
- Toscana
- Trentino Alto Adige
- Valle d'Aosta
- Veneto
- Provincia autonoma di Trento
- Provincia autonoma di Bolzano

2) What is your profession?
- Physician
- Administrative
- Clinical trial start up/Regulatory
- Other

3) In which field do you work?
- Adult oncology
- Adult hematology
- Adult oncohematology
- Adult Neurology
- Adult psychiatry
- Dermatology adult
- Adult cardiology
- Pediatric oncology
- Pediatric hematology
- Pediatric oncohematology
- Pediatric neurology
- Pediatric psychiatry
- Pediatric dermatology
- Pediatric cardiology

4) Who takes care of drafting the off label requests?
- Physician
- Physician and nurse
- Physician and study coordinator
- Other

5) Who evaluates individual off label requests?
- Multidisciplinary team
- Physicians
- Other

6) Who officially authorizes individual off label uses?
- The same group/commission that evaluates the requests with a subsequent confirmation by the health management
- Other

7) Is it possible to request the off-label use for several patients (widespread and systematic use) of a drug for a specific indication?
- Yes
- No

8) What are the evaluation times?
- <1 week
- 1-2 weeks
- 2-3 weeks
- 3-4 weeks
- >4 weeks

9) Is a faster evaluation possible in case of therapeutic emergency?
- Yes
- No

10) Are information activities carried out in your facility for patients who are prescribed an off-label drug?
- Yes
- No

Space for further comments

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