The Regulatory Challenges for Drug Repurposing During the Covid-19 Pandemic: The Italian Experience

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INTRODUCTION

The search for safe and effective treatments for Covid-19 started early and focused in particular on drug repurposing of available molecules in the hope of finding valuable therapeutic options as quickly as possible. As reported on Covid19db, a free online database of trials of medicinal products to prevent or treat Covid-19, the percentage of trials including repurposed drugs exceeds 60% of the total number of interventional drug-based trials (AnticancerFund; Pan Pantziarka et al., 2020).

The main advantages of drug repurposing over de novo medicine research are the faster and potentially cheaper development and the reduced risk of failure due to safety concerns (Bertolini et al., 2015; Pushpakom et al., 2019; Verbaanderd et al., 2019). Therefore, the regulatory authorities were rapidly overwhelmed by requests for clinical trials and compassionate use program approval.

CLINICAL TRIALS APPROVAL: SUCCESSFUL ATTEMPT OF CENTRALIZATION

The Italian Medicines Agency (AIFA) is the Competent Authority for issuing the authorization of all clinical trials of medicinal products together with the local Ethics Committees (ECs) competent for the clinical sites for their formal approval (Supplementary Appendix 1A).

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One of the national regulatory agencies that has suffered the most because of the Covid-19 crisis has been the Italian one.

Moreover, in a situation of absolute emergency with hospitals full of critical patients, clinicians tried to save lives with off-label drugs used according to the available (although weak) evidence.
OFF-LABEL USE FOR COVID-19 AND EMERGENCY APPROVAL

According to the European Medicines Agency (EMA), off-label use “relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information” (EU, 2017).

A major advantage of off-label use is the potential and rapid satisfaction of medical needs, especially in cases where no other options are available, even if it could increase the risk of inappropriate use and medical error due to the lack of a defined risk-benefit ratio (Bellis et al., 2014). Therefore, appropriateness in off-label drug prescriptions must be carefully assessed in order to ensure this use occurs only in the presence of data supporting a favorable risk/benefit profile.

Off-label prescribing is not currently regulated by European Union (EU) legislation, but some countries have adopted specific laws (Supplementary Appendix 4) (EU, 2017).

Italy has gained a lot of experience in off-label regulation and management as a result of the so-called “Di Bella case” (Di Bella, 2010). In order to limit off-label use, to guarantee patients’ well-being and reduce unmitigated risks, the Italian Parliament issued Law 94 in 1998, which allows physicians to perform off-label prescriptions in individual and exceptional cases, provided that the following requirements are respected:

- the assumption of responsibility of the prescriber,
- an adequate informed consent of the patient,
- and the existence of scientific evidence of the efficacy and safety of the medicine derived from at least phase II clinical trials (Financial-Law, 2008).

Moreover, the Law establishes that the National Health System (NHS) does not cover the cost of treatment, which must be granted by patients themselves. In a hospital setting, prescribers must request the authorization for off-label treatment to the local Health Director, and costs are covered by the hospital budget.

The only case in which the Italian NHS can reimburse an off-label drug is its use under Law 648/1996 as reported in specific lists, updated based on new scientific evidence resulting from at least phase II clinical trials (Law 648, 1996).

The Covid-19 emergency obliged national authorities to consider the possibility to allow a systematic off-label use of some medicines notwithstanding the aforementioned rules (Figure 1). In particular, this happened for hydroxychloroquine/cloroquine, lopinavir/ritonavir, and darunavir/cockicistat, whose use in patients with Covid-19 was promptly and provisionally approved for reimbursement, despite the non-applicability of the Law 648/1996 (above all due to the lack of evidence from phase II clinical trials), in order to manage their uncontrolled off-label use, which was already spreading nationwide. This decision allowed the standardization of prescriptions giving official instructions on how to use these medicines, but also to carry out an appropriate surveillance because of the obligation for prescribers to promptly share data about treated patients.
Recently, AIFA published the Report on Medicines used during the Covid-19 epidemic showing a very high increase of hydroxychloroquine use compared to January 2019, a sign of clinicians hopes for this drug in the absence of available alternatives (AIFA, 2020e).

Subsequently, due to the lack of evidence and the possible risk of serious adverse events (Boulware et al., 2020; Cao et al., 2020; EMA, 2020a; FDA, 2020; Lother et al., 2020; Mehra et al., 2020a; Mehra et al., 2020b; WHO, 2020a; WHO, 2020b), AIFA revoked the authorization.

It is noteworthy that the next drug in terms of use following the anti-malarial is the antibiotic azithromycin, the use of which has never been officially authorized outside clinical trials (AIFA, 2020e; AIFA, 2020a). These findings deserve further analyses.

The case of tocilizumab is different, it has been provided free of charge by the Company since the beginning of March. In this case, in order to monitor all patients treated with the drug and to collect solid real-world data, AIFA together with Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale (Napoli) promoted a nationwide trial that involved hundreds of clinical centers and enrolled thousands of patients (AIFA, 2020c). The final results of the study are expected to be published in the near future.

**CONCLUSION**

The Covid-19 pandemic tested the regulatory authorities’ ability to react to an emergency. In this context, Italy promptly implemented many measures (including centralization of clinical trials approval, simplification of the trial management obligation, financial support for research proposals, off-label use funding and governance) in order to simplify the practice of drug repurposing but also to maintain a strict control on drug access. Although some decisions were later withdrawn, the Italian regulatory authority was vigilant, efficient, and adaptable to face such a great challenge. Moreover, centralization has proven to be a successful choice, and a way forward in the future, albeit perfectible.

This success can be useful in order to start reviewing some old regulations and to further simplify some procedures, to make the system competitive and guarantee equal access to patients.

Finally, a dialogue among European member states and other authorities worldwide is desirable to set common criteria for proper off-label use management.

**AUTHOR CONTRIBUTIONS**

LG wrote the first draft of the manuscript. FD checked and revised the draft manuscript. All authors contributed to the article and approved the submitted version.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.588132/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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