

Medical-legal aspects of the fungal infection drug therapy in neonatology: evidence-based medicine and off-label prescribing

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Abstract

The aim of this paper is to focus on the well-known issue of the clinical use of off-label drug therapy in neonatology with respect to evidence-based medicine, with particular reference to antifungal products, in comparison with the wider use in pediatric and adult population.

Then we considered the new regulatory approaches carried out in the past decade by the FDA (Food and Drug Administration) and the EMA (European Medicine Agency), aimed to improve newborn and children population inclusion into scientific trials and to promote drug labeling with respect to pediatric indications, and the goals nowadays achieved through the *American Pediatric Research Equity Act / Best Pharmaceuticals for Children Act* and the European Pediatric Investigation Plans. Finally we pointed out, on the basis of the Italian regulatory framework, the Italian medical-legal liability profiles related to the use of off-label therapies in neonatology.

Further efforts are required in the international context to carry forward the process started while in the particular Italian scenario it is to be hoped that a general change of mind towards the off-label drug use in neonatology clinical practice may take place.

Keywords

Off-label, newborn, Pediatric Investigation Plans, liability, antifungal drugs.

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Introduction

The off-label therapy, with its peculiarities of general atypia and exceptionality when compared to the regular and usual drug's prescription regulated by the Ministry of Health, represents a distinct field of clinical practice and medical-legal discussion whenever analyzed in the neonatology context. In fact, in pediatrics and even more so in neonatology, off-label prescribing loses its feature of extraordinariness up to become often the usual and customary prescribing attitude.

The already complex clinical management of the patient-newborn is made even more difficult by the lack of *ad hoc* formulations, both pharmacological and nutritional, i.e. authorized with respect to the indication for the neonatology use. This is due to the lack of neonatal trials and to the absence of economic interest by the pharmaceutical companies to undertake studies about drugs already approved for use in adults specifically addressed to a small population such as the neonatal one. As a matter of facts many drugs are not labelled for neonatal therapy.

In particular, the lack of specific dosage for the newborn is due to the shortage of pharmacokinetic (PK) studies. Furthermore, the pharmacodynamic (PD) studies made on the adult/pediatric population shall not apply to infants [1] for the diversity that in the latter has the bioavailability of molecules in relation to peculiarities in enzyme systems used for the metabolism and transport of drugs and in body composition in water, fat and proteins. In the absence of specific therapeutic indication, drug dosing should be tailored to the individual little patient's clinical condition and its comorbidities, based on physician's clinical experience compared to data available from the scientific literature regarding the pharmacokinetics, pharmacodynamics and toxicity of the drug.

Indeed, the lack of a regulatory endorsement for the majority of drugs used in the newborn clashes with the daily need for doctors to treat young patients and for children and their parents of being guaranteed the best available treatment (*best care*).

Choosing drug therapy and evidence-based medicine

The Italian legislation through the law number 94/1998 allows the administration of off-label medical products whenever physicians believe that an individual patient cannot be successfully treated with on-label ones "*provided that such use is known and complies with studies appeared in scientific publications internationally accredited*". The law number 244 of 24 December 2007 ("Finanziaria" 2008), at paragraph 348 of the second article, states that in order to prescribe a drug data at least of the second phase of clinical trials must be available.

In this way the physician's discretion [2] is circumscribed in the sense that doctors have to choose an off-label drug on the basis of scientific papers published in accredited journals which support that the proposed therapeutic use is already known and verified even if not definitively recognized by the regulatory authorities. In this way it is possible to mediate between physicians' freedom and care autonomy and the need to ensure that each treatment is always previously scientifically validated.

There is an inevitable time lag between the acquisition of scientific knowledge and the development of regulatory pathways for extension of drug indications. In fact scientific research is self-employed, not necessarily aimed to drug registration and of course in continuous and rapid evolution. A similar asymmetry is observed between production of scientific data and enactment of clinical guidelines [3].

In this scenario the Italian legislation allows the off-label medication ensuring, on the one hand, doctors the ability to set their own treatment decisions based on the best current scientific knowledge and, on the other hand, making it possible for every patient to receive clinical care both validated through scientific criteria applied to a homogeneous generality of cases and especially the most appropriate possible on the basis of each clinic individuality (*tailored therapy*).

In this sense it is possible to contextualize the use of off-label therapy in the broader application context of evidence-based medicine [4] which is a movement, born in the 90s of last century, under the impetus of whom has become essential the use of a method based on literature's systematic reviews and on the indication of recommendation's level [5] in order to support the scientific evidence and to derive the best current scientific one. In the decision-making about the treatment of each patient, current

best evidence must be integrated with individual practitioner's clinical experience, namely the set of skills acquired through the individual training, personal experience and clinical practice. In this way, each time doctors are required to assess the appropriateness and applicability of the available external evidence, even the excellent one, on the specific patient, based on the case's specific clinical features and the weighted evaluation of the risk and benefit ratio of a therapeutic choice.

This is even more evident in a context, namely the neonatology one, where the lack of evidenced-based treatment guidelines and therapeutic drugs with specific labels for age (on-label) is due to the want of studies involving the population below the first month of life. It is clear that the neonatologist experience, considered his "clinical loneliness", takes on a particular importance in the decision-making process leading to the administration of a drug, even more so if this is an off-label one.

Fungal infections in the newborns and regulatory status of antifungal drugs with regard to neonatal therapy

Fungal infections represent an important therapeutic issue in newborns and particularly in preterm infants [6] in relation to their potential morbidity, also due to the possibility of dissemination of the infection to the brain, and their associated mortality. Particularly, they are responsible for 10% of neonatal sepsis after 72 hours from birth, affecting between 0.004% and 1.5% of all newborns admitted to neonatal intensive care units, specifically between 2.6% and 3.1% of very low birth weight and between 5.5% and 10% of extremely low birth weight newborns [7]. *C. albicans* and *C. parapsilosis* are responsible for more than 9 out of 10 cases of fungal infections in preterm infants and the associated mortality rate is estimated to be between 25% and 60% in the different studies [6].

In addition to purely clinical issues, such as the difficulty of early diagnosis, and then of early treatment, due to the poor sensibility (less than 50% [8]) of hemoculture in preterm infants, the complexity of treating children suffering from fungal infections is also linked to the intricate and sometimes unclear regulatory status of antifungal drugs referred to the different pediatric age groups (preterm/full term infants, children). In this regard, we summarize below the actual regulatory status of the antifungal drugs with

an existing or, at less potential, clinical use in neonatology.

Fluconazole (Diflucan®) is commonly used for the prophylactic treatment of *Candida spp.* invasive infections in the newborns. It has poor effects towards *C. glabrata* and *C. krusei*. It is labelled for the use in newborn at term only, as reported in its Summary of Product Characteristics (SPC).

Amphotericin B deoxycholate has indications for the treatment of invasive fungal infections but its clinical use in the newborn is limited by the frequent side effects such as hepatotoxicity, renal impairment and metabolic alkalosis and by the difficulty in establishing the right dosage. It lacks regulation both for the pediatric and the neonatology use. Liposomal amphotericin B (Ambisome®) has the same clinical indications but holds better therapeutic properties and less toxicity than the deoxycholate one. It isn't recommended for use in children below 1 month of age due to lack of data on safety and efficacy while it has clinical indications for the pediatric use although it generally still lacks a clear regulatory guidance [9].

Echinocandins have fungicidal activity towards all species of *Candida spp.* and fungistatic effects towards *Aspergillus spp.* Caspofungin and micafungin are the two drugs belonging to this pharmaceutical class more studied with regard to use in children. Caspofungin (Cancidas®) is authorized for the use in pediatrics but not in neonatology. Its use in children below 12 months of age isn't supported by sufficient safety and efficacy data so its systematic use has to be avoided. Micafungin (Mycamine®) is the only echinocandin which received a marketing authorization by the European Medicine Agency (EMA). It is active, as well as against *Candida spp.* and *Aspergillus spp.*, towards the strains of *C. albicans* and *non-albicans* resistant to fluconazole. It has clinical indications for the treatment of adolescents, children, newborns and preterm newborns. In these latter Mycamine® has shown better efficacy and safety profiles than those shown by liposomal amphotericin B even if in a not statistically significant children sample [10]. However, recommended dosage for the treatment of preterm and term newborns are still variable in the different studies. It has been observed that the pharmacological treatment with micafungin may be associated, even in newborns, with significant hepatic impairment both in healthy volunteers and patients. This information is clearly reported in Mycamine® SPC.

The U.S. and the European current regulatory approaches to the use of off-label drugs in the newborn

Although off-label drug use still represents an important public health issue for preterm and full-term neonates, infants and children [11], in recent years considerable efforts have been made under the auspices of the Food and Drug Administration (FDA) and the EMA to encourage the development of medical products suitable for children, improve the information available on the use of drugs in children and promote research involving children with respect to both basic science and clinical trials [12-13].

In the U.S. the passage of two complementary federal laws, the *Best Pharmaceuticals for Children Act* (BPCA; even with the help of the Pediatric Trials Network, PTN) [14] and of the *Pediatric Research Equity Act* (PREA) [15], has resulted in more than 500 labeling changes in favor of children consisting both in approval of new drugs with pediatric indications and expanded labeling through pharmacokinetic/pharmacodynamic and safety data that inform the drug use in the pediatric age.

Particularly, the PREA has made mandatory that almost all new drugs and several already approved ones must be studied in children if there exists a potential clinical use for childhood; therefore the inclusion of children in the trials is required for the approval of the drug by the FDA.

The BPCA allows pharmaceutical sponsors to keep an additional period of six months of market exclusivity for completed pediatric studies presented to the FDA. Moreover the BPCA enables collaboration between the National Institutes of Health – acting through the National Institute of Child Health and Human Development – the FDA and the clinical physicians in order to assign priority for testing of specific drugs in children.

This strong regulatory attitude towards the need of an *ad hoc* pediatric experimentation isn't surprising, even if in the American scenario the administration of an approved drug for a use that is not acknowledged by the FDA doesn't require special additional consent or review [16] if the off-label use is based on well-known medical evidence – therefore not considered experimental – and is supposed to be done in patient's best interest.

The federal legislation discussed above, aimed to increase drug testing in children and newborn, represents only a first step to make possible reaching age-appropriate evidence sufficient for

labeling of all drugs used to treat children and to offer pediatrics the best tools for their clinical decision-making. In fact nowadays in the U.S. less than 50% [17] of products are on-label for pediatric therapy and drug companies are still reluctant to include children in their trials. This concern is particularly noticeable for neonatal studies and child-friendly formulations [18].

In the European context the pediatric studies initiative hasn't been taken by national government agencies but by the Paediatric Committee (PDCO) established within the EMA in 2007 by the European Union's Pediatric Regulation. The central instruments of regulation are the Pediatric Investigation Plans (PIPs). A PIP is “*a development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorization of a medicine for children*” [19]. Therefore, PIP's main purpose is to obtain relevant data through clinical trials without subjecting children to not essential studies in order to support marketing authorization. Pharmaceutical companies submit proposals for PIPs to the PDCO that is responsible for determining the studies that companies must carry out on children as part of PIPs and then for agreeing or refusing the plan.

PIPs comprise descriptions of trials performed to ensure medicine's quality, safety and efficacy and of the measures implemented to make formulations suitable for children (for example the use of liquid formulation instead of tablets); they care to ensure that the needs of all age groups, from birth to adolescence, are covered; they decide the timing of studies in children compared to adults. The development plan can be modified during work in progress on the basis of knowledge evolution, possible implementation difficulties, matter of appropriateness and deferred until after studies in adults have been concluded, to ensure the safety and ethicality of research.

Furthermore, the PDCO identifies the “class waivers”, namely the circumstances in which the requirement to submit a PIP should be rejected, summarized as follows: a specific medicinal products or a class of drugs are likely to be ineffective or unsafe in part or all of the pediatric population; a drug has clinical indications for diseases that only affect the adulthood; the medicinal product does not represent a significant therapeutic benefit over existing treatments for children.

Although it has already been several years since the PIPs' establishment, a recent Danish study [13] shows that in Denmark PIPs still only cover a small

proportion of off-label drugs used for neonates and children therapy. Particularly, it was found that 13 (including amphotericin B) of the 100 most common drugs are used off-label and only 4 of them have a PIP. Moreover, among the three most used off-label drugs only one has a PIP.

With regard to antifungal off-label therapy the Danish study shows that only for one indication, the invasive *Aspergillosis*, the Posaconazole's PIP, agreed to be completed in 2018, covers the entire population from 0 to 18 years, including preterm and newborn; for other invasive fungal infections Posaconazole's PIP has been implemented only for infants, children and adolescents while it has been waived for preterm and newborn according to the supposed absence of a benefit over existing treatment. Voriconazole is the only antifungal product with already approved pediatric indications (invasive *Aspergillosis*, infections with *Scedosporium spp./Fusarium spp.*, fluconazole resistance and prevention of Candidaemia) having a PIP, agreed to be completed in 2017.

At last neonates have been generally included just in one-third of PIPs while according to EMA only one-quarter of PIPs concerns neonates [20]. When consulting the EMA website searching for the proposed and approved PIPs, data show that in the last years the number of pediatric trials that are part of an agreed PIP and the proportion of pediatric trials among all trials have increased [21].

In particular, at the end of 2011, based on the data contained in the EMA 5-years report to the European Commission, it has been observed a general increase in the number (360 in 2011 versus 253 in 2005) and the proportion of pediatric trials. Particularly, PIPs have been completed for 29 active substances, 13 new medicines have been authorized, 30 new indications and 9 new pharmaceutical children formulations have been developed linked to PIPs, rewards have been obtained for 12 medicines (supplementary protection certificate extensions for 11 medicines; 1 paediatric-use marketing authorisation exclusivity). With regard to antifungal drugs in 2008 micafungin (Mycamine®) obtained a marketing authorization including pediatric and neonatal indication. In 2008 fluconazole was included, even if without a specific PIP, in the Treat Infections in Neonates (TINN) study (funded off patent medicine project), aimed to evaluate its PK and PD features in neonates and now has indication in the newborn. Caspofungin (Cancidas®) benefited from the 6-months extension of the protection certificate and in 2008 was authorized for use in children but not in newborn.

Liposomal amphotericin B still lacks a clear regulatory guidance and neonatal indication.

When comparing the broader European and U.S. contexts with the specific Italian one, it's evident that in the latter, although there has been an overall positive response to the European proposal, there still exist certain difficulties in adapting the general approach in the study and use of off-label drugs in the newborn to the new European directories. In fact, when considering data about trials funded by the "Agenzia Italiana del Farmaco" (AIFA) [22] in the period 2005-2007, it emerges that out of a total of 151 trials only 19 specifically involve children (3 of whom are dedicated to newborns). The latter data seems small, as an absolute value, when compared to the whole number of 919 pediatric trials implemented in the European Union in the same time period. But they encompass only the protocols granted by the AIFA and not receiving any funding from Pharmaceutical Sponsors.

Lastly, Italy has a legislative peculiarity, namely the constriction to comply with the anachronistic regulatory limits imposed by the law number 94/1998, based on which the prescription of off-label drugs must represent only an outstanding and no systematic occurrence. This normative approach might be considered acceptable only with respect to adult therapy being rather inadequate to the children's therapeutic needs, to the worldwide scenario and to EMA's current efforts and directives.

Off-label administration to the newborn in clinical practice: the therapeutic alliance between doctor and parents

The absence of license for any off-label drug does not necessarily indicate the lack of scientific evidence in relation to a particular therapeutic intervention [23, 24]. This is even more true in neonatology, where the majority of drugs is off-label due not to indication fault with respect to a disease (drug approved for the treatment of pathologies different from that under consideration) but to the lack of a specific instruction for the neonatal age.

The absence of labeling for a specific age group or for a specific disorder does not necessarily mean that the drug's use is improper for that age or disease [11], rather it just means that the available evidence, specially for drug efficacy and safety, is still insufficient from a regulatory point of view for the EMA and the FDA approval as on-label. Furthermore, the lack of labeling does not mean that the clinical use of an off-label drug is unsupported by

clinical experience and data in children. In particular, papers in peer-reviewed journals, policy statements and databases help pediatrics to assess the quality of evidence and guide clinical practice. Then the data contained in several sources, after being compared with clinical experience, are commonly used to create practice therapy guidelines and handbooks, continuously updated on the basis of the evolution of scientific evidences, as for example the Italian *Neonatology care pathways (Percorsi Assistenziali Neonatologici)* [25].

Thus, the fact that a drug is classified as off-label only represents a regulatory framework [26, 27] and it doesn't have an *a priori* negative implication on prescribing and therefore on its clinical use. In fact it was estimated that 78.9% [11] of children discharged from a pediatric hospital was treated at least with one off-label pharmaceutical therapy. Data from a pilot study [28] aimed at analyzing drugs prescribed during a 1-month period among a group of newborns admitted to the Neonatal Intensive Care Unit and Neonatal Pathology of Cagliari University Hospital showed that 38 out of 79 newborn infants admitted received a pharmacotherapy and a total of 88 treatments were given: 41 (47%) followed the terms of the product license while 47 (53%) were used in an off-label manner. Then 1 out of 2 newborns received an off-label drug, without differences between term and preterm infants.

But when does it seem licit and appropriate to include an off-label drug for the treatment of an infant affected by a fungal infection? In the absence of a valid on-label alternative and when the off-label therapy should be preferred to on-label one in the treatment of a single patient:

1. when the off-label therapy is supported by a high degree of documented scientific evidence, greater than the on-label therapy regarding the effectiveness on a specific pathology (the type of fungal infection based on the results of a bacterial culture);
2. when the off-label product has the same effectiveness compared with standard therapy but it is safer than the on-label one for the individual patient in relation to his clinical situation (possible presence of comorbidities).

The implementation of the decision to administer an off-label drug in clinical practice should be made as continuous concretization of a recursive evaluation decision-making process that constantly make justifiable/justified the appropriateness of the treatment choice in order

to reassure the young patient and his/her parents that are in a position of undoubted disadvantage compared to physician [29].

The stages of this process can be summarized as follows:

1. information given to parents about the therapeutic options, the existence of on-label and off-label medications, the risks and benefits of both therapies with respect to the specific pathology and patient neonatal age;
2. parents consent;
3. prompt monitoring of the clinical course, documentation of any adverse reactions and of the reasons of choosing to eventually change the treatment plan.

What has just been proposed is the same process that must also characterize the administration of on-label therapies. In this way both medical freedom and care autonomy and the right of parents to be adequately informed, in order to be consciously made partakers of the meaning of the pharmacological proposal and therapeutic project, are respected [30].

Physician's professional responsibility: what are the differences between on-label and off-label therapy?

As micafungin has become a licensed drug for the prophylactic and therapeutic treatment of systemic candidiasis in the newborn, doctors who decide hereafter to treat patients with a off-label drug may be called upon to respond to professional liability in case of damage due to an adverse reaction, lacking in this case the regulatory endorsement that *a priori* makes lawful drug therapy.

In the Italian Criminal Trial it is has been clearly stated by the Supreme Court the principle that to condemn a physician it is necessary to prove "beyond any reasonable doubt" (i.e. with high degree of logical certainty) that in that specific case the adverse event would have been foreseeable and preventable, and therefore avoidable, by the use of an alternative therapeutic choice, namely the administration of the on-label drug.

In the case of a young patient affected by a systemic candidiasis whose outcome is represented by the death or by a permanent impairment related to the infection, it should be demonstrated, with a criteria of high rate of probability, that the administration of micafungin instead of the off-label drug might be able to determine a different and better clinical outcome.

Several medical-legal considerations must be made with respect to the civil scenario in which physician's liability is always regarded as contractual. In this sense a presumption of liability exists towards the health professional and the burden of proof is reversed against him (compared to the non-contractual liability). Little patient's parents will have only to prove the existence of the contract (the relation of care) and the supposed "greater harm". On the contrary, the doctor will be called upon to document, based on the theory of "closeness to the evidence", that his clinical conduct was based on expertise's criteria in choosing the drug on the basis of the best available scientific evidence, prudence in carefully weighting the risks and benefits ratio of off-label therapy compared with on-label one in the context of the specific clinical condition and diligence in having promptly monitored the newborn's therapeutic and clinical response.

With respect to the assessment of the causal link, the conditionalistic civil criterion of the "more likely than not" is significantly less stringent than that applied in criminal matters. In fact, on its basis it is sufficient to reach the probability threshold of 50% that the medical conduct is in causative link with the harmful event in order to recognize the physician's responsibility. This is on patient's behalf, in fact it will be easier for him to obtain recognition of the suffered damage and therefore the compensation. However, the only increased risk of adverse reaction/non-healing cannot be deemed sufficient for demonstrating material causation between the administration of the drug off-label and the supposed major damage: what is to be found in every case examined, through the discussion of the classical criteria of individual causality, is the actual realization of the risk or at least the actual exposure to a risk assessed as significant.

Lastly, at least in general and from a theoretical point of view, practitioners could be held liable for treasury damage [6]. This possibility is governed by the law number 425/1996 and the settle case-law of the Italian Council of State and of the "Corte dei Conti". In fact, except for drugs delivered under the so-called compassionate use framework, the off-label prescribing has not to be guaranteed free of charge by the National Health System to the patient. Particularly, in the hospital setting the Director of a complex structure is identified as responsible for treasury damage if he/she planned protocols that provide for the systematic and widespread use of off-label drugs. The same responsibility involves

the hospital practitioners using off-label therapies in widespread and systematic manner and without having informed the manager of the complex structure.

Furthermore, the law number 648/1996 allows, in the absence of a viable therapeutic drug alternative, the free of charge deliverability, namely borne by the National Health System, of "Innovative Medicines" included in a special list drawn up and regularly updated by the AIFA Commission. The inclusion in the list is possible for drugs authorized for marketing in other states but not nationwide, medicinal products not yet authorized but ongoing clinical trial and medicines used for therapeutic indications other than the authorized ones.

The recent Italian law number 79/2014 allows the inclusion in the list above mentioned of off-label drugs also in the presence of a viable therapeutic drug alternative as part of authorized medicinal products, namely the on-label ones, resulting in free of charge drug deliverability. This is only possible – after AIFA evaluation and within the parameters of cost-effectiveness and appropriateness – for therapeutic indications supported by researches conducted nationally and internationally within the scientific community. The AIFA is responsible for the safety monitoring of the drugs included in that list. On the basis of this law, the treasury damage should only be contemplated for the systematic administration of off-label products not included in the AIFA list and for an off-label drug administration occurred outside of the specific indications contained in the same list.

Indeed, in clinical practice sometimes physicians are forced by stringent regulations to prescribe a more expensive on-label drug [31] even for the treatment of a single patient. This can happen in cases where there exists a medicinal recognized as bioequivalent to the brand-name one and obviously cheaper than the reference drug, namely a generic product which has the same approved therapeutic indications but has not been approved for use in a specific clinical indication or in all age group on the basis of what is reported in the SPC.

As previously discussed, differently from what happens in the wider and more permissive European context, using a generic medicinal product beyond the strictly clinical indications contained in the SPC still doesn't comply with the Italian regulations of off-label use, even if the use only consists in an extension of the age limits. This kind of off-label use, while not tolerated in the Italian framework, leads to certain economic advantages.

In this sense the treasury damage related to the use of off-label drugs, although contemplated by the Italian legislation, seems to be less applicable in practice, remaining mostly just an abstract occurrence.

Specific considerations must be made as regards to the use in the newborn of drug molecules belonging to different pharmacological classes but with overlapping clinical indications with respect to antifungal therapy, as the off-label liposomal amphotericin B compared to the on-label micafungin. Using Ambisome® instead of Mycamine® – with a 10-fold increased prize – in the treatment of fungal infection in the newborn, if not justified by actual clinical needs, may lead the prescriber to be responsible for treasury damage.

Conclusion

The recent available data on the European and American reality show that in recent years important regulatory steps have been made, on behalf of the FDA and the EMA, to promote the involvement of the children population in scientific research and then to make drugs use increasingly supported by shared efficacy and safety data also in pediatrics. Despite this effort children and, even more, newborns are still considerable as “orphans” with respect to drug therapy and are often treated with off-label administrations.

In order to guarantee the best therapeutic choice to all the ill children, a well-balanced approach to the pharmacological therapy is mandatory.

It is necessary to preserve the physicians freedom to cure – in accordance with parental choice – but this attitude cannot become the prescribing rule.

An external regulatory control is needed in the drugs experimental field in order to avoid, on one hand, useless and potentially harmful trials and, on the other, to demand an in-depth analysis of the risk/benefit ratio of each new principle proposed for human use.

The efforts put on the ground by the FDA and the EMA are clearly identifying a regulatory pathway aimed to let the number of drugs for the pediatric population growing, so to offer to all the physicians the best therapeutic tools to protect their little patients' health and meanwhile to guarantee them the same security and efficacy levels granted to the adult population.

This approach is time-consuming and is going to give its results in a next future, being only

applicable to all the new principles actually under studies, to those which will take the place of the drugs whose license is going to expire and to those actually employed as off-label.

Meanwhile, physicians may – or to better say has – to use the best available therapeutic option, being it either on-label or off-label, assuming “in science and integrity” the responsibility descending by their pharmacological choice.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Kearns GL, Abdel-Rahman SM, Alander SW, Bloway DL, Leeder JS, Kauffman RE. Developmental pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-67.
2. Massimino F. La prescrizione dei farmaci «off label»: adempimenti, obblighi e responsabilità del medico. *Danno e responsabilità.* 2003;(10):925-37.
3. d'Aloja E, Ciuffi M, De Giorgio F, Demontis R, Paribello F. Il valore medico-legale e giuridico delle linee guida, dei protocolli e delle procedure in tema di responsabilità del professionista della salute: “alleati o nemici (friends or foes)”?. In: Aleo S, De Matteis R, Vecchio G (Eds.). *Le responsabilità in ambito sanitario.* Padua: Cedam, 2014.
4. Sackett DL, Rosenberg WMC, Muir Gray JA, Brian Haynes R, Scott Richardson W. Evidence-based medicine: what it is and what it isn't. *Br Med J.* 1996;312:71.
5. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing guidelines. *Br Med J.* 1999;318:593.
6. Fanos V, Dessì A, Fresa R. Aspetti clinici e giuridici della gestione del neonato con infezioni fungine invasive. *J Pediatr Neonat Individual Med.* 2012;1(1):IT1-12.
7. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of Candida bloodstream infections among NICU patients in the United States: 1995-2004. *Pediatrics.* 2006;117(5):1680-7.
8. Manzoni P, Maestri A, Leonessa M, Mostert M, Farina D, Gomirato G. Fungal and bacterial sepsis and threshold ROP in preterm very low birth weight neonates. *J Perinatol.* 2006;26(1):23-30.
9. Gaspani S, Milani B. Access to liposomal generic formulations: beyond AmBisome and Doxil/Caelyx. *GaBi J.* 2013;2(2):60-2.
10. Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, Chotpitayasunondh T, Konja J, Diekmann-Berndt H, Koblinger S, Groll AH, Arrieta A. Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. *Pediatr Infect Dis J.* 2008;27(9):820-6.

11. Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason C Jr, Hyman D, Jenkins K, White ML, Levy FH, Levin JE, Bertoch D, Slonim AD. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med.* 2007;161(3):282-90. Erratum in *Arch Pediatr Adolesc Med.* 2007;161(7):655.
12. American Academy of Pediatrics. Off-label use of drugs in children. *Pediatrics.* 2014;133:3.
13. Haslund-Krog S, Mathiasen R, Rolighed Christensen H, Holst H. The impact of legislation on drug substances used off-label in paediatric wards-a national study. *Eur J Clin Pharmacol.* 2014;70:445-52.
14. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109 (2002).
15. Pediatric Research Equity Act, Pub. L. No. 108-155 (2003).
16. US Food and Drug Administration. "Off-label" and investigational use of marketed drugs, biologics, and medical devices: information sheet. Available at: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>, last access: January 2014.
17. Sachs AN, Avant D, Lee CS, Rodriguez W, Murphy MD. Pediatric information in drug product labeling. *JAMA.* 2012;307(18):1914-5.
18. Milne CP, Davis J. The pediatric studies initiative: after 15 years have we reached the limits of the law? *Clin Ther.* 2014;36(2):156-162.
19. European Medicines Agency. Paediatric investigation plans, waivers and modifications. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp, last access: June 2014.
20. European Medicines Agency. Successes of the Paediatric Regulation after 5 years. August 2007-December 2012. EMA/250577/2013. Date of publication: 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500143984.pdf, last access: June 2013.
21. European Medicines Agency. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012. Date of publication: 8 July 2012. Available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf, last access: June 2014.
22. <http://www.agenziafarmaco.gov.it/>, last access: June 2014.
23. Royal College of Psychiatrists. Use of licensed medicines for unlicensed applications in psychiatric practice. College Report CR142. Date of publication: January 2007. Available at: <http://www.rcpsych.ac.uk/files/pdfversion/cr142.pdf>, last access: June 2014.
24. Dresser R, Frader J. Off-label prescribing: a call for heightened professional and government oversight. *J Law Med Ethics.* 2009;37(3):476-86, 396.
25. Romagnoli C. Percorsi assistenziali neonatologici. Milan: BioMedia, 2013.
26. Meadows WA, Hollowell BD. 'Off-label' drug use: an FDA regulatory term, not a negative implication of its medical use. *International Journal of Impotence Research.* 2008;20:135-144.
27. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc.* 2012;87(10):982-90.
28. Dessì A, Salemi C, Fanos V, Cuzzolin L. Drug treatments in a neonatal setting: focus on the off-label use in the first month of life. *Pharm World Sci.* 2010;32:120-4.
29. d'Aloja E, Paribello F, Demontis R, Muller M. Off-label drugs prescription in neonatology: a physician's duty or a medical hazardous attitude? *J Matern fetal Neonat Med.* 2011;1:99-100.
30. d'Aloja E, Floris L, Muller M, Birocchi F, Fanos V, Paribello F, Demontis R. Shared decision-making in neonatology: an utopia or an attainable goal? *J Matern Fetal Neonatal Med.* 2010;3: 56-8.
31. Zajdel J, Zajdel R. Brand-name drug, generic drug, orphan drug. Pharmacological therapy with biosimilar drugs – provision of due diligence in the treatment process. *Contemp Oncol (Pozn).* 2013;17(6):477-83.