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## ***THE DEBATE CONCERNING THE OFF-LABEL PRESCRIPTIONS OF DRUGS: A COMPARISON BETWEEN ITALIAN AND U.S. LAW***

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# THE DEBATE CONCERNING THE OFF-LABEL PRESCRIPTIONS OF DRUGS: A COMPARISON BETWEEN ITALIAN AND U.S. LAW

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## **Abstract:**

So-called off-label drug prescription is the administration of a registered medicine or medical device that is not included nor disclaimed in the product information.

In this paper we deepen the questions arising from the above-mentioned medical practice from a legal and medico legal point of view, illustrating what is meant by off-label prescription and the reasons for the growth of this phenomenon, as well as the procedure for authorising drugs and for administer off label treatments in Italian and American law.

Finally, we try to summarise short conclusive reflections about the differences between the two above mentioned legal systems, as well as about the unavoidable role of off label prescriptions in current medical practice, concluding that, under a seeming paradox, scientific uncertainty will lead to an increase of off label uses.

*Key words:* off-label drug prescription; scientific uncertainty; professional autonomy; medical liability.

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## Introduction

So-called off-label drug prescription is the administration of a registered medicine or medical device<sup>1</sup> that is not included nor disclaimed in the product information: different to consumption indications, patient age range or dose instructions that is approved by regulatory authorities<sup>2</sup>.

This topic is, among several, particularly debated in the field of sports law, where it is interlaced with doping phenomenon<sup>3</sup>.

Off-label prescribing is strictly connected with the doctors' professional autonomy concerning the choice of therapy for a patient, if more than one is considered suitable<sup>4</sup>.

The present paper intends to deepen the questions arising from the above-mentioned medical practice, which, to the best of our knowledge, are common both in Europe and in North America<sup>5</sup>.

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<sup>1</sup> Even though, as recalled by B. Patsner, *Symposium: Pharmaceutical Innovation: Law & the Public's Health: Riegel v. Medtronic, Inc.: Revisiting Pre-emption for Medical Devices*, 37 *J.L. Med. & Ethics* (2009) 305, 314, "off-label use of medical devices may be relatively uncommon because of the relative specific nature of the surgical situation (e.g., cardiac pacemaker) for which a medical device is designed or could reasonably be used for (...)".

<sup>2</sup> See D.M. Fritch, *Speak No Evil, Hear No Evil, Harm The Patient? Why The Fda Needs To Seek More, Rather Than Less, Speech From Drug Manufacturers On Off-Label Drug Treatments*, 9 *Mich. St. J. Med. & Law* (2005) 315, 331 and E. Polubinski III, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, 83 *Va. L. Rev.* (1997) 991, 997. Indeed, according to R.F. Hall, E.S. Sobotka, *Inconsistent Government Policies: Why Fda Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 *Food Drug L.J.* (2007) 1, 4, regulatory authorities approve "a specific use, or «indication», for the product, not the product in general" (referring to FDA, but this consideration may be applied to Italian authorities too). In the Italian literature, see A. Fiori, *Medicina legale della responsabilità medica*, Giuffrè, Milano, 1999, 83 ff.

<sup>3</sup> For an outline of the Italian law on this matter, please refer, among several, to C.F. Grosso, *Irrelevanza penale della somministrazione off label di medicinali non vietati*, in *Giurisprudenza italiana*, 2006, 1720 ff. and E.M. Giarda, *Somministrazione di farmaci e di sostanze medicinali in modalità off-label ed ambito di operatività dell'art. 445 c.p.*, in *Corriere del merito*, 2006, 1443 ff. We must recall that, according to Art. 445 of the criminal code, the administration of off label medicines in a dangerous way for public health is a crime punished with imprisonment of between six months and two years and with a fine of between € 103 and € 1032. Furthermore, if this conduct is aimed to reach better sports performances, according to the Law of the 13<sup>th</sup> December 1989, no. 401 and to the Law of the 14<sup>th</sup> February 2000, no. 376, it constitutes a different and adjunctive crime ("sport fraud"). In this regard, we can recall a decision (Cassazione penale 29<sup>th</sup> March 2007, no. 21324, in *CED Cassazione*, 2007), that lead to much media attention, which analysed the case of some members of the staff of the famous Italian football team "Juventus" that administered off label medicinal products to some football players in order to enhance their performance. In this decision the Court stated that such conduct constituted a crime, although the same Court, due to limitation period, did not declare the criminal liability of the accused people.

<sup>4</sup> See, among several, G. Iadecola, *Prescrizione di farmaci "off label" e responsabilità penale del medico*, in *Diritto penale e processo*, 2006, 1125 and M. Zana, *Ai limiti della responsabilità medica: l'uso off label dei farmaci*, in *Liber amicorum per Francesco Donato Busnelli. Il diritto civile tra principi e regole*, Giuffrè, Milano, 2008, 729.

<sup>5</sup> In the American scholarship, where one can find much deeper analysis of the problem as opposed to Italian scholarship, see, among others, S. Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 *Penn. St. L. Rev.* (2005) 41; R.F. Hall, E.S. Sobotka, *Inconsistent Government Policies: Why Fda Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, quoted, 1; S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 *Fla. L. Rev.* (1999) 181; R.C. Ausness, "There's Danger Here, Cberie!" *Liability For the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, 73 *Brooklyn L. Rev.* (2008) 1253; R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 *J.L. Med. & Ethics* (2009) 476; M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 *Hastings L.J.* (2007) 967; D.B. Klein, A. Tabarrok, *Who Certifies Off Label?, Regulation* (2004), 60.

Yet, off label prescription is an instrument to guarantee the progress of scientific evolution, interlacing itself with the professional autonomy of a doctor: on the other hand, it is simultaneously associated with important clinical, legal, and ethical issues.

For instance, as we will see, a critique of off label prescribing recalls that the off label uses of drugs have not been analysed through the same randomized and theoretically exhaustive clinical trials as on label uses have. Thus, an off label prescription can produce serious risks for patients, who can be deprived of efficient therapeutic instruments for being cured with therapies, of which the effectiveness has still not been (or at least not fully) demonstrated<sup>6</sup>.

In the worst hypothesis, a patient might be also damaged by an off label prescription<sup>7</sup>.

We chose to analyse both legal and medico legal aspects of this topic, since we believe that only by combining these two fields, we might pursue a full comprehension of the problems posed by off label prescription. As an example, in order to verify whether a doctor is liable or not for having prescribed a “non-conventional” therapy, we must consider whether the therapies normally used in that sector are efficient and in which measure. Furthermore, since in some medical sectors (for instance, as we will see, in Paediatrics) off label prescription is very common, it is quite evident that the verification of the alleged negligence of a doctor in deciding such practices will be influenced by the usual treatments practiced in his/her field.

The analysis of the medico legal aspects, therefore, allows us to have a more complete knowledge of the reasons why off label prescriptions are nowadays so common, of possible alternatives, and of the consequences in case of damage caused by it to a patient.

Finally, we will study our topic in a comparative perspective, by analysing the state of the art of legal and medico legal aspects of the off label prescription in Italy and in the United States, where there exists a large body of case law and scholarship on the matter.

We shall follow this schedule. We will start by analysing the evolution of Italian case law regarding the doctors’ professional autonomy concerning the choice of the therapy, by showing that the rigorous approach, which has been characterising medical liability for several decades, is nowadays fully adhered to in this area (par. 2).

Following this, in paragraph three, we will illustrate what is meant by off-label prescription and the reasons for the growth of this growing phenomenon.

In paragraph four, we will study the procedure for authorising drugs in Italian and European law.

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<sup>6</sup> See J. Rogers, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, 76 *Geo. Wash. L. Rev.* (2008) 1429, 1433.

<sup>7</sup> See R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476; M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 969.

Subsequently, we will summarise the so called “Di Bella case”, a very famous Italian case, leading to much interest in the international debate, revolving around the development of a new powerful treatment for most cancers, which influenced the Italian pharmaceutical regime (par. 5).

This will lead us (in par. 6) to an analysis of the rules applicable and the conditions imposed to make off-label prescriptions in Italy, as well as the procedure (par. 7).

In paragraphs eight and nine, finally, we will deepen the important questions concerning the informed consent of a patient and of the liability arising from the damages which may be provoked by the treatment.

After that, we will examine the American experience of off label use and prescription, firstly by analysing, in paragraph 10, the approval process of a new drug and, immediately after, by studying the requisites imposed by American law to off label use and prescription (par. 11).

Paragraph 12 will deepen the role played by the patients’ informed consent in the off label prescription and the doctors’ liability for off label prescription in the USA.

Considering this, in paragraph 13, we will mention the problem of off label marketing, which still captures great attention in American scholarship and case law.

Finally, in paragraph 14, we will try to summarise short conclusive reflections about the unavoidable role of off label prescriptions in current medical practice: to our mind, under a seeming paradox, scientific uncertainty will lead to an increase of off label uses.

## **1. Doctors’ professional autonomy in Italy**

In Italy, for a long time the prevailing case law has given professionals a remarkable autonomy in the choice of the treatment to be practiced, both in case of diagnosis and in therapy.

On one side, this corresponded to the therapeutic freedom, traditionally bestowed on doctors; on the other, this trend recognised the significant difficulties that judges would have met in evaluating the therapeutic choices made by physicians, above all in cases where in theory more than one therapy would be available, all of which considered as valid by the scientific community.

Following the principle which has been synthesised above, Italian case law stated that the application of a determined school of medical thought or indeed the choice to neglect it did not constitute fault on the part of the doctor, especially when other authors and statistical data defend the validity and the goodness of the employment of both methods<sup>8</sup>. Holding a doctor liable for the choice of a therapy, in fact, according to this opinion, would produce an abnormal widening of the sphere of responsibility, in contrast, also, with very precise requirements of logic.

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<sup>8</sup> See Cassazione civile, 13<sup>th</sup> October 1972, no. 3044, in *Foro italiano*, 1973, I, 1176. In the scholarship see also M. Bilancetti, *La responsabilità penale e civile del medico*, 6<sup>th</sup> ed., Cedam, Padova, 2006, 737 ff. and, for a medico legal approach, A. Fiori, *Medicina legale della responsabilità medica*, quoted, 429 ff.

As a consequence, as stated, a doctor should always prescribe the treatment, which, according to him/her, is more efficient for a particular patient<sup>9</sup>.

Yet, a doctor practicing in fear of liability based on the fact that certain risks are inherent due to imperfections and unavoidable uncertainties in science and in medical practice, would end up practicing so called defensive medicine<sup>10</sup>, which could give rise to serious damage above all for the patient.

It is clear, on the other hand, that, given the primary importance of the juridical goods in play, *i.e.* the life and health of a patient, some limits must be put in place in order to avoid a possible arbitrary use of this freedom. Thus, the above-mentioned decision states also that the overcoming of those rules that, for the common consent of the scientific community and for consolidated experimentation can be considered acquired to science and to medical common practice, is prohibited. This way, such rules constitute the necessary, cultural and experimental, equipment of the professional who dedicates himself/herself to a particular field of medicine<sup>11</sup>.

According to this, so to speak, “bifurcation”, a doctor can practice experimental therapies only in the field of medical experimentation, by observing the rules and the limits provided for the latter.

More recently, however, the prevailing case law tendencies have defined the ascertainment of medical liability through an inversion of well-established rules.

Actually, in order to ease the proof of medical malpractice by patients, the concept of medical fault has been widened<sup>12</sup>. Furthermore, Italian decisions, both civil and criminal, in the last decades had favoured an approach through the use of a simple statistical probability in the ascertainment of individual causation<sup>13</sup>.

Following the above-mentioned trends, there seems to be an important change also in this field, beginning with a decision of the Italian Supreme Court (*Corte di Cassazione*)<sup>14</sup> that has asserted the responsibility of a doctor for opting for a treatment, which later revealed itself ineffective.

We must also stress that the above mentioned decision involved a case where there was an emergency clinical situation, but the difficulty of it was not taken into account by the judges to exclude the liability.

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<sup>9</sup> See P. Minghetti, I. Palmieri, F. Selmin, *La terapia farmacologica in assenza di medicinali registrati per la patologia diagnosticata*, in *Rivista italiana di medicina legale*, 2007, 994.

<sup>10</sup> On this please refer to G. Calabresi, *Funzione e struttura dei sistemi di responsabilità medica*, in F.D. Busnelli, G. Scalfi (eds.), *La responsabilità medica*, Giuffrè, Milano, 1982, 61 and, in the common law scholarship, M.A. Jones, *Medical Malpractice in England and Wales – A Postcard from the Edge*, 3 *Eur.J. Health Law*, (1996) 109, 117 ff., who stresses that “the term «defensive medicine» is used in a pejorative sense, to indicate that the risk of liability induces doctors to adopt practices which are not medically required or justified”.

<sup>11</sup> See Cassazione civile, 13<sup>th</sup> October 1972, no. 3044, quoted.

<sup>12</sup> See G. Comandé, G. Turchetti (eds.), *La responsabilità sanitaria. Valutazione del rischio e assicurazione*, Cedam, Padova, 2004 and, more recently, R. De Matteis, *Responsabilità e servizi sanitari. Modelli e funzioni*, Cedam, Padova, 2007.

<sup>13</sup> See, lastly, B. Tassone, *La ripartizione di responsabilità nell'illecito civile. Analisi giuristica e comparata*, E.S.I., Napoli, 2007, 237 ff.

<sup>14</sup> See Cassazione 29<sup>th</sup> March 2001, no. 4609, in *Danno e responsabilità*, 2001, 828 ff. commented on by F. Agnino, *Interventi d'urgenza ad alto rischio e responsabilità del medico*. More recently, in the same sense, see also Tribunale di Lecce 7<sup>th</sup> February 2007, in *Giurisprudenza di merito*, 2008, 188.

The widening of responsibility, which derives from the above-mentioned tendency, introduced serious margins of risk for doctors, in consideration of the fact that the practiced treatment had been chosen by a physician since the other possible ones had an uncertain outcome as well.

Consequently, it would be difficult to define the medical conduct as negligent.

Therefore, this decision infringes the consolidated rule according to which, in such hypothesis, liability of the doctor could only be established only if the treatment increased the risk for a patient.

At the same time, we must recall that, in other decisions, the same Italian Supreme Court stated, partially contrarily with what had been said before, that the autonomy of a physician in therapeutic decisions derives from the absence in medicine of scientific protocols based on mathematic certainties. Therefore, the treatment to be practiced is to be chosen carefully in consideration of the substantial number of variants, related to the specific case, which only the contingency of medical therapy, can appreciate.

As it has been stated, “*this concept of freedom in the choice of medical treatment is a value that cannot be compressed or lost at any level for any reason (...). Obviously, the choice made by a doctor cannot be founded on mere personal experiences, being a duty, however, to adhere to the complex experience that is the compendium of the practice in the field*”<sup>15</sup>.

In connection with what has been above described, it is opportune to dedicate some reflections to the responsibility for drug prescription in general.

In these cases, a professional can be convicted only if his/her imprudent or negligent conduct, as well as the causal nexus between the damage and the administration of medicine, can be established.

Thus, it is necessary to verify whether a doctor conducted the preliminary diagnosis in a correct way, conscious of identifying possible contraindications and/or the necessity of particular cautions. The lack of anamnesis pacifically gives rise, in fact, to the responsibility of a physician<sup>16</sup>.

A doctor, moreover, in such a case will not be able to request the application of Art. 2236 of the Civil Code, in virtue of which the responsibility of a professional is limited to malice and gross negligence in cases in which his/her performance implies the overcoming of technical problems of particular difficulty, not being a case of “special difficulty”.

The Court of Cassation has been clear on the point, stating that a doctor, except in cases of extraordinary emergency, before prescribing a drug to his/her patient, must assess whether there is any incompatibility to the assumption<sup>17</sup>.

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<sup>15</sup> Cassazione 8<sup>th</sup> February 2001, no. 2865, in *Diritto penale e processo*, 2002, 459.

<sup>16</sup> See, among several, F. Montagna, L. Daleffe, *I farmaci*, in F. Montagna, D. De Leo, P.O. Carli, *La responsabilità nella professione odontoiatrica*, Cedam, Padova, 1998, 403 ff. In the case law, please see Cassazione penale 29<sup>th</sup> July 2005, no. 28549, in [www.leggiditalia.it](http://www.leggiditalia.it).

<sup>17</sup> Cassazione 24<sup>th</sup> June 1983, no. 9817, in *Cassazione penale*, 1984, 307.

Another case from which the doctors' liability surely derives is the wrong indication of the drug consumption modalities, albeit outside the scope of medical autonomy, as well as the cases of omitted indications and instructions of correct consumption and wrong administration.

Finally, an ulterior hypothesis of responsibility results from a lack of surveillance of the patient, above all in cases where the practiced therapy has risks for the patient himself/herself<sup>18</sup>.

As it has been stated, “*after the choice of a therapy, a physician must observe any possible changing circumstances in order to intervene immediately should it become apparent that specific symptoms incline to deem inappropriate the treatment chosen*”<sup>19</sup>.

On the point, scholarship and case law adopt an almost unanimous guideline in concluding that the obligation of a doctor extends to some additional duties.

In fact, there appears to be a consolidated trend according to which the professional performance of a surgeon is not limited to the fulfilment of the pure and simple operating action, but comprises a series of operating treatments both prior to and following the treatment itself, comprising of a complex web of cures and remedies which a patient must be subjected to in order to minimise the risk and to assure a subsequent favourable end of the illness<sup>20</sup>.

In short, what is concerned is not only the choice of the intervention or the method used, but also the failure to adopt a series of cautions following the intervention itself, among which, for example, the surveillance of the patient after the administration of pharmacological therapy<sup>21</sup>.

## **2. The off label use of drugs: cases, reasons and risks**

Professional autonomy in the health care decision making process renders the physician free to prescribe a drug for purposes other than that which it has been approved, where it is considered both safe and effective according to his/her professional judgement.

The use of unlicensed and off-label medicines is a widely used medical practice mainly in certain clinical settings.

The off-label use is common in Paediatrics<sup>22</sup> and Oncology.

The majority of medications prescribed to infants and newborns are not licensed for use in this age group. Comprehensive and systematic trials demonstrating safety and effectiveness of drugs before

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<sup>18</sup> Among several, see Cass. 18<sup>th</sup> April 2005, no. 7997, in *Corriere giuridico*, 2006, 257, commented on by F. Rolfi, *Il nesso di causalità nell'illecito civile: la Cassazione alla ricerca di un modello unitario*.

<sup>19</sup> Cassazione 8<sup>th</sup> February 2001, no. 2865, quoted.

<sup>20</sup> See Cassazione 8<sup>th</sup> March 1979, no. 1441, in *Giurisprudenza italiana*, 1979, I, 1, 1494.

<sup>21</sup> In this way see P. Stanzione, V. Zambrano, *Attività sanitaria e responsabilità civile*, Giuffrè, Milano, 1998, 129.

<sup>22</sup> L. Cuzzolin, A. Zaccaron, V. Fanos, *Unlicensed and off label uses of drugs in paediatrics: a review of the literature* in *Fundamental & Clinical Pharmacology* 2003;17:125-31.



their release on the market are not performed on children. The pharmaceutical companies rarely undertake the work necessary to gain a licence for children.

The literature reports that at least one-third of children in hospital and up to 90% of newborns in neonatal intensive care units receive such drug prescriptions. The more often granted drugs comprise analgesics, antibiotics and bronchodilators.

At best, product information includes age-specific warnings due to lack of dosing data for infants and children.

In the field of oncology, a considerable portion of medicine is used outside the labelled indications, in the absence of systematic evaluation.

Off-label prescription of anticancer drugs is supposed to be widespread, but very few surveys have been conducted to ascertain its real extent in clinical practice.

Findings of prospective analyses showed a percentage of unlicensed prescribing of 6.7-33.2% in infants and adults.

Most off label prescriptions are reported in patients treated for palliative purposes, some are associated with clinical benefits, and in specific cancers it formed the standard of care.

Thalidomide, developed as a non barbiturate sedative agent and recently approved for erythema nodosum leprosum's treatment, has currently been rediscovered because of its immunomodulator and antiinflammatory effect, suggesting the possibility of its use in the treatment of different, serious diseases. Its "new" pharmacological properties include modulation of cytokine production and inhibition of angiogenesis.

These mechanisms of action are still under investigation in a number of clinical conditions. The drug has shown to have promising clinical effects in curing multiple myeloma in both advanced or refractory state, and can be used either by itself or along with chemotherapy medicine.

Thalidomide has been studied in other different conditions including graft-versus host disease, discoid lupus erythematosus, sarcoidosis, relapsed/refractory multiple myeloma, Waldenström's macroglobulia, myelodysplastic syndromes, acute myeloid leukemia, myelofibrosis with myeloid metaplasia, renal cell carcinoma, malignant gliomas, prostate cancer, Kaposi's sarcoma, colorectal carcinoma<sup>23</sup>.

Evidence of its efficacy however still requires findings based on controlled clinical trials.

The use either of Docetaxel (authorised in lung and breast malignant neoplasm therapy) for hormone refractory prostate adenocarcinoma and for locally advanced and metastatic gastric and gastroesophageal junction cancers, or of Irinotecan and new oral fluorouracil in the treatment of advanced adenocarcinoma of stomach is an off-label prescription.

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<sup>23</sup> J. Matthews, C. McCoy, *Talidomide: a review of approved and investigational use in Clinical Therapeutics* 2003;25:342-95.

The Pegylated Liposomal Doxorubicin used in chemotherapy treatment for breast cancer has demonstrated activity in Cutaneous T-cell lymphomas and in non-Hodgkin lymphoma.

Fludarabine, Flavopiridol and Rituximab are administered to patients with mantle-cell lymphoma, indolent B-cell non Hodgkin's lymphomas without statutory authorisation.

Prescribing off-label is widespread also in Cardiology, Neurology, Psychiatry and Ophthalmology<sup>24</sup>.

Intravitreal Triamcinolone, tissue plasminogen activators, intracameral Vancomycin or Lignocaine are just a few off-label drugs used in ophthalmology.

Atypical antipsychotics such as Risperidone, Olanzapine, Quetiapine are used for dementia, even though they increase the risk of cerebrovascular events<sup>25</sup>.

Off-label prescribing is common in the area of headache conditions. In fact, scientific studies support the use of antiepileptics and antidepressants for the prophylaxis of hemicranias<sup>26</sup> and treatment of various chronic pain syndromes<sup>27</sup>: Gabapentin, labeled as an anticonvulsant, is widely used in therapy for chronic nonspecific pain (in Italy it is recognized the indication for neuropathic pain)<sup>28</sup>.

Selective serotonin reuptake inhibitor (SSRI) antidepressants (paroxetine, fluoxetine and sertraline) and the tricyclic antidepressant clomipramine increase ejaculatory control and delay ejaculation in men with premature ejaculation<sup>29</sup>.

The Italian Republic protects health as an individual fundamental right, safeguards the principle of scientific pluralism and ensures the freedom of choosing therapeutical treatment by individuals while simultaneously renders doctors independent in their professional practice, as stated by the Supreme Court (*Cassazione*, Sentence n.301, February 8, 2001).

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<sup>24</sup> See P.C. Taylor, R.O. Williams, M. Feldman, *Tumor necrosis factor as a therapeutic target for immune-mediated inflammatory diseases*. in *Curr Opin Biotechnol* 2004;15:557-63; and G.J. Silverman, S. Weisman, *Rituximab therapy and autoimmune disorders: prospects for anti-B cells therapy in Arthritis Rheum* 2003;48:1484-92.

<sup>25</sup> K.N. Fountoulakis, I. Nimatoudis, A. Iacovides, G. Kaprinis, *Offlabel indications for atypical antipsychotics: a systematic review in Ann Gen Hosp Psychiatry* 2004;3:4 and C. Barbui, A. Danese, G. Guaiana, L. Mapelli, L. Miele, E. Monzani, et al., Study Group. *Prescribing second-generation antipsychotics and the evolving standard of care in Italy in Pharmacopsychiatry* 2002;35:239-43.

<sup>26</sup> G. Trifiro, E. Spina, O. Brignoli, E. Sessa, A.P. Caputi, G. Mazzaglia, *Antipsychotic prescribing pattern among italian general practitioners: a population-based study during the years 1999-2002 in Pharmacoepidemiol Prescr* 2005;61:47-53 and S.M. La Roche, S.L. Helmers. *The new antiepileptic drugs*. in *JAMA* 2004;291:615-20.

<sup>27</sup> E.W. Loder, D.M. Biondi, *Off-label prescribing of drugs in speciality headache practice in Headache* 2004;44:636-41. See also E. Spina, G. Pertugi. *Antiepileptic drugs: indications other than epilepsy in Epileptic Disord* 2004;6:57-75.

<sup>28</sup> D.R. Grothe, B. Scheckner, D. Albano, *Treatment of pain syndrome with venlafaxine in Pharmacotherapy* 2004;24:621-9.

<sup>29</sup> G. Piediferro, E.M. Colpi, F. Castiglioni, F.I. Scropo, *Premature ejaculation. 3. Therapy in Arch Ital Urol Androl* 2004;76:192-8. See also M.D. Waldinger, A.H. Zwinderman, B. Olivier, *On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment in Eur Urol* 2004;46:510-5 and M.D. Waldinger, B. Olivier, *Utility of selective serotonin reuptake inhibitors in premature ejaculation in Curr Opin Investig Drugs* 2004;5:743-7. D.K. Montague, J. Jarow, G.A. Broderick, R.R. Dmochowski, J.P. Heaton, T.F. Lue, et al., *AUA Erectile Dysfunction Guideline Update Panel. AUA guideline on the pharmacologic management of premature ejaculation in J Urol* 2004;172:290-4. M.D. Waldinger, A.H. Zwinderman, D.H. Schweitzer, B. Olivier, *Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis in Int J Impot Res* 2004;16:369-81.

D.A. Adamopoulos, S. Nicopoulou, E. Koukkou, A. Pappa, E. Billa, *Responsiveness to tamoxifen citrate and testosterone undecanoate is independent of the severity of idiopathic oligozoospermia*. in *J Androl* 2005;26:565-6.

F. Comhaire, *Clinical andrology: from evidence-base to ethics. The 'E' quintet in clinical andrology in Hum Reprod* 2000;15:2067-71.

P. Vandekerckhove, R. Lilford, A. Vail, E. Hughes, *Clomiphene or tamoxifen for idiopathic oligo/asthenospermia*. in *Cochrane Database Syst Rev* 2000;CD000151.

Physician's autonomy in healthcare decision making represents an instrument to guarantee the progress and evolution of scientific knowledge and to realise in the meantime the most effective safeguard of health protection and promotion.

Therapeutic choice must be conducted according to the principle of science and conscience and adhering to recognised scientific data in order to avoid the encroachment of freedom on "unrealism, experimentation, empiricism, personal pleasure and unjustified subjectivism"<sup>30</sup>.

In Italy guidelines for the regulation of off-label prescription drugs and for outlining risk evaluation and management, by defining safety criteria for patients, are non-existent.

Some drugs are used more frequently to treat conditions other than those specified by their labels and approved indications.

Though off-label prescription is common and sometimes necessary for providing a pathway to clinical practice innovation, it presents significant risks. This practice may lack rigorous scientific scrutiny and there is little known about the degree of scientific evidence supporting it. According to the literature, a high percentage, around the 73% of off-label use had little or no scientific confirmation<sup>31</sup>.

The fact that prescribing drugs outside their product licence is a common practice, does not make it safe. Unexpected adverse effects represent a possible risk.

It is also true that the same outcome can occur with labelled new medicines: some harmful reactions become apparent only after a prolonged and/or extensive use in patient population. There are several examples of undesirable dangerous side effects after the marketing of a registered therapeutical agent.

Since the off-label practice may expose patients to avoidable risks and may even result in the prescription of more expensive [new] drugs rather than the [older], equally effective, safer and cheaper authorised ones, it is mandatory for doctor to follow the lawful direction and ethical recommendation (CDM).

### **3. The therapeutic orthodoxy: rules for the authorisation of new drugs**

In Italy, as in the rest of the European Union, the registration of a new drug passes through three different processes. The marketing authorisation can be obtained by means of 1) Centralised Procedure; 2) Mutual Recognition-Decentralised Procedure; and 3) National Procedure.

The European Medicines Evaluation Agency (EMA) represents the central organisation, established in London since 1995. Applying directly to the EMA, a pharmaceutical agent can be approved and made available for use in each Member State, Iceland, Liechtenstein and Norway.

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<sup>30</sup> M. Barni, *La prescrizione dei farmaci: libertà terapeutica e responsabilità del medico* in *Riv it med leg.*, 1994, 557

<sup>31</sup> D.C. Radley, S.N. Finkelstein, R.S. Stafford, *Off-label prescribing among office-based physicians* in *Arch Intern Med* 2006; 166: 1021–1026.

The centralised procedure is mandatory for biotechnology process products (drugs emerging from genetic engineering); “orphan medicines”<sup>32</sup> pursuant to Regulation (EC) 141/2001; new pharmaceutical agents with therapeutic indication for treatment of certain chronic disease (HIV infection/AIDS, cancer, diabetes or neurodegenerative, autoimmune and other immune dysfunction disease), as set out in the Annex to Regulation (EC) 726/2004. Two scientific committees, the CHMP (Committee for Medical Products for Human Use) and the CVMP (Committee for Veterinary Medicinal Products), go through an initial evaluation before the formal authorisation by the Commission is given. In the approval process, a Standing Committee representative of all EU countries assists the works of the Council.

If a drug has just obtained the product licence in one country, the Pharmaceutical Industries can obtain mutual recognition of that drug in other Member States. In other words the mutual recognition permits EU Member States to approve the authorisation released by another EU country<sup>33</sup>.

The decentralised procedure should be used for drugs not yet authorised in an EU member state, permitting a concurrent market licence in different countries<sup>34</sup>.

The mutual recognition and decentralised procedure cannot be used if 1) the pharmacological agent is one for which is compulsory the centralised procedure; 2) the industry has chosen the centralised procedure; 3) the agent is a homeopathic product (referred to Directive 2001/83/EC, as amended); 4) the product is a traditional herbal medicine long since used in the Community (subject to a simplified registration, according the Directive 2001/83/EC)

Finally, if a product is to be sold in a single country a request can be submitted to the licensing authority of that state under a national procedure. This system operated until 1998 and continued to be active for some agents like products intended for national use in one Member State only.

Independently of the type of registration procedure, *applications for authorisation to place a medicinal product on the market have to be accompanied by a dossier containing particulars and documents relating in particular to the results of physic-chemical, biological or microbiological tests as well as pharmacological and toxicological tests and clinical trials carried out on the product and thus proving its quality, safety and efficacy*.<sup>35</sup> These trials have to be practiced and conducted in accordance with the principles of good clinical practice and the equivalent ethical requirements (Directive 2001/20/EC).

In Italy, the National Health Service (SSN) comprises: the Ministry of Health holding the head position in charge of all the sectors; the Italian Medicine Agency (AIFA) playing a role in market

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<sup>32</sup> According to the definition provided by the EMEA, “an orphan medicine is one licensed for treating or preventing life-threatening rare disease affecting fewer than 5 in 10,000 people in the European Union”.

<sup>33</sup> Each EU Member State has 90 days for approving or rejected the decision made by the original country.

<sup>34</sup> The applicant may request one or more concerned Member States to approve a draft assessment report, summary of product characteristics, labelling and package leaflet as proposed by the chosen reference member state in 210 days.

<sup>35</sup> Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

authorisation, vigilance, pricing and reimbursement by different Commissions as the Scientific Technical Commission responsible for assessing quality, efficacy and safety of drugs in accordance with the market licence and reimbursement status; the Pricing and Reimbursement Committee that negotiates with Pharmaceutical Industries on the price of reimbursable drugs, Tecnic-Scientific Committee (CTS, Commissione Tecnico Scientifica previously the Commissione Unica del Farmaco) which carries out pharmacovigilance activity<sup>36</sup>, controls healthy expenses and drugs approval; the Liaison Centre between AIFA-Regions ensuring coordination with local organisations.

The National Observatory on the Use of Pharmaceuticals (OsMED) administered by AIFA monitors all reimbursable prescribing.

The rules of repayment established at national level are locally applied by regional governmental boards. When a marketing licence is authorised, either by the European Medicine Agency or the Italian Medicine Agency, manufacturers may apply for repayment<sup>37</sup>.

Prescribing activity is lawful when a licensed drug is used inside the term of its official labelling, in respect of fixed reimbursement system.

This general principle has been confirmed by the legislator. Following the legal provision of the so called “Legge Di Bella” (L 94/98) the: “physician has to prescribe a drug following the indications registered and reported on the product licence issued by the Ministry of Health”.

Now comes the exception to this rule.

The same law establishes that “in single cases the physician, under his/her own responsibility, may prescribe an off label medicine if there are no other available registered products effective for that pathological treatment, under the condition of existing international scientific evidence confirming the validity of using it”.

So a general principle has been affirmed that beyond the historical circumstances allows the off-label practice, defining application’s field and boundary.

#### **4. Di Bella Multi-therapy, the “doctor Hope”.**

##### ***4.1. Medical aspects***

In this regard, we must open a parenthesis concerning the so called “Di Bella case”, a very famous event which in the nineties captured, at least for a while, the attention of Italian public opinion and

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<sup>36</sup> “In order to ensure the adoption of appropriate and harmonised regulatory decisions concerning the medicinal products authorised within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall operate a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically”, Directive 2001/83/EC art. 102.

<sup>37</sup> On the National Pharmaceutical Formulary a drug can be assigned to class A, H or C. Class A includes essential medicine and product for chronic disease and are fully reimbursed by National Health System . Class H comprises pharmaceutical agents fully reimbursed in hospitals. Class C includes products not classifiable into class A or H and not reimbursed.

literature, both medical and juridical, and which surely influenced the above-mentioned law and also the medical deontological code of 1998 (which will be discussed below).

At the end of the past century a new, “powerful” cure for cancer was proposed by an Italian physiologist, Luigi Di Bella (1912-2003).

The cure named “Di Bella Multi-therapy” aroused the interest of national and international media, giving full coverage to this treatment claimed to be effective in most malignant neoplasms.

Di Bella multi-therapy comprised a combination of melatonin, bromocriptine-cabergoline, somatostatin, a solution of retinoids, vitamins E, D, C, also cyclophosphamide or hydroxyurea (effective for some types of cancer), associated to micro-doses of antiproliferative agents. These drugs carry out a synergic action with immunostimulant, anti-proliferative, anti-oxidant and anti-angiogenic effects, inducing apoptosis of tumoral cells and cellular differentiation. The aim is to reverse cancer biology into physiological biology.

The choice of these components rested on the consideration that neoplasm, even in the form of a solid tumour, is a systemic disease caused by a biological and physiological distress or imbalance due to different etiopathogenic factors. Differently from chemotherapy, Di Bella Multi-treatment causes tumour cell death without being cytotoxic; it reinforces the mechanisms of natural defence and struggles with neoplasm proliferation, inhibiting growth factors.

The use of somatostatin and bromocriptine-cabergoline permits the inhibition of growth factors, whose role in cancer etiopathogenesis is known and scientifically well-documented.

In particular, the drug inhibits the pituitary release of GH and prolactin hormones.

Growth Hormone has an anabolic effect, it stimulates cell reproduction and the synthesis of other mitogenic factors like Somatomedin C (or IGF1, insulin-like growth factor), EGF (epidermal growth factor), VEGF (vascular endothelial growth factor).

Public opinion pressured the Italian government to guarantee the Di Bella Multitherapy under the National Healthcare System. These voices could not be ignored, the National Cancer Advisory Committee recommended that the Minister of Health should verify the efficacy of the treatment by performing a series of uncontrolled phase II trials.

In February 1998, the Italian Parliament issued a decree-law (n 23, 17 February 1998, subsequently assumed in law n 94, 8 April 1998) authorising the experimentation, under the responsibility of the Istituto Superiore di Sanità (Superior Institute of Health).

At the end of each of the clinical trials, the evidence suggested that the Multi-therapy did not show efficacy in tumour size reduction, consequently the National Health System didn't authorise the cure in public cure institutes.

## 4.2. Legal aspects

The fact that somatostatin was difficult to find in Italy, as well as the fact that such treatment was not covered by the National Health Service, induced some oncological patients, the greater part of which were terminal patients, to request the emanation of an urgent legal provision, provided for by Art. 700 of Italian civil procedure code<sup>38</sup>. The aim was to order the National Health Service to provide free distribution of this drug to patients<sup>39</sup>.

The reasoning behind the request made by those patients was the existence of a right to adopt non-conventional therapies or, in other words, therapies that are not diffused according to the procedures established by law. The patients' right to have those therapies free of charge was connected to this freedom<sup>40</sup>.

The reconstruction proposed by the Ministry of Health – and by the judges who adhered to it<sup>41</sup> – was the opposite: since at that time there was no rule (the rule was only enacted at a later stage) allowing a doctor to administer off label treatments, the possibility to charge the State with the cost of such kind of therapy was contrary to the Italian system of reimbursement of the cost of therapies. Furthermore, according to the Ministry, the risk was to move economic resources from efficient therapeutic instruments to therapies of effectiveness still not demonstrated.

Besides, the compulsory nature of experimentation procedures is not, so to speak, a consequence of a bureaucratic approach to medicine, but an instrument to guarantee the patient himself/herself<sup>42</sup>.

At the same time, a consumer association asked the Regional Administrative Tribunal for Lazio (T.A.R. Lazio: “*Tribunale Amministrativo Regionale per il Lazio*”)<sup>43</sup> to declare unlawful the provision of the “*Commissione unica del farmaco*”<sup>44</sup>, which denied the free somatostatin distribution<sup>45</sup>.

Since the decisions of the above mentioned judicial bodies were often favourable to patients, the Government was forced to enact the above mentioned decrees, which are partially still in force, to reduce the uncertainties which different judicial decisions had created.

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<sup>38</sup> Please see, for further references, F.M. Gallo, *Tutela della salute e procedimento d'urgenza*, in *Il lavoro nella giurisprudenza*, 1998, 317 and A. Fiori, *Medicina legale della responsabilità medica*, quoted, 88 ff.

<sup>39</sup> It is necessary to keep in mind that in Italy, in favour of some kinds of patients, like the oncological ones, a regime of full exemption from the payment of therapies and medicines has been established whereby the cost is charged to the National Health Service.

<sup>40</sup> See M. Bona, A. Castelnuovo, *Il “caso Di Bella” e le nuove frontiere del diritto costituzionale alla salute: quali limiti al c.d. “diritto alla libertà terapeutica”?*, in *Giurisprudenza italiana*, 1998, 6.

<sup>41</sup> See A. Fiori, *Medicina legale della responsabilità medica*, quoted, 88 ff.

<sup>42</sup> See F. Giunta, *Il caso Di Bella: libera sperimentazione terapeutica e responsabilità penale*, quoted, 667.

<sup>43</sup> The judicial organ which the most part of the controversies among citizens and public administration are attributed. The Lazio region is the Italian region which comprises Rome, the capital of the Republic, and where the majority of public offices and bodies are situated.

<sup>44</sup> The Italian public body to which the decision to burden either the State or patients with the cost of medical treatments is attributed.

<sup>45</sup> T.A.R. Lazio 9<sup>th</sup> March 1998, no 580 and T.A.R. Lazio 9<sup>th</sup> February 1998, no. 384, in *Giurisprudenza italiana*, 1998, 5, commented on by M. Protto, *Nilil magis aegris prodest quam ab eo curari, a quo volunt: il giudice amministrativo e il caso Di Bella*. See also the decision rendered by the *Consiglio di Stato* (Consiglio di Stato 24<sup>th</sup> February 1998, no. 384 and Consiglio di Stato 25<sup>th</sup> March 1998, no. 518), the most important Italian judicial body in the field of administrative law.

Yet, the Constitutional Court declared the unlawfulness of a part of decree no. 23 of 1998, since it did not establish the free administration of somatostatin to oncological patients<sup>46</sup>.

## 5. The regime of off label drugs in Italy

Continuing on from the above discussion, a doctor can administer off label drugs in so far as s/he provides the obtainment of the patient's consent and can demonstrate that the patient's illness cannot be effectively treated with medicines already in commerce.

Similarly, a doctor may also alter the approved administration or the use of medicines whenever s/he shows that the therapeutic indication, or the modality of administration currently in use, are not useful for the specific condition of that specific patient.

This requisite has been criticised by a part of scholarship, stressing that, since in some fields, such as oncology, there are currently no treatments that can guarantee the recovery of a patient, it might be rather ambiguous, giving too much discretionary power to a physician<sup>47</sup>.

Moreover, another requirement that the non-conventional use of a drug should fulfil is that its use should be well-known and in compliance with professional opinion published in scientific reviews credited in the international field<sup>48</sup>.

The legislative reference to the international credit allows the exclusion that, for instance, a conference presentation or a mere abstract would be sufficient since the publication must be inserted in a peer-reviewed international journal (*e.g.*: Lancet)<sup>49</sup>.

Important problems can arise however when differing opinions regarding the particular off label treatment at issue can be detected in the international literature. In such cases, the assessment of the negligence in the choice of the treatment should take into account the effective possibility for a doctor to have access to all the scientific data, because there is a tendency to publish only positive data, while simultaneously silencing the failures<sup>50</sup>, particularly in cases where sponsored research is concerned<sup>51</sup>.

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<sup>46</sup> Constitutional Court 26<sup>th</sup> May 1998, no. 185, in *Giornale di diritto amministrativo*, 1998, 1037, commented on by C. Anzecchiarico, G. France, *Il caso Di Bella dinanzi alla Consulta: profili giuridici, economici e di efficacia clinica* and in *Giurisprudenza italiana*, 1999, 1, commented on by C. Colapietro, *La salvaguardia costituzionale del diritto alla salute e l'effettività della sua tutela nella sperimentazione del "multitrattamento Di Bella"*. Yet, the Constitutional Court rendered also another decision in relation to this fact. See Constitutional Court 2<sup>nd</sup> April 1999, no. 121, in *Giornale di diritto amministrativo*, 1999, 443, commented on by P. Carluccio, R. Finocchi, *Terapia Di Bella* and in *Corriere giuridico*, 1999, 962, commented on by M. Bertolissi, *La Corte Costituzionale chiude il "caso Di Bella"?*

<sup>47</sup> See D. Micheletti, *La speciale disciplina del multitrattamento di bella*, in *Diritto penale e processo*, 1998, 694.

<sup>48</sup> Requisite criticised for being too generic by F. Giunta, *Il caso Di Bella: libera sperimentazione terapeutica e responsabilità penale*, in *Diritto penale e processo*, 1998, 667. According to this author, it is not specified which should be the degree of completeness of the publication, nor the conditions to assess the scientific character of it.

<sup>49</sup> P. Piras, *La responsabilità del medico per la prescrizione off-label*, in *Cassazione penale*, 2009, 1963. See also M. Zana, *Ai limiti della responsabilità medica: l'uso off label dei farmaci*, quoted, 736 f., who wonders whether the legislative reference to international publications should be interpreted literally.

<sup>50</sup> See the advice rendered by the Italian National Bioethics Committee (*Comitato Nazionale per la Bioetica*) on 8<sup>th</sup> June 2006 about conflict of interests in the biomedical research and in the clinical practice (*"Conflitti d'interessi nella ricerca biomedica e nella*



Thus, there emerges a regime in virtue of which off label prescription is not banned in itself, but is subordinated to specific circumstances and conditions.

Yet, as it has been recalled by scholarship<sup>52</sup>, the normative basis of this principle is to be found in Art. 33, 1<sup>st</sup> paragraph of Italian Constitution, which establishes the principle of the freedom of science, and in Art. 9, 1<sup>st</sup> paragraph of Italian Constitution, according to which the Republic promotes scientific research.

Lastly, an important legislative reform, made by Art. 2, paragraph 348 of Law 24<sup>th</sup> December 2007, no. 244 must be taken into account. It provides that “*in no case a doctor can prescribe, for the treatment of a determined pathology, a drug the commerce of which is not authorised when on the proposed use of the drug there are no available favourable data of clinical experimentations of phase two*”<sup>53</sup>.

Such a restrictive attempt is apparently in line with the indications given by the Italian Constitutional Court, which explicitly asserted that legislative decisions regarding the therapies which are allowed and, in general, on the merit of therapeutic choices, must be based on their appropriateness and cannot be born from purely political appraisals of the legislator<sup>54</sup>.

Yet, the above-mentioned Law no. 244/2007 seems to have partially modified the requirements for off label prescription, which were previously introduced by the Law no. 94/1998<sup>55</sup>.

In fact, it is difficult to understand the difference between the “old” (but still in force, as it seems) requirement according to which the off label employment should be well-known and in compliance with publications in scientific reviews credited in the international field, and the “new” requirement concerning the availability of favourable data emanating from phase two clinical experimentations.

The new formulation seems to be more restrictive compared to the previous one, binding doctors to limit off label prescriptions only to hypotheses where clinical experimentations are well advanced and rendering insufficient the requirement of publications on international scientific journals<sup>56</sup>.

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*pratica clinica*”). For an analysis of the biases of peer review process, see L. Noah, *Sanctifying Scientific Peer Review: Publication as a Proxy for Regulatory Decisionmaking*, 59 U. Pitt. L. Rev. (1998) 677-717 and B.A. Liang, T. Mackey, *Confronting Conflict: Addressing Institutional Conflicts of Interest in Academic Medical Centers*, 36 Am. J. L. and Med. (2010) 136-187.

<sup>51</sup> See J.E. Bekelman, et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 JAMA 454 (2003). The conclusion which has been reached is that “*strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions*”. See also M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 985 ff., for an explanation of pharmaceutical marketing abuses, and C.D. De Angelis, *The Influence of Money on Medical Science*, 296 JAMA 996 (2006).

<sup>52</sup> See P. Piras, *La responsabilità del medico per la prescrizione off-label*, quoted, 1964.

<sup>53</sup> In clinical experimentation there are three phases: phase 1, in which the maximum dose for a determined period of time which can be administered is determined; phase 2, in which the effectiveness of the drug is preliminarily assessed; phase 3, to establish the benefit-risk relationship and therefore the role of the new drug in the therapy; there follows a phase 4 that takes place after commercialisation and in which the toxic effects of the drug are monitored. See the Italian Bioethics Committee, advices published on the 17<sup>th</sup> November 1992 on pharmacological experimentation (“*La sperimentazione dei farmaci*”) and the 24<sup>th</sup> April 2009 on bioethical problems in clinical experimentation with not-inferiority design (“*Problemi bioetici nella sperimentazione clinica con disegno di non-inferiorità*”).

<sup>54</sup> Corte Costituzionale, 26<sup>th</sup> June 2002, no. 282, in *Giurisprudenza italiana*, 2002, 2006, commented on by F. Covino, *Nota sulla potestà legislativa concorrente*.

<sup>55</sup> M. Zana, *Ai limiti della responsabilità medica: l'uso off label dei farmaci*, quoted, 739 f.

<sup>56</sup> See M. Zana, *Ai limiti della responsabilità medica: l'uso off label dei farmaci*, quoted, 740.

According to advice made available on 16<sup>th</sup> January 1998 by the Italian National Bioethics Committee<sup>57</sup>, a doctor, according to current knowledge, may not only be authorised, but even bound to use alternative therapies.

To this end, it is necessary to verify that there is a state of urgent necessity, because a patient is facing a life-threatening or serious and irreversible damage to health and there seems to be no realistic possibility of using therapies already known and officially accepted by medical science, or if these treatments have produced no positive effect.

It is also necessary that off label treatments have a reasonable justification, although the same are not yet verified experimentally in the proper form nor officially approved, and that they produce no harmful effects.

Yet, regarding the last condition, we must stress that it cannot be literally interpreted: indeed, the fact that the treatment does not produce any damage at all might be verified only at the end of the experimental procedure which, in the mentioned case, by definition is not yet concluded.

Besides, it might happen that in some circumstances, a particularity at an earlier stage of the experimentation might be classified as adverse but with further investigation the same particularity may be reconsidered.

Therefore, we should interpret the requisite of the absence of harmful effects in the sense that the scientific data provided by the doctor should demonstrate that, at the stage of the experimentation and at the state of scientific knowledge, the off label treatment did not produce any clear damage or disadvantage to the patient.

In the same above cited statement of advice, the Committee recalled that the professional responsibility of a doctor, in trying the off label treatment, must avoid giving unjustified illusions to patients.

Thus, as we can see, the medical issues are always strictly connected with ethical and deontological aspects. Yet, it is quite probable that the substitution of usual therapies with experimental practices shall indeed produce such “illusions in patients”. Therefore, the legal duty, imposed on a doctor, to limit off label treatments to the above mentioned cases and conditions, is juxtaposed to, so to say, a moral obligation not easily fulfilled.

Particularly, regarding the requisite of the comparison between the benefit a patient can obtain from a conventional treatment and the benefit s/he can gain from a non-conventional treatment, it has been argued that this benefit does not have to be estimated in absolute terms, but in comparison, that is, in other terms, documenting that the adoption of a still unrecognised cure could be in any case susceptible

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<sup>57</sup> Advice published on 16<sup>th</sup> January 1998 on the testing and use of new drug therapies (“*Nota sulla sperimentazione e l’impiego di nuove terapie farmacologiche*”).

in determining an advantage to a patient compared to the therapy formally accepted by the Ministry of the health<sup>58</sup>.

Regarding the topic of the off label prescription of drugs, as we have seen above, Italian law does not offer univocal answers. The same conclusion is true also with regard to the Italian medical deontological code.

First of all, we must stress that the medical deontological code is not, in itself, a rule of law. It is binding only for physicians, and its violation, committed by a doctor, causes his/her liability only in relation to the medical body. On the other hand, nobody might be held liable in law for simply not behaving according to the code.

At the same time, we must also recall that the principles affirmed by the code are usually an expression of the laws in force. Thus, for that reason, it is important to analyse its content and its prescriptions.

As an example, the Italian medical deontological code of 1995, which established for a doctor “*full autonomy in the choice, the application and the programming of diagnose and therapy*” (Art. 12, par. 1), limited recourse to new therapies “*within the clinical experimentation*”, subjecting it also to relative discipline (Art. 12, par. 4).

Such rules have been substantially confirmed by the code of 1998, enacted immediately after the above-mentioned “Di Bella case”, by which, as previously stated, the code has been surely influenced.

The 1998 code maintained (Art. 12, paragraphs 5 and 7) the limit according to which a doctor, who wanted to prescribe off label treatments to patients, should have been able to demonstrate the scientific basis of the therapies, as well as of the drugs not in commerce that a doctor would decide to prescribe. The code established also that a doctor could not prescribe “non conventional medical practices” in substitution of conventional therapies of sure effectiveness (see Arts. 82 of the code of 1995 and 13 of the code of 1998).

Finally, Art. 15 of the medical deontological code of 16<sup>th</sup> December 2006, that has replaced the previous one of 1998 and is, currently, still in force, has established that the use of non conventional practices must respect the honour and the dignity of the profession. These practices must be prescribed exclusively within the direct and not delegable professional responsibility of a doctor. In any case, a doctor should not replace scientifically consolidated conventional treatments with non conventional ones, must always give specific and exhaustive information to the patient and must obtain his/her informed consent.

It is also prohibited for doctors to collaborate or to favour the exercise of so-called non conventional practices<sup>59</sup>.

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<sup>58</sup> See F. Massimino, *La prescrizione dei farmaci “off label”: adempimenti, obblighi e responsabilità del medico*, in *Danno e responsabilità*, 2003, 927 and M. Zana, *Ai limiti della responsabilità medica: l’uso off label dei farmaci*, quoted, 733. See also the advice published on 16<sup>th</sup> January 1998 by the Italian National Bioethics Committee (*Comitato Nazionale per la Bioetica, Nota sulla sperimentazione e l’impiego di nuove terapie farmacologiche*).

## **6.Modality of the off-label prescription**

The essential purpose of drugs regulation is the public health's protection. Health represents a fundamental human right, hence medicines have additional social value.

Physicians and patients pressed the regulator organism for a faster licensing process removing bottlenecks and giving an initial approval even in situations where only the preliminary clinical data were available, especially for some serious diseases (for example, cancer and HIV/AIDS).

On the basis of this argumentation, these types of requests founded the "expanded access" or "compassionate use" for drugs not yet authorised during clinical experimentation which would however be useful for seriously ill patients.

In Italy, expanded access has been regulated by the legislator with the DM 8/5/03, which sets out a list of pathologies for which the unlicensed use is lawful, and charged to the SSN<sup>60</sup>.

According to the rule, compassionate use is recommended for medicine useful in treating patients with a life-threatening, long-lasting or seriously disabling illness, one which cannot be treated satisfactorily with medicines that have already been authorised.

The permission to use requires that: 1) the drug has to be the object of completed or in progress phase III clinical trials, or concluded phase II clinical trials for life-threatening diseases. 2) available experimentation data must be adequate to express a favourable judgment on effectiveness and the tolerability of the agent. The prescribing physician has to forward the request to the local Ethic Committee which through an urgency decree conducts its evaluation.

For the authorization of an "expanded use" the prescriber has to specify either the clinical rationale and the efficacy, tolerability's data of drug. It's necessary the description of patient to enrolled for the evaluation of comparability with those patients already included in the clinical trial. The drug is provided freely by the firm authorized.

The local Ethic Committee has to require a written assertion subscribed by the pharmaceutical industry's legal representative in which is guarantee the furniture also after the commercialization until the evaluation of the "Prontuario Terapeutico Aziendale".

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<sup>59</sup> The original text is the following: "*Il ricorso a pratiche non convenzionali non può prescindere dal rispetto del decoro e della dignità della professione e si esprime nell'esclusivo ambito della diretta e non delegabile responsabilità professionale del medico. Il ricorso a pratiche non convenzionali non deve comunque sottrarre il cittadino a trattamenti specifici e scientificamente consolidati e richiede sempre circostanziata informazione e acquisizione del consenso. È vietato al medico di collaborare a qualsiasi titolo o di favorire l'esercizio di terzi non medici nel settore delle cosiddette pratiche non convenzionali*".

<sup>60</sup> The EMEA can provide recommendations to the member states on how to administer and use certain medicines for compassionate use. It can also identify which patients may benefit from compassionate use programmes. However, compassionate use programmes remain co-ordinated and implemented by the member states. The recommendations from the EMEA are complementary to the national legislation and do not create any legal framework in the member states, according to Article 83 of regulation (EC) No 726/2004.

For those drugs not included in the ministerial list, for avoiding therapeutic treatment interruptions, local health services have developed a decision making process for evaluating the appropriateness of any proposed off label use and for surveying patient reactions to medicine.

The Regional Therapeutic Commission is the institute that judges the request and verifies the essential requirements for the authorisation: a written informed consent, a clinical report with high quality references specifying the type of scientific evidence (i.e. randomised controlled trials, clinical trials, case series, case reports); the lack of labelled and licensed drugs.

More in detail, at the regional level, in health-care institutes clinicians have to make a request of authorisation for unlabelled prescription, through a special form draw-up by pharmaceutical units.

In this form, it is necessary to specify the type of unlabelled prescription between the four categories designated.

A) The new drug has been authorised in a state other than Italy, or it is under clinical experimentation and not yet licensed, or it is administered for an outside labelled indication and included in the ministerial list (periodical updates, last revision in December 2009), in accordance with the law 648/96.

B) 1) the therapeutic agent is effective in the cure of solid and hematologic tumours and it is comprised within a list (“positive list”) of anticancer drugs with extended indications, in accordance with the DGR 394/08)

2) the medicine is used as an anticancer treatment in paediatrics or as a support to chemotherapy treatment and it is included in a list, in agreement with the DGR 622/08.

3) extended indication of the drug concerns the cure of rheumatological disease, the product is inserted in a list of approved off label prescriptions if the unlicensed use is supported by at least three authoritative scientific publications, in accordance to the DGR 836/08.

4) the product is administered off label to patients receiving organ transplants as anti-rejection treatment and it is just included in a list of granted extended indications, as provided by the DGR 918/08.

C) prescription is not part of the above categories nor it is present in a “negative list”, which includes the off labelled use of drugs not reimbursable by the SSN (or regional).

When off-label use is not well justified in the opinion of the local drug committee judgment, the outsider indication is incorporated into the negative list. Reimbursement of the drug is guaranteed where treatment has already begun until its completion.

For the assessment of the application, the physician has to supply a clinical report specifying drug naming, pharmaceutical framework, dosing, and pathology, in association with scientific literature (three or more internationally recognised works) supporting it.

This report is passed on to the health direction and to The Regional Drug Committee that approves or rejects the application. If the off label use is authorised then prescription requires the previous patient informed written consent.

The clinician has to give details on the risk attached to an off-label treatment; the patient has to be aware of the partial scientific evidences on efficacy and safety.

In the informed consent form, which is carbon copied, it is necessary to report any potential benefits and expected side effects.

Prescribing off-label or unlicensed drugs is lawful as long as it is subjected to the “scientific reasonableness” of the treatment and to the informed consent of patient<sup>61</sup>. Therefore (professional) freedom has to be comforted by science.

It is the duty of physicians to adopt the necessary precautions to avoiding the overcoming of the level of “not-allowed” risk or foreseeing and controlling the development of an adverse reaction. As established by the rule and the deontology, the scientific experience or better the scientific evidence becomes considerable as a condition justifying the off label drug use, which must be “known and conformed” to authoritative publications.

Considering that the activity of the doctor has always had a curative purpose, it would seem strange to practice pure experimentalism where the drug used does not find any correspondence among medical literature, guide lines, or protocols.

In this case, if the patient has psycho-physical damage or dies as consequence of the administration, becomes concrete the hypothesis of personal injuries or even murder.

More frequent are the border-line occurrences where the off-label prescription is made without a solid scientific ground.

An “eccentric” therapeutic choice requires the scientific assessment of the reliability of the precedents reported and of the seat of divulgation, in order to exclude medical liability.

The verification of the credibility of “alternative cures” settles the score with the accreditation procedure of medical journals which represents another issue deserving a thorough analysis. The ISI (Institute for Scientific Information) as well known, represents the binding reference for recognition of formal standards of suitability compared to international values. Only formal criteria with different epistemological content, whose adoption however constitutes a significant factor of public accreditation, is socially recognised for certifying the quality of scientific research.

*Sine die* a clarification of rules and process is lacking, i.e. the need for no more tacit rules but rather declared and publicly certified ones, effective for scientific experience appraisal.

So peer-review does not ensure the quality of evidence. In addition as reported by some authors, «medical literature landscape is riddled with instances of breaches of integrity, including the influence of

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<sup>61</sup> M. Barni, *Un'illuminazione “toscana” sulla prescrizione di farmaci* in *Toscana Medica* 2006; 9: 27-28

the pharmaceutical industry in ghost writing, ghost management, publication planning, and more recently the discovery of the conduct of “seeding trials”»<sup>62</sup>.

## 7. The requirement of the informed consent

Particularly important is the obligation of a doctor to obtain the consent of the patient after previously informing him/her about what we can generally call the principal aspects of the treatment<sup>63</sup>.

First of all, we must recall that, according to the most recent Italian case law, if a doctor subjects a patient to a treatment different from that one in relation to which the informed consent has been given, the medical conduct is not illicit in itself<sup>64</sup>.

However, to avoid liability it is necessary that such intervention has been executed in respect of the protocols and of the so called “*leges artis*” and has been concluded with a favourable outcome, in the sense that it has produced an appreciable improvement of the patient’s health conditions, also compared to the possible therapeutic alternatives.

The objective of this reasoning is to avoid the risk for a doctor to be convicted in cases in which no guilt is imputable to him/her and, above all, where the aim of the medical treatment has been satisfactorily reached.

At the same time, the above mentioned decision stated that the lack of informed consent cannot constitute in itself the fault of a doctor, since the act of obtaining the consent is not aimed to avoid damages, but to protect the right to self-determination of a patient.

According to scholarship<sup>65</sup>, however, there may also be fault on the part of a doctor, as well as the violation of the right to self-determination of a patient, if the lack of the informed consent of the patient has determined a situation in which the physician was not able to detect the effective health condition of the patient and to perform a correct diagnosis.

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<sup>62</sup> F.R. Curtiss, K.A. Fairman, *Contradictory Actions on Off-Label Use of Prescription Drugs? The FDA and CMS Versus the U.S. Justice Department*. in *JMCP* 2009; 15(2): 161-165. See also C.D. De Angelis, P.B. Fontanarosa, *Impugning the integrity of medical science-the adverse effects of industry influence* in *JAMA* 2008; 299 (15): 1833-35. And J.S. Ross, K.P. Hill, D.S. Egilman et al., *Guest authorship and ghostwriting in publications related to rofecoxib. A case study of industry documents from rofecoxib litigation* in *JAMA* 2008; 299 (15): 1800-12.

S. Sismondo, *Ghost management: how much of the medical literature is shaped behind the scenes by the pharmaceutical industry?* in *PLoSMed*.2007; 4(9):1429-33.

<sup>63</sup> See for an application of this principle to the so-called “end-of-life decisions”, Cassazione civile, 16<sup>th</sup> October 2007, no. 21748, in *Famiglia e Diritto*, 2007, 12, 1162 (the famous “Englaro case”, which authorised the withdrawal of life sustaining treatment in a case in which a woman had been in a persistent vegetative state for almost twenty years).

<sup>64</sup> Cassazione penale, Sezioni Unite, 18<sup>th</sup> December 2008, no. 2437, in *Corriere del merito*, 2009, 303, commented on by P. Piccialli, *Il consenso informato e la responsabilità del medico*.

<sup>65</sup> See P. Piccialli, *Il consenso informato e la responsabilità del medico*, quoted, 305.

An older case law trend, on the contrary, stated that a medical treatment could be licit only if the patient had given his/her informed and explicit consent to it, notwithstanding its outcome<sup>66</sup>. In the absence of informed consent, in fact, a doctor would have been guilty of voluntary inflicted injuries.

Thus, according to the most recent case law, in the field of off label treatments, liability of the doctor may not be established, even though s/he has not fully informed the patient about the fact that the treatment administered was not “conventional”, so long as the same treatment produced a favourable outcome.

Moreover, as we shall see by analysing the most recent case law of the Criminal Division of the “*Corte di Cassazione*”<sup>67</sup>, also in the case of a negative outcome of an off label treatment, a doctor shall not be in any case convicted of a voluntary damage, but rather of a negligently inflicted injury (which might result in a very minimal punishment in the case of a criminal trial, while, in tort law, the result of the judgement should not be altered since, as it is well known, negligence is sufficient to be condemned).

Obviously, this approach might lead to a reduction in the protection of a patient’s self-determination, since the latter might theoretically be subject to a specific treatment without any consent and also without the possibility to sue the doctor (in the case of a positive prognosis).

In this regard, we should recall that, according to the most recent case law<sup>68</sup>, medical liability arises not only in cases where a damage has been caused to a patient by a wrong treatment, but also when the latter did not produce any outcome at all. Thus, the exclusion of the responsibility for lack of informed consent operates only as long as the treatment has been carried out diligently and has produced the desired result.

An important problem, which can arise when analysing whether informed consent has been given, is the effective self-determination of a patient.

Yet, we must recall that the relationship between a physician and a patient is not symmetric: very often a patient accepts everything that is prescribed or also only advised to him/her by the doctor.

This situation is more dangerous in our cases. Yet, as we have discussed before, in order to prescribe an off label treatment, Italian law asks that a patient cannot be effectively treated with conventional treatments. Therefore, it is conceivable that, as in fact the Italian National Bioethics Committee reflected in the above mentioned advice of 16<sup>th</sup> January 1998, a patient faces “*a life-threatening or serious and irreversible damage to health and there seems no realistic possibility of use of therapies already known*”.

In such circumstances, the risk is therefore that the consent given by a patient, even though the same is well documented and has preceded the relaying of full and correct information by the doctor, is not entirely free, since an off label treatment might be seen by a patient as a sort of “last resort”.

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<sup>66</sup> See, among several, Cass. 13<sup>th</sup> May 1992, no. 5639, in *Rivista italiana di medicina legale*, 1993, 460.

<sup>67</sup> Cassazione 24<sup>th</sup> June 2008, no. 37077, in *Corriere del Merito*, 2009, 303.

<sup>68</sup> Cassazione 13<sup>th</sup> April 2007, no. 8826, in *Rivista italiana di medicina legale*, 2008, 849, commented on by A. Fiori, D. Marchetti, *Un altro passo verso l'obbligazione di risultato nella professione medica?*



Thus, in case of trial, a patient might try to demonstrate that, had s/he had different psycho-physic conditions, s/he would not have given his/her consent.

Regarding the content of informed consent, we must recall that the duty to inform should regard in particular the aspects of diversities between an off label treatment and a conventional one<sup>69</sup>.

It is necessary, in other words, that a physician not only informs the patient (or his/her proxy) that s/he is subjecting him/her to “a non conventional” treatment: the patient should indeed be informed also about all the aspects which could hypothetically produce a greater risk, and of the possible collateral effects of the therapy, as well as of the margins of expected greater effectiveness of an off label therapy.

Favourably, within the limits of the abilities of understanding of a patient, moreover, a doctor should summarily indicate to the patient the reasons for which s/he is considering the administration of an off label treatment rather than an on label treatment, as well as the sources of such opinion.

That hopefully would allow the same patient to estimate the reliability of the scientific data upon which the doctor bases his/her conviction and, if it is necessary, in case s/he thinks that the same is unaffordable, to opt for the “traditional” treatment.

## 8. Profiles of responsibility emerging from Italian case law

To the best of our knowledge, there are few decisions in the Italian case law regarding medical liability related to the off label prescription of drugs (a topic which, to be honest, has not been profoundly investigated by Italian legal scholarship).

With regard to this issue, an important decision of the most important Italian judicial body<sup>70</sup> evidenced that the use of new therapies is permissible only within clinical experimentation, thus limiting considerably the possibility to prescribe off label drugs<sup>71</sup>.

A part of legal scholarship, therefore, negatively reacted to this case law, referring to a rigorous defence of what is called “*therapeutic orthodoxy*”<sup>72</sup>.

That leads to a clean separation of implementations, modalities of performance and purposes between the typologies of pharmaceutical cures which are authorised by the Ministry of Health and, therefore, can be ordinarily prescribed by a doctor, and, on the other hand, the various treatments which are not

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<sup>69</sup> See F. Massimino, *La prescrizione dei farmaci “off label”: adempimenti, obblighi e responsabilità del medico*, quoted, 929.

<sup>70</sup> Cassazione, Sezioni Unite, 19<sup>th</sup> February 1997, no. 1532, in *Foro italiano, Repertorio*, 1997, voce *Professioni intellettuali*, n. 212.

<sup>71</sup> Indeed, we must stress the difference between off label and experimental treatments, since the latter can be defined as medical therapies, aiming at relieving the suffering of people and restoring them to health, and not aimed to acquire a better understanding of the processes involved in the human body. See, on this regard, J.M. Beck, E.D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 *Food and Drug Law Journal* (1998) 71, 81.

<sup>72</sup> See F. Massimino, *La prescrizione dei farmaci “off label”: adempimenti, obblighi e responsabilità del medico*, quoted, 932 and F.D. Busnelli, *Ricerca medica*, in Id., *Bioetica e diritto privato. Frammenti di un dizionario*, Giappichelli, Torino, 2001, 217 f., who applies Art. 2050 of the civil code to the all kinds of research on human beings.

specifically approved by the authority and can be administered only in compliance with the rules of clinical experimentation.

In the absence of indications from civil case law (since the greater part of case law is connected with criminal cases), scholarship<sup>73</sup> has advanced that the dangerousness of an off label treatment would render applicable the presumption of guilt foreseen by Art. 2050 of the civil code, according to which “*anyone who causes damage to another in pursuit of a dangerous activity, by its nature or by the nature of the means employed, must compensate the damage, if s/he does not demonstrate that all reasonable steps to prevent damage were taken*”<sup>74</sup>.

Following this reconstruction, which at the moment has still not been applied by any decision, a doctor would be burdened to prove to have fulfilled all the precautions necessary to avoid the damage.

Yet, it is necessary to stress that Italian case law<sup>75</sup> has affirmed the principle of the “closeness of the proof”, according to which the burden of the proof should be accomplished by the party who is in the best condition to know and prove the facts, who of course, in the field of medical liability, is a doctor.

Consequently, the above-mentioned reconstruction, which was hypothesised by scholarship before the Supreme Court expressed the above synthesised apportionment of the burden of the proof, would be now perfectly in line with the preponderant trend, also without the application of the Art. 2050 of the civil code.

In addition to what has been sanctioned by the case law with reference to on label healthcare treatments, moreover, a doctor should be held liable also in cases where the patient’s health conditions have not changed at all<sup>76</sup>. In fact, it has been assessed by case law that the doctors’ duty is not limited to a generic “*neminem laedere*”, *i.e.* a duty not to harm his/her patients, since s/he is obliged to reach a positive effect.

Indeed, in an off label treatment, such a conclusion must be reached “*a fortiori*”, above all when it is certain, or also only probable, that the traditional therapies would have produced a benefit to the patient<sup>77</sup>.

Contrarily to the lack of civil decisions, the casuistry emerging from criminal case law is plentiful.

In the decision of the Italian Supreme Court No. 17499/2008<sup>78</sup>, for example, a doctor who prescribed a young woman affected by hirsutism an off label therapy, which on label is prescribed for the treatment

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<sup>73</sup> See F. Massimino, *La prescrizione dei farmaci “off label”: adempimenti, obblighi e responsabilità del medico*, quoted, 934 f.

<sup>74</sup> Our translation. The original text is the following: “*Chiunque cagiona danno ad altri nello svolgimento di un’attività pericolosa, per sua natura o per la natura dei mezzi adoperati, è tenuto al risarcimento, se non prova di avere adottato tutte le misure idonee a evitare il danno*”.

<sup>75</sup> See Cass. 19<sup>th</sup> May 2004, no. 9471; Cass. 28<sup>th</sup> May 2004, no. 10297; Cass. 21<sup>st</sup> June 2004, no. 11488, in *Danno e responsabilità*, 2005, 23, commented on by R. De Matteis, *La responsabilità medica ad una svolta?*, and Cass. 30<sup>th</sup> October 2001, no. 13533, in *Giustizia civile*, 2002, I, 1934.

<sup>76</sup> See Cassazione 13<sup>th</sup> April 2007, no. 8826, quoted.

<sup>77</sup> See also See F. Massimino, *La prescrizione dei farmaci “off label”: adempimenti, obblighi e responsabilità del medico*, quoted, 937.

<sup>78</sup> Cassazione 13<sup>th</sup> March 2008, no. 17499, in *Foro italiano*, 2008, 376. The decisions of first (Tribunale di Genova, 6<sup>th</sup> December 2004, no. 1052) and second instance (Corte d’Appello di Genova, 9<sup>th</sup> May 2006), to our knowledge, are not published.

of prostate cancer in male patients, was held criminally liable. Following the therapy, the patient died of fulminant hepatitis.

In this decision, the Supreme Court stated that the professional negligence of the doctor consisted in having prescribed an off label use of a drug having serious side effects on liver function and that for this reason has been allowed only in the treatment of prostate cancer.

Therefore, the doctor subjected the patient, a patient who was not suffering of a serious disorder and one which was otherwise curable, to a significant risk of poisoning. Further, the death could not be considered as exceptional, since the statistic was not significant due to low experimentation on females. Furthermore, flutamide was not very useful for a radical cure of the disease suffered by the patient, *i.e.* polycystic ovary syndrome, as it acted on the secretion of gonotropine while producing antiandrogenic action: that made unlawful this off label prescription, since the use of a drug not approved for a specific treatment can only be lawful when there are no alternative tested treatments (and in this case contraceptives were more confident) and the patient has given his/her informed consent.

The analysis of the decisions previously rendered by the Courts of first and second instances might be useful to understand the topics which has been deepened by the Supreme Court.

The Genoa Tribunal condemned the doctor in first instance for manslaughter.

Against this decision, he appealed arguing that he had prescribed flutamide for the treatment of hirsutism after sound consideration of the pros and the cons of his decision, since the onset of hepatitis was found in only one per cent of cases in relation to even triple doses of the above mentioned substance. After the first application cycle the patient had been completely healed and in perfect condition, and only during the second treatment, which had been requested by the patient herself due to the reappearance of some pimples on her face, fulminant hepatitis had manifested itself.

Moreover, he said, the patient had been fully informed of the side effects caused by the use of the recalled drug especially since she was suffering from the disease of polycystic ovaries that could affect the reproductive system. Besides, he had tried to prescribe “Mercilon”, a contraceptive drug, but it had revealed itself to be ineffective since clinical signs had continued.

The doctor stated also that flutamide was used in gynaecology as an anti-androgen, at doses lower than those indicated for the treatment of prostate cancer. Therefore, according to the doctor, the hepatitis had been an exceptional event, so the court had erroneously considered the predictability of it.

In addition, according to the doctor, the patient had consented to the treatment, and in fact it was she who had requested a different treatment as opposed to the one based on “Mercilon” on which she had been treated for over two years but had not given results. Also, in relation to the choice of drug to be used in this particular case, a further possibility, a drug called “Diane”, which was indicated by first-

instance experts, would have posed the same risk and the use of flutamide had been sufficiently tested in gynaecology without major problems, being found toxic only in men.

The Court of Appeal dismissed the appeal alleging that the information given to the patient was not clear and exhaustive; that it would have been more prudent to give another type of contraceptive pill than the one already used by the girl, like “Diane”; that experience concerning the use of the drug was limited, particularly its consumption by women. Therefore the risk of side effects was not fully known due to poor testing and a better assessment should have been carried out before the prescription.

Furthermore, it was not enough to verify whether the young patient was in good health at the beginning of the off label treatment, but more thorough examinations and tests were needed also and especially after the first treatment cycle.

Regarding the existence of a causal link, the Court assessed that the fulminant hepatitis had been caused by the administration of flutamide, because the patient did not assume other potentially hepato-toxic drugs and the same information referred to by the leaflet of the drug warned against the possible occurrence of severe liver damages.

In substance, the fault emerged because the doctor had used a drug recently tested, toxic, without preventive controls on the functioning of the patient's liver, its possible allergic reactions and also for the treatment of disorders of little importance (hirsutism).

Finally, as said before, the Supreme Court confirmed the professional negligence of the doctor and, as a result, his liability.

The above mentioned decision is not particularly innovative for the assessment of causal link, since it is strictly connected with the Italian dominant case law establishing the judge's duty to arrange the entire available evidence and to condemn where there is not any possible alternative factor to have caused the effect<sup>79</sup> and, in this case, as above referred, it was assessed that the patient did not take other potentially hepatotoxic drugs (such as flutamide)<sup>80</sup>.

It is rather important to stress the assessment of a doctor's negligence.

Firstly, an aspect is that the physician did not precede the administration of the off label treatment with an accurate evaluation of the patient's physical conditions nor did the physician control the evolution of them.

Secondly, and probably more importantly, the physician opted for an off label treatment which, however, was not very useful in curing the specific disease.

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<sup>79</sup> Cassazione, Sezioni unite, 11<sup>th</sup> September 2002, no. 30328, in *Danno e responsabilità*, 2003, 195, commented on by S. Cacace, *L'omissione del medico e il rispetto della presunzione d'innocenza nell'accertamento del nesso causale*.

<sup>80</sup> But for a critique see A. Roiati, *La somministrazione di farmaci in via sperimentale tra consenso informato ed imputazione colposa dell'evento*, in *Cass. pen.* 2009, 2382 ff., according to whom the assessment of the causal chain should have deepened further and should not have been limited to general causation.

Thus, the Court did not express itself against off label treatments; on the contrary, it stated that off label treatments are lawful in so far they can produce a more effective result than an on label treatment. In the case previously examined, there was a lack of scientific data showing these more effective expected results, therefore an off label treatment is not allowed, falling under the category (and the limits) of experimentation.

Another decision rendered immediately after the above mentioned by the Supreme Court substantially conformed to the principle previously expressed.

In this case a doctor had prescribed high dosages of an antiepileptic medicine (in Italy called “Topamax”) within a therapy for obesity, without adequately monitoring the patient, who was also a minor (a twelve year old girl), and without estimating the reasons for the lack of a positive reaction to inferior dosages<sup>81</sup>.

The first-instance judge assessed that the off label use of the drug, in order to let a paediatric and obese patient lose weight, by trying to take advantage of one of its possible side effects (the anorexic effect), was not supported by publications in scientific reviews credited in the international field. Consequently, this kind of therapy should have been considered clinical experimentation.

Furthermore, it was ascertained that the above mentioned administration of the drug was not preceded by the divulgence of adequate information to the minor’s parents, that other medical alternatives had not previously been searched and that a by far increased dose, with respect to the one recommended by the pharmaceutical company (200 mg/*die* rather than 25 mg/*die*), had been administered, without first following a slow progression and without any control about the possible side effects on the child.

The physician carried on in the administration of the drug although the parents of the minor had represented the existence of side effects, in particular a nervous disease culminating in headaches, sleepiness, nightmares, depression, excitability and a single episode of hallucination, as well as physical disturbs such as calculus and ophthalmic disturbs for more than forty days.

Thus, the judge concluded therefore that the doctor was conscious of the fact that the administration of the drug, beyond the probable and hoped benefit consisting in the loss of weight, could also have produced (as then it effectively produced) a damage to the physical integrity of the child.

In addition, the doctor did not monitor the side effects of the drug.

The judge therefore stated that the doctor had accepted the risk of these ulterior effects of the off label therapy and that she was criminally guilty not for accidental injuries, but for malicious injuries (on this original but not shared solution see below)<sup>82</sup>.

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<sup>81</sup> Tribunale di Pistoia, 24<sup>th</sup> November 2005, in *Corriere del Merito*, 2006, 621, commented on by A. Bassi and in *Rassegna di diritto farmaceutico*, 2006, 755.

<sup>82</sup> For a critique of this reconstruction see A. Roiati, *La somministrazione di farmaci in via sperimentale tra consenso informato ed imputazione colposa dell'evento*, quoted, 2382 ff.

Regarding the causal link between the administration of the therapy and the damages suffered by the victim, the judge ascertained that not all of them had been caused by the illicit medical conduct. In any case, since the doctor did not show the existence of possible alternative causal factors, the judge concluded that the causal nexus was proved. Yet, those side effects are not merely possible but should be considered as probable, since they are specifically described by scientific literature.

Contrary to this statement, the Court of Appeal of Florence<sup>83</sup> and, finally, the Supreme Court<sup>84</sup> decided to reduce the charge, opting for the crime of accidental injuries.

The courts observed that the products made up of topiramate (like the “Topamax”) were regularly in commerce to cure epilepsy with the indication of a loss of weight as one of the secondary effects. Besides, the prescription made up by the physician was based on studies already published at that time, which were subsequently totally confirmed: therefore, the above mentioned drug prescription could not be considered as a pure experimentation, since there were scientific publications specifically related to the use of the collateral effects of the drug. Furthermore, before attempting cure with the drug in question, other and more traditional roads had been tried, among which diets, but with insufficient results.

Notwithstanding, the behaviour of the doctor had been imprudent in the choice of the drug for the disturbance of the alimentary behaviour of the minor and negligent in the choice of the therapeutic dosage (since the age of the patient had not been taken into account) and the cause of the alimentary disturbance of the minor had been psychological.

Therefore, the Court of Appeal and the Court of Cassation concluded that the intentional behaviour of the doctor, characterised by the will to cause lesions, even if the same lesions were known as possible side effects of the therapy, had not been proven.

There emerged, instead, a culpable behaviour of the doctor, who had not observed, imprudently and negligently, the protocol to which the off label uses of the topiramate were subordinated (adequate informed consent, with exact indication of the possible side effects of the drug and a continuous monitoring of the conditions of the minor, especially during the treatment).

Finally, the Supreme Court, adhering to the reasoning of the Court of Appeal, stated that a doctor, who prescribes an off label therapy, is liable for the damages negligently caused to the patient, where s/he did not conduct a careful comparative appraisal between the pursued benefits and the risks connected to the particular use of the drug based on a review of the clinical situation of the patient.

The last mentioned passage of this decision seems particularly important: in a very agreeable way, the decision emphasised that the duty to monitor the patient, which is absolutely central in the doctor-patient relationship, is even more important in cases of off label prescription of drugs. In fact, the

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<sup>83</sup> Decision which, to the best of our knowledge, has not been published.

<sup>84</sup> Cassazione 24<sup>th</sup> June 2008, no. 37077, quoted.

adopted therapeutic off label choice made by a doctor, which is not, in itself, as stressed by the Court, a negligent choice, since the previous therapies did not produce any useful result, must always pursue the benefit of the patient, and this set aside the observance of the risk-benefit relationship that passes through a careful appraisal of the clinical data.

In any case, probably the most important aspect that should be considered is the maliciousness of the medical conduct assessed by the first-instance judge and rejected by the Court of Appeal and the Supreme Court.

This is neither the first nor a unique Italian court case of voluntary responsibility in the off label administration of medical treatments.

Some years beforehand, the Tribunal of Milan<sup>85</sup> affirmed the criminal liability of a doctor, according to Art. 582 of the penal code which punishes voluntarily inflicted personal injuries, since the doctor had applied a therapy outside the scope of a particular protocol accepted by the scientific community and, also, in absence of the explicit consent by the patient.

The case heard by the Tribunal of Milan, therefore, is partially different from the one analysed by the Tribunal of Pistoia, where theoretically the requisites for the administration of an off label treatment were in play.

The reasoning of the Tribunal of Milan proceeded as follows.

The lack of the requisites for an off label treatment renders the same unlawful, lacking the curative purpose of the doctor. Thus, the lack of the informed consent does not concern a medical treatment as such, which by definition is accepted by the legal system since it is aimed at the patient's health, but a conduct, which is illicit, as with any personal injury.

Thus, since the medical conduct was only formally a therapeutic act, it was not possible to say that the result aimed at by the doctor was the health of the patient. Consequently, in lacking the patient's consent, the doctor's conduct is considered, as we have said before, just like a generic (voluntary) personal injury<sup>86</sup>.

Yet, this "revolutionary" reconstruction would have created the risk of over-deterrence on the part of doctors, forcing them to refrain from opting for off label treatments even in cases where, according to the above mentioned advice of 16<sup>th</sup> January 1998 of the Italian National Bioethics Committee, a doctor is not only authorised, but also bound to use alternative therapies, that is in cases where his/her patient faces life-threatening damages and there are no other realistic possible therapies officially accepted by the medical community.

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<sup>85</sup> Tribunale di Milano, 21<sup>st</sup> July 2000, no. 251, in *Bollettino italiano di farmacologia*, 2001, 134, cited by P. Minghetti, I. Palmieri, F. Selmin, *La terapia farmacologica in assenza di medicinali registrati per la patologia diagnosticata*, quoted, 993 ff. and by M. Zana, *Ai limiti della responsabilità medica: l'uso off label dei farmaci*, quoted, 732.

<sup>86</sup> F. Massimino, *La prescrizione dei farmaci "off label": adempimenti, obblighi e responsabilità del medico*, quoted, 934 seems to adopt a reconstruction in line with the one followed by the Tribunal of Milan.

Furthermore, the maliciousness theory is based on a very subtle distinction between “*dolo eventuale*” (implied malice), a state of mind sufficient to assess malice, even in the absence of a specific intent to harm, and “*colpa cosciente*” (recklessness), a case where intent to do harm is lacking but where the unreasonableness of the conduct makes it highly probable that harm would follow<sup>87</sup>.

To our mind, the above mentioned slight difference is not only not adaptable for the timing and the procedures of medical activities, but even in contrast with the Hippocratic duty to do no harm to which doctors are bound and which excludes, in such cases, the existence of a will, although merely implied, to harm the patient.

## **9. The American experience: the approval process of a new drug**

In the United States, where, similarly to Europe, the percentage of off label prescription is quite elevated<sup>88</sup>, firstly the Federal Food and Drug Act, enacted in 1906, prohibited misleading labeling. Later on, the Food Drug and Cosmetic Act of 1938<sup>89</sup>, amended in 1962 following the Thalidomide disaster, first required drug companies to label pharmaceutical products with various directions and warnings, among which a complete information regarding approved use and risks was to be included<sup>90</sup>.

It also forbade new drugs from being sold unless they had passed tests for safety and efficacy. Physicians were allowed, however, to prescribe an FDA-approved drug not only for its on-label use, but also for other off label uses. Therefore, the FDA was given absolute authority to examine the scientific evidence concerning the safety and efficacy of drugs<sup>91</sup>.

Today, the Federal Food, Drug and Cosmetic Act (“FDCA”) of 2000 authorises the FDA to regulate the manufacture and marketing of drugs and medical devices. Under the FDCA, the FDA must license any “new drug” before it may be marketed<sup>92</sup>.

Currently, a new drug is first studied in animals during “preclinical” trials and, if the drug demonstrates potential usefulness, the sponsor (usually a pharmaceutical company, an academic research centre, or

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<sup>87</sup> In the Italian literature, among others, see G.A. De Francesco, *Dolo eventuale e colpa cosciente*, in *Rivista italiana di diritto e procedura penale*, 1988, 113 ff. and, more recently, F. Agnino, *La sottile linea di confine tra dolo eventuale e colpa cosciente*, in *Giurisprudenza di merito*, 2009, 1489 ff.

<sup>88</sup> See, among several, S.H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 *Minn. J.L. Sci. & Tech.* (2008) 61 and K.A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 *Fordham Intell. Prop. Media & Ent. L.J.* (2007) 117, 122.

<sup>89</sup> For an outline of the previously provided regulation, see J.A. Wilsker, *Note and Comment: One-Half Phen in the Morning/ One Fen Before Dinner: A Proposal for Fda Regulation of Off-Label Uses of Drugs*, 6 *J.L. & Pol'y* (1998) 795, 800-802.

<sup>90</sup> See generally, R.A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 *Virginia Law Review* (1996) 1753-1866, G.W. Evans, A.I. Friede, *The Food and Drug Administration's Regulation of Prescription Drug Manufacturer Speech: A First Amendment Analysis*, 58 *Food Drug L.J.* (2003) 365-437 and K.A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, quoted, 117, 125 ff.

<sup>91</sup> See M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 973.

<sup>92</sup> 21 U.S.C. § § 301-399 (2000). See A.E. Blackwell, J.M. Beck, *Drug Manufacturers' First Amendment Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 *Food Drug L.J.* (2003) 439 ff.



another research entity) submits an Investigational New Drug Application (IND) to the FDA, which reviews INDs for safety, the scientific quality of the proposed clinical trials, and the plausibility of eventual approval<sup>93</sup>.

The evaluation of the drug must pass three phases of clinical trials before being approved by the FDA for marketing and distribution<sup>94</sup>, which takes usually seven to eight years.

During Phase 1, the experimentation involves twenty to eighty human volunteers “to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness”<sup>95</sup>.

The purpose of the subsequent Phase 2 study is to “evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug”<sup>96</sup>.

Finally, Phase 3 trials involve studies with several hundred to several thousand human volunteers, with the aim “to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labelling”<sup>97</sup>.

Thus, after following the above mentioned steps, if trials indicate that the drug is safe and effective for patients with the targeted illness, the sponsor submits a New Drug Application (NDA) to the FDA.

The FDA can also clear a device by establishing its “substantial equivalence” to a device that is already being marketed legally<sup>98</sup>. According to the scholarship, the vast majority of devices are cleared for marketing in this way<sup>99</sup>.

Manufacturers of medical devices that are not substantially equivalent to any pre-existing device can also seek FDA marketing approval through the more lengthy and rigorous pre-market approval (PMA) process<sup>100</sup>.

Lastly, the manufactures may apply for an investigational device exemption (IDE), which subjects the device to clinical trials governed by FDA and supervised by an independent institutional review board (IRB)<sup>101</sup>.

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<sup>93</sup> See P.J. Zettler, *The Implications of Post-Phase 1 and “Off-Label” Treatment Use of Experimental Drugs: How Expansive Should Expanded Access Be?*, 18 Kan. J.L. & Pub. Pol’y (2009) 135, 138.

<sup>94</sup> See J.A. Wilsker, *Note and Comment: One-Half Phen in the Morning/ One Fen Before Dinner: A Proposal for Fda Regulation of Off-Label Uses of Drugs*, quoted, 806-810.

<sup>95</sup> See 21 C.F.R. § 312.21(a)(1) (2007) and P.J. Zettler, *The Implications of Post-Phase 1 and “Off-Label” Treatment Use of Experimental Drugs: How Expansive Should Expanded Access Be?*, quoted, 135, 139.

<sup>96</sup> See 21 C.F.R. § 312.21(b) (2007) and P.J. Zettler, *The Implications of Post-Phase 1 and “Off-Label” Treatment Use of Experimental Drugs: How Expansive Should Expanded Access Be?*, quoted, 135, 140.

<sup>97</sup> 21 C.F.R. § 312.21(c) (2007) and P.J. Zettler, *The Implications of Post-Phase 1 and “Off-Label” Treatment Use of Experimental Drugs: How Expansive Should Expanded Access Be?*, quoted, 135, 140.

<sup>98</sup> 21 U.S.C. §§ 360(k) (section 510(k) of the MDA), 360c(f),(i) (detailing 510(k) criteria); 21 C.F.R. §§ 807.81-807.100 (1997).

<sup>99</sup> J.M. Beck, E.D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, quoted, 71, 73. See there for further references about the approval processes.

<sup>100</sup> 21 U.S.C. § 360e; 21 C.F.R. §§ 814.1 - 814.84.

<sup>101</sup> 21 U.S.C. § 360j(g); 21 C.F.R. pt. 50; 21 C.F.R. §§ 812.1 - 812.150.

## 10. The off label use and prescription in the USA

Nonetheless, with very rare exceptions<sup>102</sup>, the off label prescription of drugs and medical devices is generally acknowledged, and the FDA itself has recognised the value and propriety of off-label use, for instance in 1982, when the *FDA Drug Bulletin* expressly stated that “once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labelling. Such «unapproved» or, more precisely, «unlabeled» uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature”<sup>103</sup>.

In fact, the Federal Food, Drug and Cosmetic Act also prohibits the FDA to “limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease”<sup>104</sup>. Therefore, it has been said that “the agency only regulates drug manufacturers, not doctors”<sup>105</sup>.

Therefore, physicians may prescribe an approved drug for indications or patient groups not included on the label or at dosages or consumption instructions not specified on the label<sup>106</sup>.

In this regard, Courts have found that “(b)ecause the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment”. Therefore, “(i)n some circumstances, an off-label use of a particular drug or device may even define the standard of care”<sup>107</sup>.

Coherently, Medicare, Medicaid, and private insurers reimburse for off-label uses (albeit conditionally) when there is some evidence to support such uses<sup>108</sup>. Yet, according to the opinion of some, federal legislation should “require that all insurers cover off-label drug use if the use is recognized in one of the standard reference compendia or in a national, peer-reviewed professional journal, thus universalizing and expanding the standard applicable to Medicaid and Medicare patients”<sup>109</sup>.

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<sup>102</sup> See R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 477, fn. 11, recalling the case of the criminal penalties imposed on physicians prescribing human growth hormone off label.

<sup>103</sup> 12 FDA Drug Bulletin 4-5 (1982), cited by J.M. Beck, E.D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, quoted, 71, 77.

<sup>104</sup> 21 U.S.C. § 396 (2000). See also R.C. Ausness, “There's Danger Here, Cherie!” *Liability For the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, quoted, 1253, 1259 and S.H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, quoted, 61, 69.

<sup>105</sup> A. Gregory, *Denying Protection to Those Most in Need: The Fda's Unconstitutional Treatment of Children*, 8 *Alb. L.J. Sci. & Tech.* (1997) 121, 127.

<sup>106</sup> R. Dresser, *The Curious Case of Off-Label Use*, *Hastings Center Report* 37, no. 3 (2007): 9-11 and M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 976.

<sup>107</sup> *Richardson v. Miller*, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000), quoted by M. Herrmann, P. Bownas, *Keeping the Label out of the Case*, 103 *Nw. U. L. Rev. Colloquy* (2009) 477, 486. See also J. Kamp, D.E. Troy, E. Alexander, *FDA Marketing v. First Amendment: Washington Legal Foundation Legal Challenges to Off-Label Policies May Force Unprecedented Changes at FDA*, 54 *Food Drug L.J.* (1999) 555, 558.

<sup>108</sup> R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 477. See also S. Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, quoted, 41, 43 and, more recently, J. Cohen, A. Wilson, L. Faden, *Off-Label Use Reimbursement*, 64 *Food Drug L.J.* (2009) 391 ff.

<sup>109</sup> See S. Hoffman, *A Proposal for Federal Legislation to Address Health Insurance Coverage for Experimental and Investigational Treatments*, 78 *Or. L. Rev.* (1999) 203, 216.

Nevertheless, currently in the United States the majority of States have coverage mandates for some off-label drug uses, some of them applying the mandate to off-label use in cancer treatment only, while others applying the mandate generally and others applying the mandate only to drugs used in treating life-threatening or chronic and seriously debilitating conditions<sup>110</sup>.

As it has been stressed, since a drug, once it is approved, is available for any purpose, the FDA encourages pharmaceutical industries to seek a narrow approved use, in order to minimise delays of release onto the market and to reduce the investment in research required to meet FDA standards for approval<sup>111</sup>. In addition, we must consider that the FDA approval process for a new use of a drug already on the market is extremely expensive and can take several years, therefore drug manufacturers often prefer to leave off-label drug uses unapproved<sup>112</sup>.

One scholar has distinguished three possible kinds of off label activities: respectively the off label use, prescription and promotion and marketing<sup>113</sup>.

The first consists in the use of the drug different in some way from the approved use and that can be defined as a “*de facto*” freedom of the patient. Probably for this reason it was not outlawed even prior to the legislation passed in 1997<sup>114</sup>, which liberalised the marketing of such use<sup>115</sup>.

As has been recalled above, an off-label prescription of drugs occurs when a doctor prescribes a drug in any manner that varies from the labelling specifications<sup>116</sup>. Though, also this departure from the therapeutic orthodoxy has been always permissible, being, as the Supreme Court has recognised, “*an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine*”<sup>117</sup>.

Coherently with that, finally, in January 2009 the FDA confirmed that “*(o)nce a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling*”<sup>118</sup>, even though that leaves

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<sup>110</sup> See the data referred to by L. Pickering Francis, *Legitimate Expectations, Unreasonable Beliefs, and Legally Mandated Coverage of Experimental Therapy*, 1 *Ind. Health L. Rev.* (2004) 213, 235.

<sup>111</sup> See M. Oates, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research Into Off-Label Uses of Pharmaceuticals*, 80 *N.Y.U. L. REV.* 1272, 1280 (2005) and S.H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, quoted, 61, 70.

<sup>112</sup> K.J. Stoffelmayr, *Products Liability And “Off-Label” Uses Of Prescription Drugs*, 63 *U. Chi. L. Rev.* (1996) 275, 277.

<sup>113</sup> S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, quoted, 188. See also R.C. Ausness, “*There's Danger Here, Cherie!*” *Liability For the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, quoted, 1253, 1254.

<sup>114</sup> See FDA Modernization Act of 1997 21 U.S.C. 301 (1997), so-called FDAMA. For an analysis see A.M. Murphy, *Open Forum: “It's Time to Make a Good Agency Better”: The Food and Drug Administration Modernization Act of 1997 and the First Amendment*, 53 *Food Drug L.J.* (1998) 603.

<sup>115</sup> S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, quoted, 189.

<sup>116</sup> R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 477.

<sup>117</sup> *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

<sup>118</sup> *Food & Drug Admin., Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* 3 (2009), available

vulnerable populations, such as terminally ill patients, “open to greater exploitation in the name of autonomy”<sup>119</sup>.

## **11. Informed consent and doctors’ liability for off label prescription in the USA**

Actually, according to widespread opinion, doctors are not even obliged to tell patients that the administered treatment is off label and failure to inform patients does not, in itself, constitute malpractice<sup>120</sup>.

Thus, there emerges a incomprehensible difference between clinical trials, where federal regulatory agencies have imposed the requirement to secure informed consent to patients and the context of off label treatments, where “federal regulatory agencies have done little to insist that physicians secure informed consent from their patients, instead leaving that task to state tort law”<sup>121</sup>.

This being said though, recently, the duty to disclose the off label nature of the treatment to a patient has been stressed by a scholar, who has simply recalled that in clinical trials “researchers are required to disclose the uncertainties and possible costs associated with trial participation. Similarly, patients should be given an opportunity to choose whether to accept the uncertainties and possible costs associated with some off-label uses”<sup>122</sup>.

As it has been stressed, “when a drug is prescribed off-label, it has not necessarily been proven effective at all in treating the patient’s condition and has certainly not been proven more effective than older, approved drugs”<sup>123</sup>. Thus, the off-label use might produce either a better result or on the other hand be detrimental for a patient, and the doctor himself/herself may not know whether it will help or harm the patient, who should be able to choose to undergo the off label treatment, or to be treated with the traditional one.

Therefore, according to an authoritative opinion<sup>124</sup>, patients should be left free to ask doctors to elicit information about off label uses and conflicts of interest<sup>125</sup>. On the other side of the same coin, another

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at <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf> (link), mentioned by M. Herrmann, P. Bownas, *Keeping the Label out of the Case*, quoted, 477, 481.

<sup>119</sup> As noted by R.F. Hall, *RESPONSE: Right Question, Wrong Answer: A Response to Professor Epstein and the "Permititis" Challenge*, 94 *Minn. L. Rev. Headnotes* (2010) 50, 61.

<sup>120</sup> S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, quoted, 190; J.M. Beck, E.D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, quoted, 71-104; M.I. Krauss, *Essay: Loosening the Fda's Drug Certification Monopoly: Implications For Tort Law and Consumer Welfare*, 4 *Geo. Mason L. Rev.* (1996) 457, 472. For the case law, please refer, among many, to *Femrite v. Abbott Northwestern Hospital*, 568 N.W.2d 535 (Minn. App. 1997) and to the decision mentioned in M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 1013 ff.. For a recent overview upon the development of the informed consent doctrine in the USA, see also M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 1008 ff.

<sup>121</sup> See L. Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 *Am. J. L. and Med.* (2002) 361, 362.

<sup>122</sup> R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 481. See the aforementioned article also for further references on this topic.

<sup>123</sup> M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 1013.

<sup>124</sup> M. Angell, *The Truth About the Drug Companies* 271 f. (2004), quoted by M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 1023 f.

scholar has put forward that, due to the nature of being a patient and the fact that the ordinary patient is unaware of the risks of off label prescribing, rather than putting the burden on a patient to enquire, the doctor should be required to affirmatively disclose any useful information about the off label nature of the treatment<sup>126</sup>.

In any case, it seems that that stressed by a scholar, albeit in reference to the liability of the manufacturer, *i.e.* that the duty to warn should be limited to all demonstrated risks associated with off-label drug uses, provides a point of agreement on the matter. Therefore, the doctor would not be liable for failure to warn about undemonstrated risks, even those of which s/he should have known<sup>127</sup>. This reconstruction is also aimed at the avoidance of refusal of the off label treatment by the patient after being informed of all the possible risks associated with it, even of those statistically irrelevant, with an obvious damage also for the patient himself/herself.

It seems important to note that there seems to be a predominant approach in the US debate according to which “*off-label practices should be liberated from most legislative and regulatory constraints*.”<sup>128</sup>.

At trial, the burden of proof rests with the prescribing physician to justify a deviation from the standard of care<sup>129</sup>. In this field, we should recall that the individual laws of the American States apply<sup>130</sup>.

Nevertheless, physicians will not be held liable if the off-label use is in compliance with the currently accepted medical practice in the community or with reliable medical research<sup>131</sup>: indeed, off-label use sometimes constitutes itself as the “best practice” standard of care<sup>132</sup> and, as one court has recently proclaimed, “*off-label prescriptions are now an integral part of the modern practice of medicine*”<sup>133</sup>.

At any rate, while a physician is never negligent merely for prescribing a drug for an FDA-approved purpose, if s/he prescribes a drug for off-label use, there is neither immunity nor “*per se*” negligence

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<sup>125</sup> Note, however, that, according to S.H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, quoted, 61, 63 f., the conflicts of interests are not the only cause of the phenomenon of off label prescribing, whose reason should be found in the learning patterns in the medical profession and in the deficiencies in the production and dissemination of clinical knowledge.

<sup>126</sup> M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 1023.

<sup>127</sup> See K.J. Stoffelmayr, *Products Liability And “Off-Label” Uses Of Prescription Drugs*, quoted, 275, 300.

<sup>128</sup> S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, quoted, 190, 220.

<sup>129</sup> J. O'Reilly, A. Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, quoted, 295, 318. See also, C.A. Moyer, *Recent Developments in Health Care Law: Off-Label Use and the Medical Negligence Standard Under Minnesota Law*, 31 *Wm. Mitchell L. Rev.* (2005) 927.

<sup>130</sup> See G.E. Bradford, C.C. Elben, *The Drug Package Insert and the Pdr As Establishing the Standard of Care in Prescription Drug Liability Cases*, 57 *J. Mo. B.* 233, 245 (September/October, 2001).

<sup>131</sup> See P. Chen, *Education or Promotion?: Industry-Sponsored Continuing Medical Education (CME) as a Center for the Core/Commercial Speech debate*, 58 *Food Drug L.J.* (2003) 473, 497 and M. Lynn Lakomy, *A Meaningful Choice: Two FDA Approved Drugs Are Combined to Perform Medical Abortions*, 18 *Women's Rights L. Rep.* (1996) 49, 59.

<sup>132</sup> See D. Fox, *Safety, Efficacy, and Authenticity: The Gap between Ethics and Law in Fda Decisionmaking*, 2005 *Mich. St. L. Rev.* 1135, 1165, mentioning the case of oncology.

<sup>133</sup> *Richardson v. Miller*, 44 S.W.3d 1, 14 (Tenn. Ct. App. 2000), mentioned by G.E. Bradford, C.C. Elben, *The Drug Package Insert and the Pdr As Establishing the Standard of Care in Prescription Drug Liability Cases*, quoted, 233, 244.

and common law negligence principles apply<sup>134</sup>. Therefore, the physician will be held liable only if the current state of research or customary medical practice impugns the off-label use<sup>135</sup>.

## 12. Off label marketing in the U.S.

Lastly, off label promotion and marketing consist in advertising drugs for purposes, to users, in dosages, or in combinations other than the FDA-approved ones, which has been permitted only recently<sup>136</sup>.

In the past, prior to 1997, every kind of off label marketing was prohibited<sup>137</sup>, due to concerns that, absent adequate, well-controlled clinical trials that have been reviewed and approved by FDA, it would have been impossible to know whether the drug truly worked<sup>138</sup>.

According to an opinion, the above mentioned restrictions show the FDA's paternalistic regulatory approach<sup>139</sup>.

Therefore, manufacturers were “forced to circumvent, or even violate, the law if they wished to inform physicians about beneficial off-label therapies (and make money from the increased sales of their products)”<sup>140</sup>.

Now, instead, drug companies, in providing the fulfilment of the conditions imposed by the law<sup>141</sup>, among which is the attainment of the FDA's approval of the new use within a specified time, are permitted to distribute physicians articles from peer-reviewed journals and reference books that have discussed off-label uses<sup>142</sup>. Furthermore, manufacturers may provide financial support to educational

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<sup>134</sup> See G.E. Bradford, C.C. Elben, *The Drug Package Insert and the Pdr As Establishing the Standard of Care in Prescription Drug Liability Cases*, quoted, 233, 246.

<sup>135</sup> M.I. Krauss, *Essay: Loosening the Fda's Drug Certification Monopoly: Implications For Tort Law and Consumer Welfare*, quoted, 457, 472.

<sup>136</sup> 21 U.S.C. § 360aaa (2000). See, among several, J. O'Reilly, A. Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 *Ann. Health L.* (2003) 295 and K.A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, quoted, 117, 152 ff. For a comparative analysis of the different regulations on drug marketing, see T. Stoltzfus Jostt, *ARTICLE: Oversight of Marketing Relationships Between Physicians and the Drug and Device Industry: A Comparative Study*, 36 *Am. J. L. and Med.* 326-342.

<sup>137</sup> See, among many, M. Oates, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research Into Off-Label Uses of Pharmaceuticals*, quoted, 1272, 1284 and C.J. Walsh, A. Pyrich, *Fda Regulation of Pharmaceutical Advertising: Fda Efforts To Control the Flow of Information at Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose*, 24 *Seton Hall L. Rev.* (1994) 1325-1369.

<sup>138</sup> See N.K. Plant, *Prescription Drug Promotion On The Internet: Tool For The Inquisitive Or Trap For The Unwary?*, 42 *St. Louis L.J.* (1998) 89, 95.

<sup>139</sup> D.M. Fritch, *Speak No Evil, Hear No Evil, Harm The Patient? Why The Fda Needs To Seek More, Rather Than Less, Speech From Drug Manufacturers On Off-Label Drug Treatments*, quoted, 315, 367.

<sup>140</sup> R.C. Ausness, *“There's Danger Here, Cherie!” Liability For the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, quoted, 1253, 1255. See also G.C. Smith, *Avoiding Awkward Alchemy - In the Off-Label Drug Context and Beyond: Fully-Protected Independent Research Should Not Transmogrify Into Mere Commercial Speech Just Because Product Manufacturers Distribute It*, 34 *Wake Forest L. Rev.* (1999) 963.

<sup>141</sup> See J. Rogers, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, quoted, 1429, 1441.

<sup>142</sup> D.M. Fritch, *Speak No Evil, Hear No Evil, Harm The Patient? Why The Fda Needs To Seek More, Rather Than Less, Speech From Drug Manufacturers On Off-Label Drug Treatments*, quoted, 315, 336 ff.

programs where speakers discuss off-label uses<sup>143</sup>. Off label speech is also perfectly legal if the speaker is not affiliated with the manufacturer<sup>144</sup>.

The aim of the reform, which began in the 80's<sup>145</sup>, was “to enable the drug industry to distribute the most reliable research to doctors, so patients could receive necessary treatments”<sup>146</sup>.

However, off label drug promotion, in some cases, is still considered a crime<sup>147</sup>. In particular, drug companies can be held liable for off label promotional activities if the promotional efforts induced doctors to claim reimbursements for uses not covered by Medicare and Medicaid<sup>148</sup>.

The restrictions on off label marketing activities by manufacturers led, in the late 1990s, to a federal court pronouncement holding that the above mentioned provisions were more restrictive than necessary since they limited too much the right to free speech provided by the First Amendment<sup>149</sup>.

On appeal, the case was dismissed without establishing clear constitutional boundaries for government restrictions on commercial speech concerning off label uses<sup>150</sup>.

Currently, the controversy seems to remain open<sup>151</sup>, also owing to the fact that, as has been stressed, “FDAMA was a compromise between those who believed that off-label promotion would allow the public access to potentially life-saving treatments and those who believed that off-label promotion and use of drugs posed a threat to public health”<sup>152</sup>.

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<sup>143</sup> R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 478.

<sup>144</sup> See R.F. Hall, E.S. Sobotka, *Inconsistent Government Policies: Why Fda Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, quoted, 1, 9.

<sup>145</sup> For an historical outline, see R.F. Hall, E.S. Sobotka, *Inconsistent Government Policies: Why Fda Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, quoted, 1, 23 ff., analysing the alleged inconsistencies of the regime which prohibits drug manufacturers to promote off label uses of drugs and concluding that off-label speech restrictions violate the first Amendment. On this topic see also R.C. Ausness, “There's Danger Here, Cherie!” *Liability For the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, quoted, 1253, 1324 ff.

<sup>146</sup> M.Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, quoted, 967, 982.

<sup>147</sup> See, among several, M.L. Adelman, C.N. Karuga, *Department: Legal Analysis: A Low Dose Prescription: Criminal Prosecution of Off-Label Drug Promotion*, 51 B.B.J. (2007) 17 and D. Bowen Matthew, *The Moral Hazard Problem with Privatization of Public Enforcement: The Case of Pharmaceutical Fraud*, 40 U. Mich. J.L. Reform (2007) 281, 320-327.

<sup>148</sup> See M. Buhay, *Symposium: Emerging Issues in Food and Drug Law: A National Conference for Lawyers, Policy-Makers, and Corporate Leaders: Comment: Off-Label Drug Promotion Is Lost in Translation: A Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell Its Products*, 13 J. Health Care L. & Pol'y (2010) 459, 473.

<sup>149</sup> *Washington Legal Foundation v. Friedman*, 13 F. Supp.2d 51 (D.D.C. 1998); *Washington Legal Foundation v. Henney*, 56 F. Supp.2d 81 (D.D.C. 1999). See also R.F. Hall, E.S. Sobotka, *Inconsistent Government Policies: Why Fda Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, quoted, 1, 10 ff.

<sup>150</sup> *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). See R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 478.

<sup>151</sup> In fact, according to M. Buhay, *Symposium: Emerging Issues in Food and Drug Law: A National Conference for Lawyers, Policy-Makers, and Corporate Leaders: Comment: Off-Label Drug Promotion Is Lost in Translation: A Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell Its Products*, quoted, 459, “constitutional adjudication regarding pharmaceutical manufacturers' First Amendment right to market and promote their products for off-label use is hardly a picture of clarity”. The Absence of Clear Rules is also stressed by J.E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J. Health Pol'y L. & Ethics (2010) 299, 316 ff.

<sup>152</sup> S. Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, quoted, 41, 50. See also J. O'Reilly, A. Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, quoted, 295, 302.

Furthermore, a balance, between the interest to diffuse any useful medical information above all in situations where medical data are scarce, such as in the case of orphan diseases<sup>153</sup> or in the search of children suitable therapies<sup>154</sup>, with the need to carefully evaluate the risks of an off label use of drugs, which can produce even serious damages to patients since the tests and scrutiny required under the approval process prevent drugs from being used in harmful ways<sup>155</sup> should be found.

To this regard, we might recall the decision rendered in an important, and already mentioned, case by the federal District Court, which found the distributions by manufacturers of reprints about unapproved off label uses of a drug to be constitutionally protected when a manufacturer makes a disclosure that the use had not been approved by FDA<sup>156</sup>. In addition, we find it useful also the disclosure of all possible factors that affect the assessment of the reliability of the reprinted article.

The commercial speech doctrine, on its turn, cannot be considered as a tool to avoid the imposition of any limit in the marketing of off label drugs. In fact, as Justice Breyer, in his dissent in *Western States*, has pointed out, “*the commercial speech test needs «a more lenient application» that reflects the need for distinctions among contexts, forms of regulation, and forms of speech*”. Otherwise, “*an overly rigid commercial speech doctrine will transform what ought to be a legislative or regulatory decision about the best way to protect the health and safety of the American public into a constitutional decisions prohibiting the legislature from enacting necessary protections*”<sup>157</sup>.

In its turn, also the Eastern District of New York, in *United States v. Caronia*<sup>158</sup>, stated that the FDCA's prohibition against encouragement of off label uses is an appropriate, and constitutional, government exercise in light of its interest in protecting public health, making it more difficult, as argued<sup>159</sup>, “*for drug and device manufacturers to prevail on a First Amendment defense in promotion of off-label cases*”, since “*although drug companies may purport to be only passing truthful, non-misleading information to physicians, the safety and efficacy of these off-label uses have not undergone systematic evaluation*”<sup>160</sup>.

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<sup>153</sup> See J. O'Reilly, A. Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, quoted, 295, 304.

<sup>154</sup> See A. Gregory, *Denying Protection to Those Most in Need: The Fda's Unconstitutional Treatment of Children*, quoted, 121-149, R.F. Hall, T.A. Braun, *Leaving No Child Behind? Abigail Alliance, Pediatric Products and Off-label Use*, 8 *Hous. J. Health L. & Pol'y* (2008) 271 and V.M. Salvemini, *Idiopathic Short Stature or just Plain Short: Why the Federal Government Should Regulate the Administration of Human Growth Hormone To Healthy Children*, 38 *Ga. L. Rev.* (2004) 1105.

<sup>155</sup> For an evaluation of the pros and the cons of off-label uses and marketing, see E.P. Lansdale, *Used as Directed? How Prosecutors Are Expanding the False Claims Act To Police Pharmaceutical Off-Label Marketing*, 41 *New Eng. L. Rev.* (2006) 159, 165 ff. Recently, though, the U.S. Department of Justice has applied the punishment provided for by the False Claims Act to off label promotion, stressing that such conduct induces physicians to prescribe drugs that result in the filing of false claims for reimbursement. Among many, see on this topic V.W. Girard, *Punishing Pharmaceutical Companies for Unlawful Promotion of Approved Drugs: Why the False Claims Act Is the Wrong Rx*, 12 *J. Health Care L. & Pol'y* (2009) 119.

<sup>156</sup> *Washington Legal Foundation v. Friedman*, 13 *F. Supp. 2d* 51, 74(D.D.C. 1998).

<sup>157</sup> 535 U.S. 357, 368-69 (2002), at 389 (dissenting opinion).

<sup>158</sup> 576 *F. Supp. 2d* 385 (E.D.N.Y. 2008).

<sup>159</sup> See M. Buhay, *Symposium: Emerging Issues in Food and Drug Law: A National Conference for Lawyers, Policy-Makers, and Corporate Leaders: Comment: Off-Label Drug Promotion Is Lost in Translation: A Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell Its Products*, quoted, 483.

<sup>160</sup> *Ibidem*.



Therefore, even though the ability of the Caronia decision to continue to stand is uncertain, it is easy to hypothesise that drug manufacturers should be urged to submit new drug applications for off-label uses to the FDA<sup>161</sup>.

Furthermore, on January 13<sup>th</sup> 2009, FDA announced the publication of the final version of a non-binding guidance for Good Reprint Practices for the Distribution of Medical Journal Articles or Scientific Reference Publications on off label uses guidance on Good Reprint Practices.

Those guidelines do not require drug companies to submit a new drug application for off-label uses discussed in the disseminated materials. On the other hand, they permit the distribution of peer-reviewed scientific articles that describe various off label uses, but at the same time imposing several conditions, such as the fact that the publication that is distributed should be published by an organization that has an editorial board that utilizes experts in the subject of the article under review and who are independent of the organization to review; should be peer-reviewed and published in accordance with the peer-review procedures of the organization. Besides, the article should not be in the form of a special supplement or publication that has been funded by one or more of the manufacturers of the product that is the subject of the article, the information must not be false or misleading, or inconsistent with credible evidence, nor should pose significant risk to the public's health<sup>162</sup>.

Conclusively, the principle which should emerge is that *“physicians should have access to the most recent information in order to provide the best care possible to their patients. But doctors must be able to rely on the information they receive from manufacturers, without suspicion that marketing goals are more important than the delivery of safe and effective healthcare”*<sup>163</sup>.

Therefore, a general ban of off label drugs marketing is not opportune nor legitimate. On the other hand, it should be found a balance between the aim to spread as much as possible the information on all possible uses of drugs and an exigency of caution, also because, as it was observed, drug manufacturers *“seek to reach the full market potential for the drug as soon as possible in order to recoup the large cost of drug development while the drug is still under patent”*<sup>164</sup>.

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<sup>161</sup> See again M. Buhay, *Symposium: Emerging Issues in Food and Drug Law: A National Conference for Lawyers, Policy-Makers, and Corporate Leaders: Comment: Off-Label Drug Promotion Is Lost in Translation: A Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell Its Products*, quoted, 486.

<sup>162</sup> See M. Buhay, *Symposium: Emerging Issues in Food and Drug Law: A National Conference for Lawyers, Policy-Makers, and Corporate Leaders: Comment: Off-Label Drug Promotion Is Lost in Translation: A Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell Its Products*, quoted, 487 ff.

<sup>163</sup> S. Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, quoted, 41, 68.

<sup>164</sup> See M. Gilhooley, *Drug Safety and Commercial Speech: Television Advertisements and Off-Label Uses*, 47 *San Diego Law Review* (forthcoming 2010), <http://ssrn.com/abstract=1535450>, 6.

### **13. Short conclusive reflections: off label prescription and scientific uncertainty**

Conclusively, the main difference emerging from the above comparative analysis between the Italian and the American system regarding off label prescription is the fact that the former leaves much less freedom to physicians.

One example is the fact that, while the Italian legislative regime poses several conditions, although not clear, for the same kind of prescription the American Federal Food, Drug and Cosmetic Act prohibits the FDA to “*limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease*”<sup>165</sup>.

Yet, we can say that much of the American health care policy is based on the concepts of individual autonomy and privacy, both for practitioners and patients.

Therefore, as a result of what has been previously observed, physicians are not bound by off-label restrictions<sup>166</sup>.

In addition, while informed consent is a requirement specifically imposed by Italian law, it does not seem to assume the same importance in American law, including American case law, probably due to the fact that off label prescription is such a current practice that neither presupposes a specific previous mention in the doctor-patient colloquium.

That seems to create a paradox, since patients receive the least protection, compared to “ordinary” medical treatments, in those cases where they may need it the most<sup>167</sup>.

Under an only seemingly paradox, but in reality coherently with that, we should recall the authoritative opinion, expressed by a distinguished American scholar, according to whom FDA control of the licensing of new drugs should be removed, or at least sharply curtailed<sup>168</sup>.

On the other hand, the opposite – and probably “extreme” – opinion is rather rare. According to it “*an off-label use of a drug should be regarded as a new drug that falls under FDA regulation*”<sup>169</sup>, but, as it has been recalled, “*such philosophical purity would probably flounder on the rocks of medical need and patient/physician desires*”<sup>170</sup>.

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<sup>165</sup> 21 U.S.C. § 396 (2000). See also E. Polubinski III, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, quoted, 991, 999.

<sup>166</sup> D. Mossman, J.L. Steinberg, *Promoting, Prescribing, and Pushing Pills: Understanding the Lessons of Antipsychotic Drug Litigation*, 13 *Mich. St. J. Med. & Law* (200) 263, 312.

<sup>167</sup> See L. Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, quoted, 361, 399.

<sup>168</sup> R.A. Epstein, *Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 *Minn. L. Rev.* (2009) 1, 4. For a very different opinion, see also Hall, *RESPONSE: Right Question, Wrong Answer: A Response to Professor Epstein and the "Permittis" Challenge*, quoted, 50 ff.

<sup>169</sup> J.A. Wilsker, *Note and Comment: One-Half Phen in the Morning/ One Fen Before Dinner: A Proposal for Fda Regulation of Off-Label Uses of Drugs*, quoted, 806, 844.

<sup>170</sup> Hall, *RESPONSE: Right Question, Wrong Answer: A Response to Professor Epstein and the "Permittis" Challenge*, quoted, 67.

Paradoxically, instead, the problem of off label marketing, which nowadays attracts much interest and is widely discussed in the American literature<sup>171</sup>, is not even considered in Italy, thanks to the absence of any rule dedicated to such an aspect. Therefore, we should reasonably conclude that at this time nothing prohibits Italian doctors and drug manufacturers to advertise off label drug uses.

This does not mean that the problems addressed in the two legal systems are not the same. The Italian experience of the “Di Bella” case, above mentioned, can be found in American cases narrated by Prof. Epstein<sup>172</sup>.

Besides, the recent multi-million dollar settlements between the federal government and several major pharmaceutical companies show that the current federal health care system is improperly paying claims through Medicaid and Medicare for off-label use of prescription drugs<sup>173</sup>.

Moreover, even assuming that the path of liberalisation is the most efficient in protecting patients, we must admit that the off-label prescription of drugs that have still not passed either through Phase I trials should not be allowed, since their toxicity is still under scrutiny<sup>174</sup>.

In addition, it might be opportune the development of protocols for reviewing off-label prescribing, including an objective assessment of the quality of the supporting data for an off-label use, an explanation of the proposed intervention, multidisciplinary review, patient consent, and an assessment of safety and clinical outcomes<sup>175</sup>.

Furthermore, as noted, the freedom to prescribe approved drugs for off-label purposes without the protection of long-term studies and FDA approval for the new use might be “*particularly dangerous with respect to diet drugs due to the willingness of society to try anything to find the «magical relief» for obesity*”<sup>176</sup>.

The off label prescription of drugs constitutes only an example, among the many that could here be recalled, to demonstrate the persistent presence of areas of scientific uncertainty, which sometimes are the legacies of the discovery of new scientific laws, that progress not only is not able to reduce, but that risks - only in appearance paradoxically - to extend.

Also for this reason the assessment of the causal link appears therefore much more complicated, frequently imposing on judges substantially to substitute it simply with an assessment of guiltiness.

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<sup>171</sup> Also because of some recent record breaking settlements resulting from criminal prosecutions for off-label marketing. On this point please refer to T. Szivos, *Recent Developments In Health Law: Select Recent Court Decisions*, 35 *Am. J. L. and Med.* (2009) 237-241. See also M.K. Loucks, *Pros and Cons of Off-Label Promotion Investigations and Prosecutions*, 61 *Food Drug L.J.* (2006) 577-583.

<sup>172</sup> R.A. Epstein, *Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, quoted, 1, 13 ff.

<sup>173</sup> See J.L. Herbst, *The Short-Sighted Value of Inefficiency: Why We Should Mind the Gap in the Reimbursement of Outpatient Prescription Drugs*, <http://ssrn.com/abstract=1664642>.

<sup>174</sup> See R.A. Epstein, *Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, quoted, 1, 19 and 31.

<sup>175</sup> To this regard see the procedure followed by the University of Pittsburgh’s School of Medicine and Pharmacy, cited by I. Hyun, *SYMPOSIUM: Law, Science, and Innovation: The Embryonic Stem Cell Controversy: Allowing Innovative Stem Cell-based Therapies Outside Of Clinical Trials: Ethical And Policy Challenger*, 38 *J.L. Med. & Ethics* (2010) 277, 283.

<sup>176</sup> See J.A. Wilsker, *Note and Comment: One-Half Phen in the Morning/ One Fen Before Dinner: A Proposal for Fda Regulation of Off-Label Uses of Drugs*, quoted, 806, 820, recalling the very famous case of “Fen-phen”.

However, we can conclude that the spaces of scientific uncertainty will produce an increase of off label drug prescriptions.

Yet, medical protocols and guidelines, although important in the identification of diagnosis and of therapy, as has been already stressed by authoritative Italian medico legal scholarship<sup>177</sup>, cannot be binding for professionals.

As recalled by an Italian medico legal scholar, the technological progress in the research of symptoms has arrived at such a development stage that, more and more frequently, behind a pathological case, medical science allows the discovery of more etiological factors<sup>178</sup>.

This can be seen, as exemplified by another medico legal scholar<sup>179</sup>, in the recent discovery of human genome, allowing the recognition of the hereditary origin of pathologies, which in the past were attributed only to exogenous factors<sup>180</sup>.

Science, at the end of the day, is an instrument less and less efficient to assess the interactions between pathological and biological factors conducive to pathologies and, consequently, in the search for therapies as well. That renders ever more necessary the personalisation of therapies.

Furthermore, the availability of off label treatments from thousands of doctors theoretically multiplies the possibility of finding more efficient therapies, compared to a situation where experimental treatments are limited to laboratories<sup>181</sup>.

In fact, an off label prescription in any case should be based on a careful evaluation of the pros and the cons of the administration of drugs (or therapies in general) whose efficacy has been demonstrated, even where the same is only partial, with drugs (or therapies in general) not fully experimented.

For instance, an off-label use may be the only treatment for seriously ill patients. The patients' critical situation, according to a shared opinion, might "*ex se*" ethically justify the treatment, while, for less seriously ill patients, off-label prescribing should have a stronger evidentiary basis<sup>182</sup>.

On the other hand, as has been illustrated, pharmaceutical companies would be "*insufficiently motivated to invest in detailed and controlled supplementary clinical research if off-label uses are already profitable*"<sup>183</sup>.

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<sup>177</sup> F. Introna, *Metodologia medico legale nella valutazione della responsabilità medica per colpa*, in *Rivista italiana di medicina legale*, 1996, 1323.

<sup>178</sup> F. Introna, *Il problema della causalità tra diritto e medicina*, in *Rivista italiana di medicina legale*, 1992, 7 f.

<sup>179</sup> A. Fiori, *La causalità nelle malattie professionali (Parte Prima)*, in *Rivista italiana di medicina legale*, 2006, 781 f.

<sup>180</sup> See, for an explanation of the problems faced by the law with pharmacogenomics, B. Evans, *What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?*, 61 *Food Drug L.J.* (2006) 753-794.

<sup>181</sup> S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, quoted, 197.

<sup>182</sup> R. Dresser, J. Frader, *Special Supplement: Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, quoted, 476, 481.

<sup>183</sup> K.A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, quoted, 117, 166.

Therefore, as one commentator has recently argued, physicians may even face malpractice liability for failing to provide an off-label treatment in cases where it would be more appropriate in comparison to on label treatment<sup>184</sup>.

Simultaneously, the problem moves into another sphere, *i.e.* the reimbursement of off-label uses and indeed into the area of denials for last-chance experimental treatments, which is very important, both in Italy (as the “Di Bella” case demonstrates) and in the United States, above all in the case of terminally ill patients<sup>185</sup>.

In this regard, the ordinary nature of off label prescription in current medical practice seems to have led, both in Italy and in the United States, to the provision of at least some coverage for off label uses of drugs<sup>186</sup>.

On the other hand, it is possible that the large increase of the number of prescription drugs dispensed in the United States, which between 1994 and 2004 reached nearly 68%, is at least “con-caused” by the rate of abuse of off-label drugs, growing nearly 80%<sup>187</sup>. In fact, as it has stated, “*more Americans abuse prescription drugs than the number who abuse cocaine, heroin, hallucinogens, Ecstasy, and inhalants, combined*” and, in particular, “*one out of five teenagers in America has abused, or is abusing, prescription drugs*”<sup>188</sup>.

Conclusively, we believe that our research has confirmed what has been authoritatively stated, that is, that the freedom to prescribe drugs cannot transform itself in an unrealistic ambition, based on experimentalism and empiricism, with the tendency to lead to a culpable complaisance<sup>189</sup>.

Otherwise, the risk is that the off label use of prescription drugs changes into, as it was stated, “*a regulatory black hole inhabited by a plethora of industry-sponsored, poorly designed, and biased clinical trials best characterized by selective outcome reporting, frequent conflicts of interest by clinical investigators, and a lack of substantive evidentiary basis for the purported effectiveness of off-label interventions*”<sup>190</sup>.

Lastly, in order to limit the potential damages provoked by off label treatments, it might prove useful, as has already been suggested<sup>191</sup>, the provision of a post-market surveillance system to detect adverse

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<sup>184</sup> J. Rogers, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, quoted, 1429, 1431.

<sup>185</sup> See S. Hoffman, *A Proposal for Federal Legislation to Address Health Insurance Coverage for Experimental and Investigational Treatments*, quoted, 203-273, stressing the need of a federal legislation according the same protection to all Americans. See also P.J. Zettler, *The Implications of Post-Phase 1 and “Off-Label” Treatment Use of Experimental Drugs: How Expansive Should Expanded Access Be?*, quoted, 135-173, who instead concentrates her attention on expanded access.

<sup>186</sup> See for the American situation L. Pickering Francis, *Legitimate Expectations, Unreasonable Beliefs, and Legally Mandated Coverage of Experimental Therapy*, quoted, 213, 235. For the Italian situation please refer to the case law recalled in the analysis of the “Di Bella” case.

<sup>187</sup> See J.L. Herbst, *The Short-Sighted Value of Inefficiency: Why We Should Mind the Gap in the Reimbursement of Outpatient Prescription Drugs*, quoted, mentioning the opening Statement of Senator Thomas R. Carper before S. Subcomm. on fed. fin. MGMT., on Mar. 3<sup>rd</sup>, 2010. See also the data on the abuse of psychotropic drugs cited by A.O. Burton, *Article: “They Use It Like Candy”: How the Prescription of Psychotropic Drugs To State-Involved Children Violates International Law*, 35 *Brooklyn J. Int'l L.* (2010) 453-513, raising (at page 492) a concern “*because the majority of psychotropic drugs are prescribed to children off-label, without the benefit of FDA-reviewed and approved evidence of safety and efficacy for pediatric use*”.

<sup>188</sup> *Ibidem*.

<sup>189</sup> See M. Barni, *La prescrizione dei farmaci: libertà terapeutica e responsabilità del medico*, in *Rivista italiana di medicina legale*, 1994, 557.

<sup>190</sup> See B. Patsner, *Marketing Approval versus Cost of New Medical Technologies in the Era of Comparative Effectiveness: CMS, not FDA, Will Be the Primary Player*, 3 *J. Health & Life Sci. L.* (2010) 38.

<sup>191</sup> Please refer to M. Gilhooley, *Drug Regulation and the Constitution After Western States*, 37 *U. Rich. L. Rev.* (2003) 901, 927.

reactions that are not detectable within the testing limits of reliable studies, with the possibility to establish a moratorium of the marketing, production, prescription and use of the drug<sup>192</sup>.

As the Institute of Medicine found, the limits of the approval process on the ability to detect the full risks of a new proposed drug are inherent in the system, which is aimed primarily at establishing efficacy rather than safety. Therefore, the pre-approval studies do not provide information on long-term exposure<sup>193</sup>.

*Although this work is the result of a joint work of the two authors, Luca Nocco is the author of paragraphs 1-2-5.2-6-8-9-10-11-12-13-14, Benedetta Guidi is the author of paragraphs 3-4-5.1-7.*

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<sup>192</sup> Actually, on September 27<sup>th</sup>, 2007, President George W. Bush signed the Food and Drug Administration Amendments Act (FDAAA), ushering in a new regime of postmarket authority for the Food and Drug Administration (FDA). Among other things, FDAAA authorized FDA to require labeling changes, postmarket studies, and Risk Evaluation and Mitigation Strategies. See on this point J.L. Bragg, M.P. Florence, *Symposium: Emerging Issues in Food and Drug Law: A National Conference for Lawyers, Policy-Makers, and Corporate Leaders: Symposium: Life with a Rems: Challenges and Opportunities*, 13 *J. Health Care L. & Pol'y* (2010) 269-283.

<sup>193</sup> IOM, *Comm. on the Assessment of the U.S. Drug Safety Sys., The Future of Drug Safety: Promoting and Protecting the Health of the Public* 171 (2007), quoted by Gilhooley, *Drug Safety and Commercial Speech: Television Advertisements and Off-Label Uses*, quoted.