Off-Label Prescription and How it is (Not) Regulated in China

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Abstract

Off-label prescription—the use of a drug outside the scope of its marketing authorization (MA) and the content of its summary of product characteristics (SmPC)—is a medical practice spread all around the world, China being no exception. Several reasons, mostly related to financial strategies from pharmaceutical companies, can justify the decision of not requiring an MA for a certain drug use. The main reason is the purpose of having a profit without taking excessive risks, either economic or legal. This paper will define off-label prescription, discuss the various reasons leading to it, describe the general framework of this practice in Europe and in the United States and analyze off-label prescription in China, describe its regulation (actually, the lack of it) in the Chinese legal system and comment on the actual practice by Chinese health care providers. To conclude, the paper will sustain that a regulation for off-label prescription is essential to clarify for doctors the requirements of lawful off-label uses, and thus protect patients from injuries resulting from risky of-label prescriptions.

Keywords: Marketing Authorization, Drugs, Off-Label Prescription, Medical Liability, China

I. Definition of Off-Label Prescription

Before launching a product in the market, pharmaceutical laboratories need to apply for authorization to the competent regulating office—in China it is the China Food and Drug Administration (CFDA), in Europe the European Medicines Agency (EMA) and in the United States the Food and Drug Administration (FDA)—which is designated as their marketing authorization (MA).

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The granting of the MA is based primarily on the materials submitted by the applicant—the pharmaceutical company—including all studies, tests and trials that the drug was submitted to. This assessment is essential to promote consumer safety—that is, patient safety—and this is the reason why the pharmaceutical sector is highly regulated. The strict and rigorous supervision to which pharmaceutical products are subjected is related to the awareness of the many dangers that can result from the use of substances that have not been properly tested, as indeed was proved by the famous Contergan-Thalidomide scandal, which led to the birth of thousands of seriously injured people that are still demanding compensations in courts nowadays. Therefore, in order to prevent harmful results deriving from unlicensed drugs, a very strict approval procedure was established and the most decisive step of this procedure is the granting of the MA. The MA is intended to demonstrate the quality, efficiency and certification of the drug and, ultimately, to balance the risks and benefits expected from its use.  

However, and despite the fact that the current authorization mechanism focuses entirely on patient safety, it does not provide any guarantee that the patient will not be injured. First of all, the MA does not assure that the drug is totally safe, even if taken under the conditions stated in it; secondly, the MA only covers the specific uses therein stipulated and does not certificate the drug’s safety in general terms.  

Besides being such a decisive step in the lifetime of a drug—*et pour cause*—the MA also operates as a kind of drug’s “identity card.” In fact, the drug’s therapeutic indications, its frequency, dosage, route of administration and type of patients are set by the MA in accordance with the material submitted by the manufacturer for approval. These indications are subsequently included in the leaflet that accompanies the drug, technically called the summary of product characteristics (SmPC).  

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3 Working Group of NSW Tag Inc., *Off-label Use of Registered Medicines and Use of Medicines under...*
the MA and the SmPC—constitute the “script” that the doctor must follow when prescribing any drug.

But occasionally doctors prescribe medications outside the scope of the respective MA and SmPC: for a clinical condition distinct from the one for which the drug was created and tested; with a different dosage or with a different frequency; introduced in the patient’s body by a different procedure (i.e., using a different posology or route of administration); or to a group of patients not envisaged by the clinical trials to which the drug was submitted. These various scenarios in which the drug is prescribed and used in different terms from those set forth in the MA and in the SmPC are called off-label prescription.

II. Justifying Reasons for Off-Label Prescription

A. MA and Off-Label Prescription

Some situations of off-label use are temporary and only exist while the drug is not authorized for that particular use; thus, the prescription is off-label as long as the MA is not granted.

This is the case with many therapeutic innovations that have arrived for physicians without being properly authorized previously by the authorities, since the MA’s grant can be too slow and bureaucratic to keep up with scientific advances. In a way, it is that very scientific development that fosters off-label prescribing, as science evolves so rapidly that the supervisory activities of the competent authorities can hardly keep up with it. “As such, there is a discrepancy between the actual medical ‘need’ and the authorization status of a product.”

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In some other situations the MA was indeed requested, but denied by the competent authorities for lack of scientific evidences to sustain the granting of the MA. If the pharmaceutical company cannot comprehensively provide clinical and non-clinical data regarding the efficiency and safety of the drug for that particular use, the MA will be refused based on an unfavorable risk/benefit balance. In the existing regulatory system the non-approval rate of MAs for innovative medicines is worryingly high, a factor that can undermine the development of new drugs and affect public health by depriving patients of the use of authorized drugs in due time. However, this is the price that we, as a society, have decided to pay precisely to protect public health from adverse drug reactions.

But the most common scenario relates to cases where the pharmaceutical company did not submit the MA request for all possible therapeutic applications that a drug may have. Two points should be noted. First, the MA is not given in general terms for all the hypothetical uses of a drug, but only for specific uses, for select patients and for particular medical conditions specified by the MA applicants. Secondly, the MA has to be requested and cannot be granted automatically (some legal orders admit the request to be made by a third party, different from the manufacturer, but usually this possibility works more on paper than in real life). Therefore, pharmaceutical supervising authorities cannot assign MAs ex officio to fulfill the market needs, for economic reasons or to satisfy therapeutic requirements, nor can they extend the MA’s content based on those same reasons. What happens is that sometimes, grounded on this set of arguments, doctors prescribe drugs out of the limits of their respective MA. This is so because many medications have in practical terms a broader spectrum of therapeutic applications, but not all of them are listed in the SmPC or included in the MA (rectius, they are not included in the SmPC because they are not listed on the MA).

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7 Cf. Feldschreiber, supra note 1; Obermann, supra note 2; Raposo, supra note 2; Wittich, Burkle & Lanier, supra note 2.

To broaden the MA’s scope would require a larger temporal, technical and human investment, which would translate into more studies and more clinical trials, in short, into a heavier financial burden, since authorization procedures are lengthy, bureaucratic, complex and extremely costly. So, frequently pharmaceutical companies decide to request the MA for a narrower list of indications, aiming to reduce economic and/or legal risks. Ultimately, the pharmaceutical company’s decision to invest in research regarding a therapeutic application will depend on financial reasons. Sometimes pharmaceutical companies are not interested in enlarging the MA’s scope of their drugs because they know in advance that their (huge) investment will not have its expected return, as it happens when drugs already settled in the market for that use are strong competitors regarding these new indications. The same disinterest applies to cases involving clinical trials in more vulnerable populations (children, elderly, pregnant women), for they raise extremely complex ethical and legal issues that pharmaceuticals want to avoid in order to prevent court condemnations and the payment of huge compensations. In other words, pharmaceuticals will only request for a new indication if they can have benefits from it without huge economic and/or legal risks.

B. Reasons for Not Requesting the MA

1. Complex Clinical Trials

Pharmaceuticals do not want to risk testing drugs in circles of individuals for whom clinical trials are particularly complex, such as children, the elderly and pregnant women. Consequently, many drugs are not authorized for these “hazardous” patients because of the liability risk. Therefore, off-label prescription is particularly common in pediatric, geriatric, and obstetric medicine.

To demonstrate those risks, let’s take the children’s case, for instance. The clinical trial cost is much higher, due to the need of proper experts and specialized equipment, and thus demands a higher investment. On the other hand, it is difficult to find eligible patients for each age range; therefore, the study takes much more time than when carried out in adults. The very process of approval for these studies is lengthy, complex and raises intricate legal and ethical questions given the child's inability to provide consent.

9 KCE, supra note 3, p. 10 ff.
For all these reasons, even when clinical trials are effectively carried out with pediatric patients, it usually occurs several years after the drug is already in the market.\textsuperscript{10}

These obstacles explain that one of the most common off-label uses carried out all over the world consists of prescribing drugs tested and approved only for adult patients to children. So—and despite the fact that many drug labels contain references such as “it is not indicated for use in children” or “the drug is only intended for use in adult patients”—this remains a common practice. In the United States, between 50\% to 70\% of the medicines prescribed for children are offered on an off-label basis; it seems that in Europe the numbers are similar, as shown by a study carried out in the Netherlands, according to which 92\% of the children hospitalized in the country were treated with drugs not authorized specifically for them.\textsuperscript{11} These same results seem to be valid for China. In a study that analyzed patients with renal diseases, aged 1 month to 18 years, admitted in the hospital between October 2012 and September 2013, it was concluded that half of them received off-label drugs.\textsuperscript{12} In another study from 2014, including 15 top-ranked Chinese medical facilities, the researchers came to the conclusion that only 3.95\% of the prescriptions referred to drugs specifically authorized for children.\textsuperscript{13}

2. Economic Risk for the Pharmaceutical Company

Pharmaceutical companies occasionally decide—for economic reasons and even business strategy—to invest only in a specific therapeutic use from the various ones that the drugs can aspire to.

As already underlined, the whole process of obtaining an MA is arduous and financially heavy, so pharmaceutical companies choose to invest (in clinical trials, related studies, data collection) only in uses that ensure a higher \textit{ratio} cost-benefit. So, they request


\textsuperscript{11} Dinah Duarte & Helena Fonseca, \textit{Melhores Medicamentos em Pediatria}, 39 \textbf{ACTA PEDIATRICA PORTUGUESA} 17 (2008).

\textsuperscript{12} Marchella Yasinta et al., \textit{Use of Off-Label Nephrology-Related Drugs in Hospitalized Pediatric Patients: A Retrospective Study}, 12 \textbf{WORLD J PEDIATR.} 236 (2016).

the MA only for those uses, even though they know the product could be successfully used for other medical conditions. Or, although they intend to request the MA for that specific use, they prefer to wait until they are aware of the drug’s outcomes and interactions. However, and despite the fact that the pharmaceutical company has not requested the MA according to all possible uses, the drug is still prescribed for conditions not included in its MA. Whenever that happens the drug is being used off-label. If the patient suffers an injury within an off-label treatment the pharmaceutical company will not be held accountable, unless it is proven in court that the company promoted such use or, despite being aware of it, did not prevent that use.\textsuperscript{14} So, usually the liability for those injuries falls on the doctor that prescribes off-label, in similar terms to any other case of medical liability.

The so-called orphan diseases are one of the conditions related to unprofitable risks. They are chronically debilitating diseases or life-threatening conditions considered to be very rare. According to European law, an orphan disease affects a maximum of 5 people out of 10,000. This is a definition from the European Commission—the definition thus included in Regulation (EC) n. 141/2000 of the European Parliament and of the Council of December 16, 1999 is similar.\textsuperscript{15} In Chinese law there is no definition of orphan or rare diseases, though their existence was acknowledged by the Drug Registration Regulation in 1999. Its definition only came out as a result of a group of experts’ consensus in the Expert Seminar on the Definition of Rare Diseases, held in 2010, according to which a rare disease affects less than 1 person in 500,000 or has a neonatal morbidity of less than 1 person in 10,000.\textsuperscript{16} Due to the reduced number of potential consumers, it is not profitable to invest in research and approvals for such a reduced sales expectation. So, for these patients there is no drug specifically tested nor especially authorized for them; thus, it is necessary to resort to other drugs, which are expected to produce the same desired effect. European


legislators created a legal framework to accommodate the needs of patients with rare diseases by promoting pharmaceutical research in this domain, such as Regulation (EC) n. 141/2000 and the creation of the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency. Likewise, in the Chinese legal system, some regulations were issued to promote the registration and approval of orphan drugs. This is the case of the New Drug Approval Regulation (1999), the Drug Registration Regulation (2007), and the Special Review and Approval Procedures for Drug Registration (2009). However, failures regarding their implementation by the CFDA have been pointed out and they can undermine their efficiency.\textsuperscript{17}

3. Economic Savings for the Patient or for the National Health Service

There are cases in which a drug for that particular medical condition effectively exists in the market, but is prohibitively expensive, which encourages the search for an alternative that is equally effective but economically less costly. The cheapest solution is generally the off-label prescription.

For instance, Lucentis (ranibizumab) is the authorized drug for treating age-related macular degeneration (AMD); however, many doctors are using Avastin (bevacizumab) instead, a medicine originally approved for colorectal cancer, lung cancer and breast cancer, because it also produces good results for eye edema. So, although originally licensed to treat certain types of cancer, this drug is currently used worldwide to treat AMD, usually with good results. Actually, both drugs are both monoclonal antibodies developed by Genentech and, in fact, Avastin was prescribed for age-related macular degeneration long before Lucentis was released into the market. Moreover, the price of Avastin is around 10 times less than the price of Lucentis, thus, this financial difference has pushed doctors to prefer Avastin over the duly authorized drug, leading to a worldwide generalization of this off-label use. The use of Avastin for AMD is also widely spread around China to fight the increased prevalence of this eye condition, estimated to affect more than 40 million patients in the country.\textsuperscript{18}

\begin{attribution}
\textsuperscript{17} Peipei Song et al., Rare Diseases, Orphan Drugs, and their Regulation in Asia: Current Status and Future Perspectives, 1 INTRACTABLE & RARE DISEASES RESEARCH 3 (2009).
\textsuperscript{18} Y-X Chen, Urgent Action Needed to Raise Public Awareness of Age-Related Macular Degeneration in China, 45 ZHONGHUA YAN KE ZA ZHI 389 (2009).
\end{attribution}
4. Pressure from Patients

Sometimes the pressure to prescribe off-label uses comes from patients and their families, due to the exponential increase of information about drugs made available to the general public by the Internet. This is a particularly common practice regarding patients with terminal illnesses, for whom the drugs properly marketed for their particular clinical situation do not produce satisfactory effects, and who are willing to take more risks in exchange for some comfort or a faint extension of their lifespan. Pressure from patients is considered one of the major reasons leading to off-label uses in China. It is a well-known fact that in China, patients and health care providers live in dispute, sometimes resulting in violence, and it is not unusual for patients to require, demand, and even force doctors to carry out a treatment, even if it is not the duly authorized treatment, occasionally in exchange for a financial incentive. Eager to avoid conflicts with patients, doctors easily give in to patients’ claims for more medication, even if that results in over-prescription.

III. The General Legal Framework of Off-Label Prescription in Western Countries

Prima facie off-label prescription cannot be considered necessarily unlawful and contrary to medical leges artis (although some scholars sustain otherwise and claim that it is an unlawful practice, based on the respective costs and risks). It is quite the opposite, since in many situations the off-label use is imposed by the very leges artis and the best standard of care.

22 See Feng Ma & Nan Lou, Chinese Regulation of Off-Label Use of Drugs, 68 FOOD AND DRUG LAW JOURNAL 189 (2013); see also Raposo supra note 2.
In addition, it does present several benefits. On the one hand, it offers a chance of recovery to patients who cannot rely on any authorized drug; thus, without the off-label use of a drug they won’t be able to receive any treatment. On the other hand, it should be noted that many on-label uses existing nowadays started by being off-label and it was exactly the previous off-label experience that opened the path to a subsequent MA request (this was the case of the use of aspirin for preventing heart attacks, a use that started as an off-label prescription). In sum, off-label prescribing should not be subject to a general ban because of its many benefits, especially in the absence of an especially authorized drug for that clinical condition. In a way, it is an inevitable phenomenon and even countries that traditionally opposed the off-label prescribing have come to alleviate this prohibition.

A. Freedom to Prescribe

The first steps in a drug’s life—research, manufacture and marketing—are strictly controlled by specialized authorities according to strict rules that apply in general terms. In contrast, drugs prescription, as indeed any field of medical activity, requires an evaluation of the specific case. It is true that sometimes the doctor is subject to the scrutiny of ethical and disciplinary liability rules applied by their respective professional association, as well as legal liability rules imposed by courts. But in any case the evaluation of the doctor’s conduct is grounded on the unwavering principle of freedom of prescription, which allows the doctor—and solely the doctor—to decide which one is the most suitable drug for the particular case. Indeed, whereas the preparation, promotion and marketing of a drug have detailed regulations, their prescription is left to physician’s free evaluation, as long as it is guided by the patient's well-being. The freedom to prescribe is a cornerstone of the medical profession, since the doctor has the right to establish the treatment he considers most appropriate, particularly including the prescription of the drug that seems most suitable for the respective clinical condition. This basic rule of medicine is upheld in many medical deontological codes around the world. Therefore, the doctor has the power to choose

freely which drug to use, without being compelled by the content of the MA, provided he complies with the goals of medical \textit{leges artis}. Consequently, if off-label prescription founds its justification in doctors’ freedom to prescribe, this means that any decision regarding off-label uses must be up to the doctor and not to hospital administrations, professional bodies or regulatory entities. Otherwise we would be facing off-label prescriptions dictated by reasons other than the welfare of the specific patient, which only his doctor can assess. In particular, we would take the risk of having prescriptions based on competitive or financial motivations, which should never influence health care provision.

In the United States, doctors’ freedom of prescription was taken to the extreme. In the North American legal system, off-label prescription is a legal practice that fits into the sole responsibility of practitioners, without the need to obtain the FDA clearance or even to inform the agency.\textsuperscript{25} In fact, for a long time regulators did not intrude in this domain,\textsuperscript{26} as can be confirmed by this statement from the FDA, taken from a document entitled “Use of Approved Drugs for Unlabeled Indications”:

\begin{quote}
  The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a 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 labeling. 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.\textsuperscript{27}
\end{quote}

This document is from 1982, but the same idea can be found in subsequent documents

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\footnotetext[27]{FDA (Food and Drug Administration), \textit{Use of Approved Drugs for Unlabeled Indications}, 12 FDA DRUG BULL (1982), http://www.cir care.org/ida/ftpdrugbulletin_041982.pdf (last visited March 20, 2016); Commenting the passive role of the FDA, see R. S. Stafford, \textit{Regulating Off-Label Drug Use: Rethinking the Role of the FDA}, 358 N ENGL. J. MED. 1427 (2008).}
issued by the FDA, such as the “Draft Guidance for Industry—Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices,” from 2011,\textsuperscript{28} and the “Off-Label and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet,” last updated in 2014.\textsuperscript{29} This position has been welcomed by the American Medical Association on the grounds that neither the FDA nor any other control entity can replace the physician’s discretion in the evaluation of the particular case. Even the Supreme Court supported this perspective, as can be demonstrated by its decision in the case Buckman Company v. Plaintiff’s Legal Commission, in which off-label prescription was defined by the Supreme Court as “an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.”\textsuperscript{30} Therefore, the U.S. Supreme Court recognizes a wide leeway for doctors when prescribing drugs, by accepting that they must act according to their best judgment, even if outside the MA’s scope.

\section*{B. Patient’s Safety in Off-Label Uses}

One of the major medical concerns nowadays is to ensure patient safety and address adverse effects. This is a pressing concern, as studies show that a relevant percentage\textsuperscript{31} of serious adverse events result from medication—the so-called adverse drug reactions—but in most cases they are not reported because doctors fear legal, disciplinary and ethical consequences. So, off-label prescription is frequently targeted as a matter of concern regarding patient’s safety and public health. Indeed, a drug’s level of safety in its on-label use cannot be transposed nor replicated for its off-label uses.

It is a fact that off-label uses do not necessarily lead to adverse events\textsuperscript{32} and, on

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{29} FDA, Off-Label and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices: Information Sheet (June 25, 2014), http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (last visited April 18, 2016).
\item \textsuperscript{30} Buckman Co. v. Plaintiffs’ Legal Comm. (98-1768), 531 U.S. 341 (2001), 159 F.3d 817, reversed.
\item \textsuperscript{31} Studies present different conclusions regarding the risk of adverse events in off-label prescribing. Cf. Obermann, supra note 2 at 11; R. W. Pretorius et al., Reducing the Risk of Adverse Drug Events in Older Adults, 1 AM. FAM. PHYSICIAN 331, 331 (2013); G. P. Velo & P. Minuz, Medication Errors: Prescribing Faults and Prescription Errors, 67 BRITISH JOURNAL OF CLINICAL PHARMACOLOGY 624, 624 (2009).
\item \textsuperscript{32} Vikram Gota & Jigeeshu V. Divatia, Off-Label Use of Drugs: An Evil or a Necessity?, 51 INDIAN JOURNAL OF ANAESTHESIA 767 (2015).
\end{itemize}
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the other hand, such effects may as well occur in the context of on-label prescriptions.\textsuperscript{33} But it is certain that the use of a drug that does not have the support of a wide range of studies and clinical trials dangerously increases the risk of adverse effects, even if the drug has an MA.\textsuperscript{34} In effect, the MA only checks the quality of the drug with regard to its specific uses and cannot be seen as a kind of general guarantee that the drug is safe. The threat to patient’s safety is particularly pressing because doctors fear to notify adverse events caused by off-label prescription—a procedure that could prevent many injuries—since the lack of clear requisites to conform to this practice puts them at a higher risk of being sued.

\textbf{IV. Off-Label Prescription in the Chinese Legal System}

One of the basic principles of law is that the lack of regulation of a certain practice leads to its legal admissibility, under an old and fundamental rule according to which what is not forbidden by law should be considered allowed. With regard to off-label prescription in particular, this is the general understating in most legal orders where there is no explicit regulation nor clear legal authorization of off-label drug uses. However, under Chinese law the rule seems to be the opposite, and in the absence of a norm expressly providing legal grounds to conduct, it is usually considered legally forbidden. This legal reasoning had been applied to off-label prescription, thus, since no law clearly authorizes it, doctors prescribing off-label risk being subject to a warning, being suspended from medical practice, or even having their medical license revoked by health authorities.

\textbf{A. The Regulation of Medical Practice in China}

Chinese regulation of medical practice, including drug prescription, is very scarce and it is spread amongst various statutes, even leading to different forms of liability.\textsuperscript{35}

\begin{itemize}
\item \textsuperscript{33} Jamie J. Coleman & Sarah K. Pontefrac, \textit{Adverse Drug Reactions 16 Clinical Medicine} 481 (2016).
\item \textsuperscript{34} S. M. Walton et al., \textit{Prioritizing Future Research on Off-Label Prescribing: Results of a Quantitative Evaluation}, 28 \textit{Pharmacotherapy} 1443 (2008).
\item \textsuperscript{35} For a general overview of medical malpractice regulation in the Chinese legal system, see X. Chao
\end{itemize}
Despite the dubious content of the existing norms, it seems that this practice is neither expressly authorized nor clearly forbidden.\textsuperscript{36} Actually, the only situation in which the off-label use is clearly banned in Chinese legal system concerns the use of injectable Chinese traditional medicines.\textsuperscript{37} However, most scholars sustain the unlawfulness of off-label prescription in China based on the reaction of Chinese authorities to this practice.\textsuperscript{38}

The cornerstone of the doctor’s activity is his freedom to prescribe, recognized in even broader terms than the ones found in Western legal orders. This huge margin of freedom is probably due to the understanding of the physician’s role in traditional Chinese medicine as someone that can make better decisions than the patient.\textsuperscript{39} Another justification for this very broad freedom is the fact that for a long time there was no distinction between prescription drugs and non-prescription drugs in the Chinese legal system, an idea that only came into place with the Provisional Rules on the Classification of Prescription Drugs and Non-Prescription Drugs from 1999.\textsuperscript{40}

The Measures for the Administration of Prescriptions\textsuperscript{41} (处方管理办法), promulgated by the Ministry of Health in 2007, are one of the core sets of regulations on drug prescribing. Curiously, the first draft of The Measures for the Administration of Prescriptions included a norm to regulate off-label prescription, namely imposing some requisites for its admissibility. However, the final version enacted in 2007 suppressed that provision and in its current version there is no specific regulation of this issue. But despite this omission, some of its provisions can be relevant for off label prescription.


\textsuperscript{37} Ma & Lou, \textit{supra} note 15 at 193.


\textsuperscript{39} Ma & Lou, \textit{supra} note 15 at 192.

\textsuperscript{40} Provision Rules on the Classifications of Prescription Drugs and Non-Prescription Drugs (SFDA Order No. 10) available at http://www.sda.gov.cn/WS01/CL0053/24524.html. [in Chinese].

For example, Article 6 of the Measures for the Administration of Prescriptions demands that “the usage and dosage of the medicines shall be written in accordance with regular usage and dosage on the instructions; where over-dosage is required, the reason shall be noted with doctor’s signature as the confirmation.” Therefore, the first part of the norm bounds the prescriber to the drug’s instructions, whereas the second part of it seems to allow at least a modality of off-label use—increase of the drug dosage originally approved for that drug—as long as a written justification is provided.

Another relevant provision of the Measures for the Administration of Prescriptions is Article 14, which states that:

> The prescriptions shall be given by doctors based on the requirements of medical treatment, disease-prevention, health care, norms of treatment and diagnosis, and indication of the instructions on such aspects as intended use, pharmacological mechanism, usage, dosage, side effects and precautions. Related laws, regulations and rules shall be strictly followed in prescribing medicines with toxicity or radioactivity.

The norm imposes the obligation of prescribing according to the information contained in the drug’s instructions, in the sense referred to in Article 9 of the Provisions on the Administration Drug Labels and Insert Sheets:

> A drug insert sheet shall include the significant scientific data, conclusions and information concerning drug safety and efficacy in order to direct the safe and rational use of drugs. The specific format, content and writing requirements of drug insert sheet shall be prescribed and issued by the State Food and Drug Administration.

Therefore, it can be understood as a ban on off-label prescription, since it does not seem to allow any kind of deviation from the label’s content.

In sum, The Measures for the Administration of Prescriptions are silent about off-label

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42 The Measures for the Administration of Prescriptions, supra note 42.
43 Id.
44 Id.
45 Also suggesting this hypothesis, see Ma & Lou, supra note 15 at 193.
prescribing, but they do contain norms connected with this issue, some apparently supporting off-label, while others seem to disapprove it. The question is still unresolved, since neither the events that surrounded the drafting of this norm, nor the remaining provisions of Chinese legal system, provide strong grounds for a conclusion to be obtained. Nonetheless, other existing regulations seem to reinforce the idea that off-label prescribing is legally allowed, although under certain conditions. One of the main regulations concerning medical practice is the Law on Practicing Doctors of the People’s Republic of China (中華人民共和國執業醫師法) from 1998 (henceforth “Law on Practicing Doctors”). However, it does not provide any norm regarding off-label prescription. It simply states that, “[d]octors shall use medicines, sterilizing drugs and medical equipment approved for use by relevant state departments” (Article 25) and that doctors will be found in violation of the law in case they use “medicines, sterilizing drugs and medical equipment that have not been approved for use” (Article 37(6)), which can lead to their medical practice being suspended or even revoked.47

B. Other Regulations Referring Off-Label Prescription

Increasing the problem’s complexity, the Provisional Rules on Oversight of Prescribing in Hospitals (promulgated by the Ministry of Health in 2010) prohibit unjustifiable off-label prescription, a ban that only makes sense on the acceptance that justifiable off-label prescription is permitted (although the Provisional Rules do not clarify what should be understood by “justifiable off-label prescription”).48

Furthermore, the Rules on Evaluation Standards for Full-Service Hospitals of Grade Three demand that third-grade full-service hospitals implement procedures aimed to rule off-label prescribing, which, once again, implies it to be a lawful practice.49 Apart from these general rules, various provinces created some kind of regulation and certain hospitals also issued their own guidelines on off-label prescription. However, many Chinese hospitals still lack internal guidelines or protocols and this void may create

47 Law on Practicing Doctors of the People’s Republic of China, supra note 46.
48 Ma & Lou, supra note 15 at 194.
49 Id.
a problem under Article 44 of The Measures for the Administration of Prescriptions. According to this article, “The medical institution shall establish the comments system for the prescription, and fill in the table for prescription comment (appendix 2), implement the dynamic monitoring and warning system of the prescription, record and publicize the unreasonable prescription, and prevent it from being used.” This norm must be read in conjunction with Article 45 of The Measures for the Administration of Prescriptions, which states, “The medical institution shall give warning to doctors who give abnormal prescription for three times or more and limit his prescription rights; doctors who still prescribe abnormal formula for another two times afterwards shall have their prescription rights cancelled.”

C. The Facts Surrounding Off-Label Prescription in China

Due to the inexistence of proper regulation, off-label prescription still raises several legal issues in China.

Let’s take the case of Avastin mentioned above, for instance. Many Chinese hospitals have been using Avastin for a long time to deal with AMD patients, but did not publicly disclose the fact due to the lack of proper regulation in off-label drug uses. Actually, authorities were even considering Avastin as a counterfeit drug because it was not submitted to the proper authorization procedure. In 2010, several patients (different accounts represent different numbers) from the Shanghai No. 1 People’s Hospital were reported to show adverse effects after the Avastin injection, although it is not clear if the reason was that the drug was counterfeited, or if it suffered some contamination during the repackaging for the eye injection, as it is likely to

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50 The Measures for the Administration of Prescriptions, supra note 42.
51 Id.
53 Cf. F. Wang et al., Acute Intraocular Inflammation Caused by Endotoxin after Intravitreal Injection of Counterfeit Bevacizumab in Shanghai, China, 120 OPHTHALMOLOGY 355 (2013); Hong-Bing Huang, Ying Pan & Tao Liu, Shanghai Eye Treatment Outbreak: Bevacizumab Therapy for AMD in China, 96 CLIN. EXP. OPTOM. 106 (2013); X. Sun, X. Xu & X. Zhang, Counterfeit Bevacizumab and Endophthalmitis, 365 N. ENGL. J. MED. 378 (2011).
happen during the drug’s manipulation. In the aftermath of this incident both the ones commercializing and using Avastin were criminally sanctioned, so the idea that off-label prescription was a sort of a crime spread amongst health care providers. Due to this many hospitals stopped providing off-label drugs, thus leaving many patients without any treatment or, in the cases in which off-label prescription was continued, it was done in secret. The social impact of this incident and the fear of legal consequences led to the general conviction that off-label use was forbidden by Chinese law.

Actually, the problem is not an eventual legal prohibition, but the total absence of legal norms regulating off-label prescription in the Chinese legal system, leading to legal uncertainty and to the misconception of the unlawful nature of this practice. European law also deals with the lack of proper regulation, though with two main differences: off-label prescription was never considered illegal and several member States have issued their own national regulations on this issue. Not even the fact that fake drugs are a huge problem in China can operate as an argument against off-label prescription, since the danger of counterfeit drugs can happen either in off-label uses or in on-label ones.

Regardless of those incidents, the fact is that off-label prescription is widespread around China, as demonstrated in a study published in 2013 and developed in general hospitals in Shanghai, in which the authors concluded that “[t]here were 459 cases (93.10%) of off-label drug use, and 47.64% of total therapeutic drugs prescribed were off-label.”55 Sometimes off-label uses were even publically recognized, as in 2004, during the SARS epidemic, when health authorities encouraged doctors to prescribe antibiotics above the regular dosage, i.e., off-label,56 in order to manage an increasing crisis in the domain of public health.57

D. An Attempt to Provide a Legal or Ethical Framework for Off-Label Prescription in China

Frustrated with the lack of regulation for off-label prescription, in 2010 a group

56 Chance, supra note 29.
of senior chief pharmacists from the Guangdong province disclosed a public letter aimed to establish a set of requisites for off-label prescription, in order to boost this practice in Chinese hospitals. The main recommendations were: i) the unavailability of an authorized drug meant the off-label use should be “irreplaceable for treatment of the patient”; ii) the use should be meant for therapeutic purposes, not research ones; iii) approval of the off-label use can be given by the hospital’s pharmacotherapy committee and by the hospital ethics committee; iv) reasonable medical evidence regarding the safety and efficiency of the off-label use are required; v) the patient (or his legal representative) must provide his informed consent. This document—named “Consensus on the use of medications for unlabeled uses”—is actually the first set of rules (though not legally binding) for off-label prescription in China.\(^5^8\)

More recently, several other documents came out, namely a working document from 2012 issued by the China Ministry of Health (currently named China National Health and Family Planning Commission), with the consensus of the Guangdong Province Pharmaceutical Association. In 2015, its content was put into a pharmacy textbook by the previously mentioned China National Health and Family Planning Commission. Those are, until now, the only governmental texts in this regards.\(^5^9\) Other relevant documents about off-label prescription come from the Guangdong Province Pharmaceutical Association itself: the 2014 Consensus on Management for Off-Label Drug Uses in Hospitals and the List of Off-Label Drug Uses grounded on evidence-based medicine, whose latest version is from 2015.\(^6^0\)

E. Medical Liability in Off-Label Prescription

Because there is no specific regulation regarding off-label prescription, its requisites are quite unclear and there is no entity in charge of controlling this practice. In particular, the entity responsible for approving drugs, the CFDA, does not intervene in this issue (just like FDA and EMA do not have any intervention in off-label prescription in


\(^6^0\) Id.
Despite the general rejection of this practice, the fact is that even when an injury results from an off-label drug use, Chinese patients rarely present a formal complaint, since most of them are voted to fail in court. Under Tort Law of the People’s Republic of China\textsuperscript{61} (Tort Law), medical liability for acts committed in hospitals falls on the hospital as a legal entity and not on individual physicians. So, patients have to sue the institution, which, quite often, amounts to suing the State—since most of the hospitals existing in China are State-owned—which tends to discourage patients.

Another question that arises in off-label drug uses concerns informed consent. Article 55 of Tort Law imposes the obligation to obtain informed consent for “special examinations” or “special treatments.” The norm states as such:

During the diagnosis and treatments, the medical staff shall explain the illness condition and relevant medical measures to their patients. If any operation, special examination or special treatment is needed, the medical staff shall explain the medical risks, alternate medical treatment plans and other information to the patient in a timely manner, and obtain a written consent of the patient; or, when it is not proper to explain the information to the patient, explain the information to the close relative of the patient, and obtain a written consent of the close relative.\textsuperscript{62}

The question to be clarified is the following: is off-label prescription one of those medical acts requiring informed consent under Chinese law? Based on its possible disastrous consequences, on the special requisites that should surround it and in the deviation from instituted rules, off-label prescribing should be considered a “special treatment” for the purpose of the already quoted Article 55, thus demanding the patient’s informed consent.


V. Conclusions

The Chinese Government can adopt measures in order to give a solution to the shortage of new drugs, namely, the implementation of incentives to encourage research in accordance with the existing needs and the promotion of investment, as it has been done in the EU and in the United States. However, not even these measures will be enough to put an end to off-label prescription.

The fact is that off-label prescription is encouraged by the various players involved in pharmaceutical decisions. On the one hand, we have the pharmaceutical companies that want their investment—which amounts to staggering figures—to have an economic return guarantee without taking excessive risks from an economic and legal standpoint. On the other hand, we have patients who require innovative drugs, but at the same time also request safe and effective treatments. This demand imposes a range of studies and clinical trials that necessarily delay the use of innovative medicines and increases their cost. To complicate this dilemma even more, the decision regarding the use of a drug for a certain group of patients or diseases (i.e., the range of the MA) is not made by the competent authorities, but by the MA applicant.

But the fact is that off-label prescription should not be banned, since sometimes it is the only solution for patients for whom there isn’t any authorized drug available or who do not experience good results with authorized drugs. So, if the alternative is to leave patients without any treatment, off-label prescription can be the lesser evil and even a therapeutic option imposed by the best medical standard of care. Therefore, the law should not prohibit it, but regulate it instead. The major risk does not came to off-label prescription but from the lack of proper regulation on off-label prescription.

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