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Affecting FDA-Regulated Products*

## Chinese Regulation of Off-label Use of Drugs

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This article examines the following three important aspects of the Chinese regulatory mechanism for controlling the off-label use of drugs: (i) the constraints on the right of physicians to prescribe off-label; (ii) the regulation of promotion of off-label use by manufacturers and distributors; and (iii) the imposition of tort liability for harm caused by off-label prescribing. Contrary to the relatively robust regulatory system that exists in the United States, China has significant gaps and weaknesses in its regulatory oversight of the off-label use of drugs.

In China, the practice of medicine is relatively less regulated. Physicians are not prohibited by law from prescribing off-label drugs. While tort remedies are available to patients harmed by off-label use, damage awards tend to be low. While the government prohibits drug advertisements for off-label use, the available penalties are too low to be a sufficient deterrent. Furthermore, the government largely ignores non-advertisement promotion. There are no regulations or standards other than the general requirement under consumer protection laws (which carry limited administrative penalties) that promotion cannot be false and misleading. Because of this regulatory failure, inappropriate off-label promotion and use are common and injured victims are left without adequate remedies.

To better address the problem of inappropriate off-label promotion and use, China should (i) regulate both drug advertisements and non-advertisement promotion under a standard requiring off-label use to have a sound scientific basis, (ii) introduce harsher regulatory penalties, and (iii) increase compensation available for victims of medical malpractice. Such reforms would not only discourage improper off-label use by introducing penalties (or increasing existing penalties) for improper promotion, but would also provide reasonable compensation for victims harmed by off-label use.

## I. BACKGROUND

Drugs are among the most highly regulated products in the world. In many countries, a drug product must demonstrate that it meets the safety, efficacy, quality and labeling standards set by a regulatory authority. Labeling standards usually require that the label contain a description of the drug, including information on its clinical pharmacology, indications, intended patient population, contraindications, warnings, precautions, adverse reactions, dosage and route of administration. Using a drug in compliance with its approved indications, intended patient population, dosage and route of administration is referred to as “on-label use.” “Off-label use,” by contrast, refers to the practice of physicians prescribing the drug for indications, patients, dosages or routes of

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administration not yet approved by the regulatory authority. The most common types of off-label uses are using drugs for unapproved indications or for an unapproved age group.

The off-label use of approved drugs is common in the U.S. It is estimated that between 40% to 60% of all prescriptions are for off-label uses.<sup>1</sup> Off-label use is especially prevalent in certain fields, such as pediatrics, oncology and psychiatry. Such prevalence can be attributed to the expensive, time-consuming and uncertain process for seeking approval for any potential use, which discourages manufacturers from seeking approval for all potentially beneficial uses.

Off-label use is not necessarily harmful. Some unapproved uses are based on solid scientific evidence and medical judgment. In addition, because an approved drug has been approved for a specific use, it has already met the general standards for manufacturing quality and purity. Indeed, if no approved effective treatment is available or if the proposed off-label use has sound scientific bases, off-label use may be in a patient's best interest. However, off-label use may pose risks that have not been fully evaluated in terms of safety and efficacy. Physicians may also prescribe off-label drugs without sufficient evidentiary basis. According to a paper that analyzed nationally representative data from the 2001 IMS Health National Disease and Therapeutic Index, the majority (73%) of off-label uses lack evidence of clinical efficacy and less than one-third (27%) are supported by strong scientific evidence.<sup>2</sup> The greatest disparity between supported and unsupported off-label uses was found among psychiatric prescriptions, with 4% of off-label uses having strong scientific support as opposed to 96% having limited or no support.<sup>3</sup> For example, atypical antipsychotic drugs have been commonly prescribed off-label despite the lack of evidence of efficacy supporting such off-label uses and the statistically significant risks associated with this class of drugs, including death, cardiovascular symptoms, movement disorders, fatigue, sedation, and weight gain.<sup>4</sup>

A robust regulatory mechanism should seek to increase access to off-label uses that have sound scientific bases while discouraging uses that lack such evidentiary bases. Such a system must also balance the roles of physicians, patients and drug manufacturers and distributors. The U.S., for example, has developed a comparatively robust regulatory system for controlling the off-label use of drugs. Under the Federal Food, Drug and Cosmetic Act (the "FDCA"), the Food and Drug Administration ("FDA") must approve drugs for safety and efficacy for their intended uses or indications before they can be distributed.<sup>5</sup> Physicians are free, however, to prescribe any off-label uses they deem to be appropriate.<sup>6</sup> They are not required to obtain informed consent and are only liable

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<sup>1</sup> See James B. Riley, Jr. & P. Aaron Basilius, *Physicians' Liability for Off-label Prescriptions*, HEMATOLOGY & ONCOLOGY NEWS & ISSUES, May-June 2007, at 24.

<sup>2</sup> See David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021 (2006).

<sup>3</sup> *Id.*

<sup>4</sup> See Alicia Maher et al., *Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults*, 306 JAMA 1359, 1365-66 (Sept. 28, 2011); Bridget Kuehn, *Questionable Antipsychotic Prescribing Remains Common, Despite Serious Risks*, 303 JAMA 1582 (Apr. 28, 2010).

<sup>5</sup> See 21 U.S.C. § 355(a), (d).

<sup>6</sup> FDA has stated that "once a drug or medical device has been approved or cleared by FDA, generally, health care professionals can lawfully use or prescribe that product for uses or treatment indications that are not included in the product's approved labeling." FDA, Draft Guidance for Industry - Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices (Dec. 2011), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>. "FDA recognizes that these off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care." *Id.*

for medical malpractice if their action departs from the reasonable physician standard.<sup>7</sup> A patient's remedy is otherwise limited. The FDCA does not expressly prohibit the promotion or marketing of off-label use by drug manufacturers.<sup>8</sup> Nevertheless, the government has pursued criminal and civil "misbranding" cases against manufacturers on the basis that off-label promotion is evidence that the manufacturer intended a use that was not approved by FDA and for which the drug's label fails to provide directions for use.<sup>9</sup> In particular, the government has used its authority over drug promotion to target drugs with a high degree of off-label use that lacks scientific support.<sup>10</sup> FDA has issued guidance on certain "safe harbor" forums in which scientific literature on off-label uses may be distributed lawfully.<sup>11</sup>

Though off-label use of drugs is also prevalent in China, and in similar practice areas like pediatrics, oncology and psychiatry,<sup>12</sup> China has not yet established a robust and

<sup>7</sup> The case law involving informed consent and medical malpractice claims based on off-label prescribing remains sparse. See Philip Rosoff et al., *Regulation of Physicians' Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 666-67, 671 (2011) (citing cases). The available case law suggests, however, that off-label prescribing is "a matter of medical judgment [that] subjects a physician to professional liability for exercising professional medical judgment" but is not a "material risk...which a physician should disclose to a patient prior to the therapy." *Klein v. Biscup*, 109 Ohio App. 3d 855, 864 (Ohio Ct. App. 1996). While courts and juries will differ on the reasonable physician standard, the American Medical Association policy recommends off-label prescribing only when such use is based on "sound scientific evidence and sound medical opinion." *H-120.988 Patient Access to Treatments Prescribed by Their Physicians*, AM. MED. ASS'N, available at <http://www.ama-assn.org/resources/doc/csaph/csaa-97.pdf>.

<sup>8</sup> See *U.S. v. Caronia*, 703 F.3d 149, 154-55 (2d Cir. 2012) ("The FDCA and its accompanying regulations do not expressly prohibit the promotion or marketing of drugs for off-label use.") (internal quotations omitted). Regulations under the FDCA do recognize that "promotional statements by a pharmaceutical company or its representatives can serve as proof of a drug's intended use." *Id.*

<sup>9</sup> The FDCA prohibits "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded." See 21 U.S.C. §331(a). Since 2003, the U.S. government has brought many "misbranding" cases against manufacturers for off-label promotion and has won billions in criminal and civil settlements. For example, in September 2009, Pfizer paid \$2.3 billion to resolve criminal and civil liability arising from its off-label marketing of Bextra and three other drugs. See Press Release, HHS, *Justice Department Announces Largest Health Care Fraud Settlement in its History* (Sept. 2, 2009), available at <http://www.hhs.gov/news/press/2009pres/09/20090902a.html>. The Second Circuit case, *U.S. v. Caronia*, has cast doubt on the validity of such prosecutions as it held that manufacturers have a First Amendment right to truthful and non-misleading promotion of lawful off-label use. See *Caronia*, *supra* note 8, at 51.

<sup>10</sup> For example, Neurontin, an anticonvulsant, had one of the greatest proportion of off-label uses among specific medications despite the fact that only 20% of its off-label use had strong scientific support compared to 80% with limited or no support. Radley, *supra* note 2, at 1023-24. In 2004, its manufacturer, Warner-Lambert, agreed to pay \$430 million to resolve criminal charges and civil liabilities in connection with its promotion of Neurontin for unapproved uses, including for the treatment of bipolar disorder, for which there was limited or no scientific support. See *Drug Maker to Pay \$430 million in Fines, Civil Damages*, FDA Consumer Magazine (July-Aug. 2004).

<sup>11</sup> FDA, 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 (Jan. 2009) [hereinafter "Good Reprint Practices"], available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>.

<sup>12</sup> See Jing Li, Woguo ertong yongyao wu cheng chao guiding jiliang [Over-prescription of Chinese Pediatric Medicines], ECON. INFO., Apr. 27, 2012 (noting statement by Xudong Ma, an official of the Ministry of Health, that approximately 50% of pediatric medications were prescribed off-label), available at [http://dz.jjckb.cn/www/pages/webpage2009/html/2012-04/27/content\\_43806.htm?div=-1](http://dz.jjckb.cn/www/pages/webpage2009/html/2012-04/27/content_43806.htm?div=-1); Xuehua Zeng et al., *Survey and Analysis on a Written Description of the Pediatric Drug External Use of Pediatric In-patient Department*, 6 CHINA MED. HERALD 113 (2011) (describing study showing that 45.6% of the prescriptions provided by the pediatricians of Shenzhen Longgang Central Hospital in the first quarter of 2010 were off-label); Liu Yongxiao, Kang zhongliu yao chao shuomingshu shiyong qingkuang pubian cunzai [Widespread off-label use of cancer drugs], HEALTH NEWS, June 29, 2012 (describing common off-label use of cancer drugs), available at <http://finance.china.com.cn/industry/medicine/yycg/20120629/836320.shtml>; Tao Sun et al., Chao shiyong zheng yongyao shuanren [Double-edge sword of off-label use], CAIJING (Aug. 26, 2012) (describing common off-label use of antipsychotics, anti-infective drugs, and cancer drugs).

systematic mechanism for regulating off-label use. Instead, the limited provisions related to off-label use are scattered among different statutes, national government regulations and local government rules. These provisions are usually expressed in simple and broad language with important terms that are left undefined.

In China, the China Food and Drug Administration (“CFDA”), which was formerly named the State Food and Drug Administration (“SFDA”) until the recent restructuring of the central government in March 2013, plays the key role in regulating drugs (including biological products) in China. SFDA used to be under the Ministry of Health. As a result of the recent restructuring, the Ministry of Health no longer exists. Instead, the Chinese government has created a Commission for Health and Family Planning. CFDA is now a ministry-level agency headed by Mr. Zhang Yong, who was appointed on March 22.<sup>13</sup>

## II. CHINESE REGULATION OF PHYSICIANS’ RIGHT TO PRESCRIBE OFF-LABEL DRUGS

The practice of medicine has been regulated by the Ministry of Health since the establishment of the People’s Republic of China in 1949.<sup>14</sup> However, the Ministry of Health did not take the first step toward establishing a modern regulatory system until the economic reform and political opening (*gaige kaifang*) initiated by Deng Xiaoping in 1978.<sup>15</sup> Traditionally, Chinese physicians had considerable discretion in determining treatment.<sup>16</sup> Consequently, when Western medicine was introduced to China, physicians had much more discretionary authority to prescribe than their counterparts in other countries.<sup>17</sup> Indeed, China did not distinguish between prescription drugs and non-prescription drugs until 1999.<sup>18</sup> The Physician Law, which was enacted in 1998, does not include any provision on the off-label use of drugs, although it does include a general requirement that physicians use drugs approved by the national regulatory authority.<sup>19</sup>

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<sup>13</sup> Since all of the rules and regulations discussed in this article were issued prior to March 2013, we will refer to the two government agencies using their former names, SFDA and the Ministry of Health.

<sup>14</sup> See Weisheng bu lishi yange yu zhineng [History and Function of the Ministry of Health], available at [http://news.xinhuanet.com/zhengfu/2003-02/26/content\\_746374.htm](http://news.xinhuanet.com/zhengfu/2003-02/26/content_746374.htm).

<sup>15</sup> For example, only in 1987 did the State Council promulgate the Regulation on Dealing with Medical Incidents to regulate medical practice and protect the rights of patients and medical staff. See Dean Harris et al., *Medical Malpractice in the People’s Republic of China: The 2002 Regulation on the Handling of Medical Accidents*, 33 J. L. MED. & ETHICS 456, 460 (2005) (describing regulatory background and history); see also Zhu Wang et al., *Yangge Dance: The Rhythms of Liability for Medical Malpractice in the People’s Republic of China*, 87 CHI.-KENT L. REV. 21, 28 (2012).

<sup>16</sup> Historically, there was no centralized training or regulation of TCM practitioners. See Theresa Schroeder, 11 PAC. RIM. L. & POL’Y J. 687, 689 (2002) (“The lack of regulation of TCM may be explained by its historical status as a cultural institution.”). The lack of regulation derives from the philosophy underlying traditional Chinese medical practice. See Qingkang Dai, *Informed Consent in China: Status Quo and its Future*, 6 MED. L. INT’L 53, 54 (2003) (“Traditional Chinese medicine was and is still regarded as the art of *Ren* (benevolence or humanity), and doctors took themselves as the benevolent Savior or Benefactor [and] got used to considering themselves as having the authority to make medical decisions on behalf of his patients rather than to advise them, and so to judge what was in the patients’ best interest.”) “Prescription” in the practice of TCMs traditionally refers to a physician creating or selecting a formulation. The patient then buys the TCM raw material or semi-processed TCMs to make the formulation at home.

<sup>17</sup> Dai, *supra* note 16, at 57.

<sup>18</sup> The Provisional Rules on the Classification of Prescription Drugs and Non-Prescription Drugs were promulgated in June 1999 and came into force in January 2000. See *Chufangyao yu feichufangyao fenlei guanli banfa* (shixing) (ju ling di 10 hao) [Provision Rules on the Classifications of Prescription Drugs and Non-Prescription Drugs (SFDA Order No. 10)] (promulgated by SFDA, June 11, 1999, effective Jan. 1, 2000) (P.R.C.), available at <http://www.sda.gov.cn/WS01/CL0053/24524.html>.

<sup>19</sup> *Zhiye yishifa* [Physician Law] (promulgated by the Standing Comm. Nat’l People’s Cong., June 26, 1998, effective May 1, 1999), art. 25, LAWINFOCHINA (last visited March 3, 2013) (P.R.C.). It sets forth a general requirement that physicians must not use unapproved drugs, but does not *prohibit* off-label prescribing.

The right to prescribe off-label remains lightly regulated at the national level.<sup>20</sup> While the Ministry of Health has promulgated measures addressing certain aspects of off-label prescribing, there is no national standard for the practice. Instead, off-label use has largely been left to individual provinces and medical institutions to regulate.<sup>21</sup> Off-label standards proposed by provinces and hospitals have included requiring a solid scientific basis for the off-label use, informed consent, and approval of off-label prescribing by a supervising committee.

The Measures for the Regulation of Prescribing, promulgated by the Ministry of Health, contain the only potential source for any prohibition against off-label use. Article 14 of the Measures states that physicians should prescribe drugs based on medical need and medical standards, as well as the indications, pharmacology, dosage forms, strengths, contraindications, warnings and adverse reactions set forth in the drug's approved package insert.<sup>22</sup> This language, which states a positive obligation to prescribe drugs based on information included in the approved package insert, could be interpreted, in the converse, as a prohibition against off-label prescribing.

Such an inference, however, is unsupported by the drafting history of the Measures for the Regulation of Prescribing, other related provisions, rules and regulations, and the current system of oversight at the provincial and hospital level.

When the Ministry of Health drafted the Measures for the Regulation of Prescribing in 2006, the agency included a provision that permitted and regulated off-label prescribing in the third draft dated April 18, 2006. The draft provision would have limited a physician's right to prescribe off-label drugs to the following conditions: (i) the physician has authoritative medical literature supporting off-label use; (ii) the proposed off-label use is reviewed and approved by a prescription supervisory committee; and (iii) the physician obtains informed consent.<sup>23</sup> When the Measures for the Regulation of Prescribing were stipulated in February 2007, however, the paragraph on off-label prescribing had been removed. The only express requirement on off-label prescribing that remained (other than the mandate to base prescribing decisions on information included in the drug's approved package insert) was a provision regulating prescription of higher than approved doses. Pursuant to that provision, if there is a special need for a higher dose, a physician may prescribe above the approved range, but he must document his reasons and sign his statement.<sup>24</sup> The final draft contained no express conditions for off-label prescribing for unapproved patient groups, unapproved routes of administration or unapproved indications.

This drafting history suggests that the drafters may have viewed the provision that physicians base prescribing on a drug's label as being consistent with the traditional right to prescribe off-label. The third draft of the Measures for the Regulation of Prescribing contained both limits on prescribing off-label and an obligation to base prescribing

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<sup>20</sup> There is one narrow exception. In China, the off-label use of injectable traditional Chinese medicines ("TCM") for unapproved indications is prohibited. *See* Notice on Further Strengthening Administration of the Manufacture and Use of Injectable TMCs, jointly issued by the Ministry of Health, SFDA and the State Administration of Traditional Chinese Medicines in 2008, as a response to reports on deaths caused by injectable TCMs. The Notice prohibits the off-label use of injectable TCMs for unapproved indications, but does not specify the penalties for non-compliance.

<sup>21</sup> Chufang guanli ban fa [Measures for the Regulation of Prescribing] (promulgated by the Ministry of Health, Nov. 27, 2006, effective May 1, 2007), arts. 8-13, 43-46 (P.R.C.), *available at* <http://www.satcm.gov.cn/English2010/Policy/2010-10-06/152.html>.

<sup>22</sup> *See* Measures for the Regulation of Prescribing, *supra* note 21, art. 14.

<sup>23</sup> Chufang guanli ban fa [Third Draft of Measures for Regulation of Prescriptions] (drafted by the Ministry of Health, Apr. 18, 2006), art. 11 (P.R.C.), *available at* <http://wenku.baidu.com/view/3b0a7868a98271fe910ef904.html>.

<sup>24</sup> *Id.*, art. 6(9).

on a drug's label without comment on any inconsistency. Moreover, the retention of special conditions for prescribing increased doses off-label, while removing the other drafted conditions for general off-label prescribing, suggests that physicians preserve their traditional rights to prescribe.

Subsequent rules and regulations support the lack of a national prohibition against off-label prescribing. For example, a subsequent rule on the oversight of hospital prescribing promulgated by the Ministry of Health contains a vaguely worded prohibition against "unjustifiable" off-label prescription.<sup>25</sup> This prohibition would be superfluous if the Measures of the Regulation of Prescribing already prohibited off-label prescribing. By limiting its prohibition to "unjustified" off-label prescribing, the rule also presupposes a general right to "justified" off-label prescribing.

A prohibition against off-label prescribing would also be inconsistent with the rules issued by the Ministry of Health and many provincial health departments that medical institutions internally regulate off-label prescribing. For example, in 2011, the Ministry of Health issued Implementation Rules on Evaluation Standards for Full-service Hospitals of Grade Three, which required all third-grade full-service hospitals to have in place procedures for off-label prescribing.<sup>26</sup> Similarly, the health department of Chongqing Municipality set forth standards for off-label prescribing in its Criteria for the Recognition of Grade Three Hospitals.<sup>27</sup> The standards set forth by the health department of Jiangxi Province echo the deleted requirements in the Measures for Regulation of Prescribing: (i) off-label prescription must be documented with analysis; (ii) off-label prescription may not be made at outpatient clinics; (iii) off-label prescription must be approved by the relevant committee in the responsible medical institution; and (iv) the prescribing physician or medical institution must obtain informed consent from the patient.<sup>28</sup> Some medical institutions have even drafted policy for off-label prescribing, in which they state that appropriate off-label use of drugs is permitted if certain procedural protections are met.<sup>29</sup>

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<sup>25</sup> See *Yiyuan chufang dianping guanli guifan (Zhanxing)* [Provisional Rules on Oversight of Prescribing in Hospitals] (promulgated by the Ministry of Health, Feb. 2010), art. 19, available at [http://www.gov.cn/gzdt/2010-03/04/content\\_1547080.htm](http://www.gov.cn/gzdt/2010-03/04/content_1547080.htm). The Rules do not define "justification" or "justifiable."

<sup>26</sup> See *Sanji zonghe yiyuan pingshen biao zhun shishi xize* [Implementation Rules on Evaluation Standards for Full-service Hospitals of Grade Three] (promulgated by the Ministry of Health, 2011), §4.15.3.1 (P.R.C.), available at <http://www.moh.gov.cn/mohylfwjgs/s3577/201112/53721/files/02b5187a195c42e0855e4e27445fc2f0.pdf>.

<sup>27</sup> *Chongqing shi sanji zhonghe yiyuan pingshen biao zhun* [Chongqing Municipality Criteria for the Recognition of Grade Three Hospitals] (promulgated by Chongqing Municipal Health Bureau, March 2012), available at <http://www.cqwsj.gov.cn/zfxgk/zcgw/yzgl/2012-3/9713.html>. The Chongqing rules also require that off-label use be supervised and documented.

<sup>28</sup> See *Jiangxi sheng yiliao jigou linchuang yongyao guanli banfa (zhanxing)* [Provisional Rules on Proper Clinical Use of Drugs by Medical Institutions] (promulgated by Jianxi Province Dept. of Health, Mar. 15, 2005), arts. 6-7, available at [http://www.jxwst.gov.cn/cszw/yzgl/zhgl/201005/t20100527\\_28846.htm](http://www.jxwst.gov.cn/cszw/yzgl/zhgl/201005/t20100527_28846.htm).

<sup>29</sup> See, e.g., Appendix 2: Yaopin wei zhuce yongfa zhuanjia gongshi [Consensus Statement Regarding Off-label Use], Guangdong sheng yaoxuehui wenjian [Guangdong Pharmaceutical Association Statement] (2010); Zhihua Zheng et al., *Chinese Pharmacists Propose Patient Consent for Unlabeled Use of Medications*, 16 *JMCP* 640 (Oct. 2010) (describing consensus statement by 20 senior pharmacists from 17 hospitals in Guangdong province regarding off-label use); Henan xing renmin yiyuan chao shuomingshu yongyao guanli guiding [Policy on the Off-label use of Drugs of Henan Provincial People's Hospital], available at <http://wenku.baidu.com/view/0d5a70bc1a37f11f1855b3e.html>. The senior chief pharmacists from 17 hospitals in Guangdong province created a consensus statement regarding off-label use. The statement restricted off-label use to circumstances in which (i) there is no effective drug to treat the patient's condition and the benefits of the off-label use outweigh the risks; (ii) the use must not be for research purposes; (iii) the use must be based on reasonable evidence and be approved by the hospital's pharmacotherapy and hospital ethics committees; and (iv) consent must be obtained from the patient or guardian. The People's Hospital of Henan province, the largest state-owned hospital in the province, also established similar principles for the off-label use of drugs: (i) off-label use must benefit the patient; (ii) off-label use must not be for research purposes; (iii) the

While some standards for off-label prescribing exist, their self-regulating nature can lead to lax enforcement. The Ministry of Health requires all medical institutions to establish prescription review systems in order to record inappropriate prescribing,<sup>30</sup> warn a physician who has prescribed drugs improperly three times and restrict his prescription authority.<sup>31</sup> In cases where the warned physician prescribes drugs improperly two or more consecutive times, the institution is required to suspend his prescription authority.<sup>32</sup> In practice, however, medical institutions are usually reluctant to punish physicians who have improperly prescribed off-label uses because doing so may expose the institutions to malpractice claims.<sup>33</sup>

### III. CHINESE REGULATION OF OFF-LABEL PROMOTION

The dissemination of drug information can be classified into three types: (i) drug advertisements, (ii) non-advertisement promotion, and (iii) the non-promotional dissemination of scientific or medical information. In the U.S., the government has historically regulated advertisement and non-advertisement promotion of off-label use through the FDCA's "new drug" and "misbranding" provisions.<sup>34</sup> While there are no formal regulations on non-promotional dissemination of scientific or medical information, FDA has issued guidance recommending specific forums for dissemination.<sup>35</sup>

In China, while advertisement of off-label use is strictly prohibited, enforcement has historically been lax. Except in limited circumstances, parties cannot be criminally prosecuted for violations of drug advertisement rules.<sup>36</sup> Administrative and civil penalties are often too low to be a deterrent. Furthermore, non-advertisement promotion is rarely regulated and no government agency regulates non-promotional dissemination of scientific or medical information.

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benefits of off-label use must outweigh the risks; (iv) off-label use must be supported by solid scientific bases and sufficient medical literature; and (v) the patient must be informed of the use of off-label drugs. Under the policy, physicians must provide relevant medical literature and seek approval from the Committee for the Use of Drugs and Medical Practice and such approval must be recorded by the Department for Medical Practice. The physician must also inform the patient of the treatment procedure, possible consequences and potential risks. If the off-label use has been widely adopted, the physician may inform the patient orally. If the off-label use has not been widely adopted, the physician must explain all of the potential risks and obtain written informed consent.

<sup>30</sup> Measures for Regulation of Prescribing, *supra* note 21, art. 44.

<sup>31</sup> *Id.*, art. 45.

<sup>32</sup> *Id.*

<sup>33</sup> See Qinquan zeren fa [Tort Law] (promulgated by the Standing Comm. Nat'l People's Cong., Dec. 26, 2009, effective July 1, 2010), art. 54, LAWINFOCHINA (last visited March 3, 2013). Under the Tort Law, institutions, not individual physicians, are liable for medical malpractice.

<sup>34</sup> See Allison Burroughs et. al, *Off-Label Promotion: Government Theories of Prosecution and Facts that Drive Them*, 65 FOOD & DRUG L.J. 555, 558-65 (2010) (describing government enforcement of illegal off-label promotion). This strategy is now in doubt after the Second Circuit's ruling in *U.S. v. Caronia*. See *supra* note 9.

<sup>35</sup> Section 401 of the Food and Drug Administration Modernization Act, and its implementing regulations, provided a "safe harbor" for the dissemination of journal articles and reference publications about off-label uses under certain conditions. See 21 U.S.C. § 360aaa. However, Section 401 ceased to be effective on September 30, 2006 and FDA has provided its current views on the subject by industry guidance. Good Reprint Practices, *supra* note 11.

<sup>36</sup> Parties can only be criminally prosecuted for "false advertisement" if they make a significant illegal profit or cause significant harm to consumers, or there are other serious circumstances. See Criminal Law, Art. 222; see also Zuigao renmin jianchayuan, gongan bu guanyu gongan jiguan guanxia de xingshi anjian lian zhuisu biaozhun di guiding [Supreme People's Procuratorate and the Ministry of Public Security's Prosecution Standards for Criminal Cases under the Jurisdiction of the Public Security Organs], art. 75, available at <http://www.mps.gov.cn/n16/n1282/n3493/n3778/n4303/2417768.html>.

To advertise any drug, an enterprise must seek approval from the provincial food and drug administration (“PFDA”) of the province, autonomous region or municipality in which the enterprise is located.<sup>37</sup> Prescription drugs may be advertised only in medical or pharmaceutical professional publications jointly designated by the administrative department for health and the drug regulatory department under the State Council,<sup>38</sup> while direct-to-consumer advertisements for prescription drugs are prohibited.<sup>39</sup> All drug advertisements must include the drug’s generic name, certain required statements, the drug advertisement approval number, the drug manufacturing approval number and other specific statements.<sup>40</sup> In addition to these requirements, statements in drug advertisements must be true and legitimate and be based on information included in the approved package insert.<sup>41</sup> No names or images of government departments, medical or pharmaceutical research institutions, academic institutions, experts, scholars, physicians or patients may be used in advertisements to support claims about the safety, efficacy or quality of the drug.<sup>42</sup> Drug advertisements may not contain safety or efficacy comparisons with other drugs or descriptions of rates of effectiveness (e.g., cure rates).<sup>43</sup>

The term “advertisement” is poorly defined in China. Thus, it is difficult to demarcate clearly the difference between drug advertising (which is highly restricted) and mere promotion (which, as discussed below, is not as restricted). Under the Advertisement Law, an advertisement is defined as “any commercial advertisement, which a commodity or service provider bears the costs for, through certain media or forms, directly or indirectly introducing their commodities being sold or services being provided.”<sup>44</sup> The definition is self-referential: it defines an advertisement as a “commercial advertisement” without a clear definition of what this means.

The Advertisement Law provides no clear distinctions between advertising and non-advertisement promotion. At first glance, the definition of “advertisement” would seem to require the involvement of a third-party vendor (e.g., a business pays a third-party television station to run a television advertisement). In practice, however, the definition may be somewhat broader. The State Administration for Industry

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<sup>37</sup> Yaopin guanli fa [Drug Administration Law] (promulgated by Standing Comm. Nat’l People’s Congr., Feb. 28, 2001, effective Dec. 1, 2001), art. 60 (P.R.C.), available at <http://former.sfda.gov.cn/cmsweb/webportal/W45649037/A48335975.html>. In mainland China, there are 31 administrative divisions at the provincial level, of which 22 are called provinces, five are autonomous regions and four are municipalities. For entities that have facilities in more than one provincial administrative division, the PFDA of the domicile provincial division (usually the registered address) has jurisdiction.

<sup>38</sup> *Id.* The current administrative department for health is the newly created Commission for Health and Family Planning (formerly the Ministry of Health) and the current drug regulatory administration is CFDA (formerly SFDA).

<sup>39</sup> *Id.* The rules that govern the advertisement of over-the-counter drugs are somewhat more permissive. For example, over-the-counter drug advertisements are permitted on the Internet, although a permit from the PFDA is still required. See Hulianwang yaopin xinxi fuwu guanli banfa [Measures Regarding Internet Information Services for Drugs] (promulgated by SFDA, May 28, 2004, effective July 8, 2004), art. 10 (P.R.C.), available at <http://www.sfda.gov.cn/WS01/CL0053/24486.html>.

<sup>40</sup> If the drug is a prescription drug, the advertisement is required to state that “this advertisement is only for medical or pharmaceutical professionals.” Yaopin Guanggao Shencha Fabu Biaoqun [Standards of Review of Applications for Drug Advertisements], art. 8. If the drug is an OTC drug, the advertisement is required to state “please purchase and use in accordance with the drug instructions or under the guidance of pharmacist” and to include the symbol for OTC. *Id.*, arts. 7-8.

<sup>41</sup> *Id.*, art. 61.

<sup>42</sup> *Id.*

<sup>43</sup> *Id.* See also Guanggao fa [Advertisement Law] (promulgated by Standing Comm. Nat’l People’s Congr., Oct. 27, 1994, effective Feb. 1, 1995), art. 14, LAWINFOCHINA (last visited March 3, 2013) (P.R.C.).

<sup>44</sup> Advertisement Law, *supra* note 43, art. 2. The Advertisement Law applies generally to all types of products, including drugs. It gives the SAIC power to enforce the law. Although the SFDA has been granted the authority to review and approve drug advertisements, the SAIC is still the government agency responsible for the enforcement of rules on advertisements.

and Commerce (“SAIC”) has clarified that promotional material disseminated by a business itself without the involvement of a third-party advertiser can be regulated as an “advertisement.”<sup>45</sup> The SFDA has taken enforcement actions against the distribution of self-printed flyers for drugs where no permit for drug advertisement was obtained.<sup>46</sup>

Nor has the SFDA provided clear guidance about which drug promotional activities constitute advertising. The agency has clarified only that a “drug advertisement” exists if the drug name and indications or other information are mentioned in an advertisement.<sup>47</sup> As discussed above, drugs may be introduced in medical or pharmaceutical professional publications jointly designated by the SFDA and the Ministry of Health. According to the SFDA, as long as these introductions contain only the drug’s name (both brand and generic) without additional information such as indications, then no PFDA permit is required.<sup>48</sup>

Because drug advertisements are subject to approval and must be based on information provided in the approved package insert, drug advertisements for the off-label use of drugs are prohibited in China. Under Chinese law, the penalties for launching drug advertisements without a permit from the appropriate PFDA can include: (i) the issuance of an administrative order to stop the advertising activity, (ii) the confiscation of funds/fees for the advertisement, (iii) the issuance of a fine of one to five times the advertisement fee,<sup>49</sup> (iv) the temporary suspension of drug sales regionally or nationally,<sup>50</sup> and (v) the issuance of notice to the public about the violation.<sup>51</sup> Penalties (i) to (iii) can be administered by the Administration for Industry and Commerce (“AIC”), while the remaining two penalties are issued by the SFDA and/or PFDA.

In most cases, the SFDA and PFDA, rather than the AIC, investigate drug advertisement violations. Where the authority to implement the desired penalty rests with the AIC, the SFDA or PFDA will transfer the case to the local AIC for the penalty decision. In the past five years, PFDA have suspended the sales of an increasing number of drugs for launching advertisements for off-label uses.<sup>52</sup> They usually lift the suspension of sales in their jurisdictions once the manufacturers or distributors have made corrective statements on local television or in newspapers as required.<sup>53</sup>

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<sup>45</sup> Yinshuapin guanggao guanli banfa [Measures for the Administration of Advertising on Printed Matters] (promulgated by the SAIC, Nov. 30, 2004, effective Jan. 1, 2005), art. 2, LAWINFOCHINA (last visited March 3, 2013) (P.R.C.).

<sup>46</sup> See Bulletin Publicizing Violations of Rules on Advertisements for Health Food, Drug and Medical Device, <http://www.sfda.gov.cn/WS01/CL0085/>.

<sup>47</sup> Yaopin guanggao shencha banfa [Measures for Review of Applications for Drug Advertisements] (promulgated by SFDA, May 1, 2007), art. 2, available at <http://eng.sfda.gov.cn/WS03/CL0768/61649.html>

<sup>48</sup> *Id.*

<sup>49</sup> Advertisement Law, *supra* note 43, art. 43.

<sup>50</sup> Measures for Review of Applications for Drug Advertisements, *supra* note 47, art. 21. This sanction must be imposed when unapproved drug advertisements promote off-label uses, seriously exaggerate efficacy or seriously mislead consumers.

<sup>51</sup> Weifa guanggao gongshi zhidu [Establishment of the Publicity System for Illegal Advertisements] (promulgated jointly by the SFDA, the SAIC, the Ministry of Health and a number of other government agencies, Nov. 21, 2006), available at [http://www.law-lib.com/law/law\\_view.asp?id=181703](http://www.law-lib.com/law/law_view.asp?id=181703).

<sup>52</sup> For example, Jiangsu PFDA suspended the sales of seven drugs for violations of rules on drug advertisements on June 26, 2012. See Jiangsu zanting xiaoshou “nu jin dan wan” deng qi zhong weifa guanggao yaopin [Jiangsu suspends sales of seven drugs that violate drug advertisement laws], China Med. Rep., available at <http://www.chinamsr.com/2012/0703/52820.shtml>. Five of these seven cases involved advertisement for off-label uses. All seven cases involved multiple violations and none of the violators was punished only for advertising for off-label uses.

<sup>53</sup> For example, Jiangsu PFDA removed its sales suspension of one drug on January 31, 2012, after the manufacturer made corrective statements in two newspapers on November 22 and 23, 2011. See Jiechu zanting xiaoshou yi qi congming wan de gonggao [Notice of removal of sales suspension of “yiqi conming” pills] (promulgated by Jiangsu PFDA, Jan. 31, 2012), available at [http://www.jsfda.gov.cn/art/2012/2/1/art\\_325\\_95908.html](http://www.jsfda.gov.cn/art/2012/2/1/art_325_95908.html).

In China, there are no specific requirements for non-advertisement promotion of drugs, except with respect to the promotion of drug information on the internet.<sup>54</sup> There is, however, a general requirement under consumer protection laws that non-advertisement promotion of any merchandise cannot be false and misleading.<sup>55</sup> Both the SAIC and the local AIC have the power to levy an administrative fine of between RMB 10,000 to RMB 200,000 for false and misleading promotion.<sup>56</sup> While the SAIC has not issued any significant guidance on this topic, China's Supreme People's Court has stated in a judicial interpretation that the following types of promotions may be considered false or misleading: (a) a one-sided promotional introduction of a product; (b) presentation of inconclusive scientific theories or phenomena as if they were conclusive; and (c) use of any other misleading methods in a promotion.<sup>57</sup>

As for the dissemination of non-promotional scientific or medical information related to drug products, such activities are not subject to significant regulation under Chinese advertising and promotion laws and regulations. Chinese law does not give SFDA the power to take any enforcement action against the dissemination of non-promotional scientific or medical information related to unapproved drugs. A trade association in China has stated that the scientific community and the public have a right to access and exchange scientific and medical knowledge on unapproved drugs.<sup>58</sup>

In summary, while advertisements for off-label uses of drugs are prohibited in China, punishment for violations is relatively light. Moreover, non-advertisement promotion and non-promotional dissemination of scientific and medical information exist in a gray area that is not regulated by the Chinese government.

#### IV. LIABILITY FOR OFF-LABEL PRESCRIBING UNDER CHINESE TORT LAW

In China, the majority (around 90%) of physicians are employed by state-owned medical institutions.<sup>59</sup> Chinese law provides that medical institutions, not physicians, bear the civil liabilities for any wrongful act committed by a physician during the course

<sup>54</sup> See Measures Regarding Internet Information Services for Drugs, *supra* note 39. The majority of the provisions relate to procedural requirements for obtaining a license for internet promotion. Before releasing any drug information through the internet, the website operator must, *inter alia*, obtain an Internet Drug Information Service Certificate from the appropriate provincial food and drug administration and must assure that the drug information provided on the internet is accurate and has a scientific basis.

<sup>55</sup> Xiaofei zhe quanyi baohu fa [Law on the Protection of Rights and Interests of Consumers] (promulgated by the Standing Comm. Nat'l People's Cong., Oct. 31, 1993, effective Jan. 1, 1994), arts. 19, 50, LAWINFOCHINA (last visited March 3, 2013); see also Fan bu zhengdang jingzheng fa [Anti-unfair Competition Law] (promulgated by the Standing Comm. Nat'l People's Cong., Sept. 2, 1993), art. 9, LAWINFOCHINA (last visited March 3, 2013).

<sup>56</sup> See Anti-unfair Competition Law, *supra* note 55, art. 24.

<sup>57</sup> Guanyu shenli bu zhengdang jingzheng minshi anjian yingyong falu ruogan wenti de jieshi [Judicial Interpretation on Application of Anti-unfair Competition Law at Trials] (promulgated by Sup. People's Ct., Jan. 12, 2007), art. 8, available at [http://www.court.gov.cn/qwfb/sfjs/201006/t20100609\\_5953.htm](http://www.court.gov.cn/qwfb/sfjs/201006/t20100609_5953.htm).

<sup>58</sup> In October 2006, the China Pharmaceutical Industry Association published a draft self-regulatory code "Yiyao daibiao xingwei zhunze" [Code for Sales Representatives of Pharmaceutical Products]. See [www.cpia.org.cn/download/0610zhunze.doc](http://www.cpia.org.cn/download/0610zhunze.doc). The draft code stated: "No drugs can be sold in China before an approval from the SFDA. However, this requirement does not prevent the right of the scientific community and the public to be informed concerning scientific and medical progress. The approval requirement is not intended to restrict an appropriate exchange of scientific information, including the publication or dissemination of research results in designated media or at scientific conferences." No final code has been issued.

<sup>59</sup> At a meeting organized by the Ministry of Health on April 11, 2012, Mr. Ma Xiaowei, Vice Minister of Ministry of Health, stated that only 10% of physicians in China work with private healthcare institutions. See MOH Press Release, Weisheng bu zhaokai jiaqiang mingying yiyuan fazhan yu guanli gongzuo zuotan hui [MOH Forum on Strengthening the Development and Management of Private Hospitals] (Apr. 17, 2012), available at <http://www.moh.gov.cn/mohylfwjgs/s3586/201204/54509.shtml>.

of medical practice.<sup>60</sup> In the instances where a healthcare professional or a medical institution has violated a legal requirement, regulation or standard of good practice, there is a rebuttable presumption of a wrongful act.<sup>61</sup>

In China, there is a general requirement that a physician keep the patient informed of his condition and treatment.<sup>62</sup> It is not clear what this means in practice. The Tort Law requires that in cases of surgery or “special treatment,” the physician must inform patients about any risks and alternative treatment and obtain written consent in a timely manner.<sup>63</sup> If the physician fails to obtain informed consent as required and the treatment harms the patient, the patient is entitled to bring a suit for damages.<sup>64</sup> However, the term “special treatment” is undefined in the statute and has not been interpreted by the judiciary. Therefore, the law is unsettled as to when a physician is required to obtain informed consent.

Whether informed consent is required for off-label prescribing under the Tort Law remains unresolved. Where a medical institution or province requires informed consent, a medical institution may have an increased risk of civil liability if its physicians fail to inform patients about off-label prescribing or fails to obtain written consent. However, even if there were a duty to inform or to obtain consent, successful plaintiffs in medical malpractice cases are not usually awarded adequate compensation.<sup>65</sup>

In China, one defense a physician or medical institution may raise in a malpractice lawsuit is that off-label prescribing is an experimental treatment. Under the Physicians Law, a physician may conduct experimental treatment if he obtains approval from the local medical institution and consent from the patients or their family members.<sup>66</sup> Again, the Physicians Law does not define an “experimental treatment,” and there has been no clear interpretation of the term by either a regulatory or judicial authority.

It is not always clear whether a physician’s off-label prescribing is an experimental treatment, which does not require approval by the SFDA, or clinical research, which must be pre-approved by the SFDA. In practice, most off-label prescribing in China could fall into the category of experimental treatment because the primary purpose of off-label prescribing is usually not to test a hypothesis for a new use of the drug, but rather for patient treatment. Again, a medical institution may have an increased risk of civil liability if its physicians fail to inform the patient about off-label prescribing and do not obtain consent.

Therefore, in order to avoid possible civil liabilities for off-label prescribing, a medical institution must ensure that its physicians prescribe off-label drugs only when there are sound scientific bases and the physicians follow established procedures, including obtaining informed consent.

## V. CONCLUSION

Physicians may prescribe off-label drugs in China, but there are certain restrictions to this practice. Such restrictions vary depending on where the physician practices and the restrictions the physician’s medical institution places on his or her practice.

<sup>60</sup> Tort Law, *supra* note 33, art. 54. In practice, this means that the injured patient may have to sue the government because most hospitals are state-owned. Harris, *supra* note 15, at 459.

<sup>61</sup> *Id.*, art. 58.

<sup>62</sup> *Id.*, art. 55.

<sup>63</sup> *Id.* If it is not appropriate to inform a patient, the physician should inform the patient’s family members and gain written consent.

<sup>64</sup> *Id.*

<sup>65</sup> Li Xiaohong, *Medical Malpractice Compensation Too Low in China*, PEOPLE’S DAILY, August 18, 2010, available at <http://english.people.com.cn/90001/90776/90882/7110218.html>.

<sup>66</sup> Physicians Law, *supra* note 19, art. 19.

Drug advertisements for off-label use are strictly prohibited by law. However, there is no criminal prosecution for violators and administrative punishment is generally an insufficient deterrent. While a medical institution may have an increased risk of civil liability if its physicians prescribe off-label drugs without sound scientific bases or fail to follow established internal procedures, compensation for successful plaintiffs in malpractice claims for off-label prescribing is generally low.

In order to formulate a more robust mechanism for regulating off-label prescribing, China needs to strengthen its oversight of the promotion of off-label use by manufacturers and distributors. This should be done by introducing harsher regulatory penalties. China should also reform its tort law to allow courts to award adequate compensation to patients who have suffered harm from improper off-label prescribing.