JOURNAL OF FOOD AND DRUG ANALYSIS 26 (2018) 481–486

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Review Article

Regulatory analysis on the medical use of ephedrine-related products in Taiwan

*Wan-Nan Yu, Li-Hsuan Wang, Hui-Wen Cheng**

School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 11031, Taiwan

ARTICLE INFO

Article history:
Received 26 October 2017
Accepted 13 November 2017
Available online 2 December 2017

Keywords:
Ephedrine-related products
Taiwan Food and Drug Administration (TFDA)
Controlled Drugs Act
Pharmaceutical Affairs Act
Pharmacists Act

ABSTRACT

To prevent ephedrine-related products from being misused to produce amphetamine and/or its analogs, there's a need for more effective and achievable regulatory mechanisms for the health, police, investigational, prosecution and judiciary authorities in Taiwan. This review was conducted to evaluate the international and Taiwan's regulatory policies and management of medical ephedrine-related products through the corresponding information collected from international and Taiwan government agency authorities. The combat of illegal drugs should involve both supply and demand sides to be successful. Health authorities in Taiwan do not have the investigational power to manage the forbidden transformation, abusing and manufacture of the illegal drugs from ephedrine-related products. Take the judicial interventions in the United States and in Japan as the examples, the organizational cooperation in Taiwan can be one of the main key strategies to combat against illegal drugs from ephedrine-related products. It is necessary to integrate the judicial, police and health agencies to prevent the production of illegal drugs from the ephedrine-related products in Taiwan. The efforts and regulatory control measures should be integrated to speed up the collaboration between different government authorities. It might be achieved through reorganization involving Taiwan Food and Drug Administration.

1. Introduction

Medical ephedrine products, containing ephedrine, pseudoephedrine or methyl-ephedrine, could be used as the precursor chemicals in the illegal production of amphetamine and/or its analogs. Therefore, these products were listed as "Schedule 4 Controlled Drug Ingredients" in the Controlled Drugs Act in Taiwan [1]. However; those ephedrine-related materials are also produced as pharmaceutical products mainly for the treatment of cold, cough, asthma or allergy. In this case, these products are categorized as prescription or over-the-counter (OTC) drugs depending on their dosages and/or risk levels. These ephedrine-related medications are not listed as controlled medications but are managed and regulated as general medications by regulations of the Pharmaceutical Affairs Act. As a result of such regulation gap loophole leads to

* *Corresponding author*. School of Pharmacy, College of Pharmacy, Taipei Medical University, No. 250, Wu-Hsing St., Taipei 11031, Taiwan.
E-mail address: dhwcheng@tmu.edu.tw (H.-W. Cheng).

https://doi.org/10.1016/j.jfda.2017.11.002

the drug distributors buying large volume or quantities of ephedrine-related products to extract the necessary ingredients and further produce amphetamine and/or its analogs accordingly. In fact, some law enforcement agencies have uncovered several similar cases and this phenomenon began to attract social and political attention in Taiwan.

To prevent ephedrine-related products from being misused to produce amphetamine and/or its analogs, this article reviewed the international regulation systems regarding medical ephedrine-related products, and compared them with Taiwan's own pharmaceutical and controlled drugs regulations. As a result of this analysis, we have proposed seven effective and achievable regulatory management initiatives to the health, prosecution, police, investigation and judiciary authorities, based upon the premise of worry-free medical usage purposes and the corresponding circulation responsibility, for ephedrine-related products production and circulation.

2. Regulatory analysis

2.1. *Severity of the misuse problem*

It is not difficult to produce amphetamine and/or its analogs with ephedrine ingredients through halogen reduction and hydrogenation. Thus, producing methamphetamine with ephedrine-related ingredients has become a common concern of circulation loophole both domestically and internationally. It began as a means of profiteering just among few pharmaceutical manufacturers. However, some pharmacies and pharmaceutical distributors jumped on the bandwagon and got involved in inappropriate use or in events of transforming high dose ephedrine cold medications into amphetamines. According to the news report, the 60 mg ephedrine can be extracted from one commercially available tablet of cold medication and 1 g of ephedrine could be obtained from 20 tablets of cold medications costing about 200 NTD (approximately 6.50 USD) [2,3]. However, 1 g of amphetamine could easily be sold at 5000 NTD on the market. The profit of this kind of illegal transaction is tremendous.

Fraudulent persons purchased cold medications, containing high doses of ephedrine-related ingredients, from unwitting pharmaceutical manufacturers, and then sold the products to drug distributors [2–4]. They were familiar with the corresponding sales channels and utilized the following approaches to obtain these medications and avoid being investigated accordingly: borrowing pharmacy permits, forging approved medical organization certificates, and setting up paper companies for exporting declaration.

There are many possible ways to obtain these large volume medical ephedrine-related products between different parties in the supply chains. For instance, the ephedrine products could be ordered in large quantities from pharmaceutical manufacturers or the distributors by dishonest staffs at hospitals and/or clinics and then being intercepted the shipment on the halfway. Otherwise, these products could be obtained as prescription drugs at hospitals, clinics, pharmacies or pharmaceutical manufacturers, or be purchased as OTC drugs with big volume. The possible circulation scenarios are explained in Fig. 1.

2.2. *International regulations and strategies*

Ephedrine products are usually not categorized as controlled substances internationally. To prevent ephedrine products from being illegally transformed into the amphetamine and/or its analogs, these products are usually packaged and supplied in the limited quantities, and cannot be openly displayed in pharmacies. Furthermore, the buyers' information usually has to be recorded in pharmacies as well.

The United Nations (UN) requests all member countries to implement the monitoring mechanism of precursor chemicals, "PEN Online (Pre-Export Notification Online)" to control the production, circulation and sales of ephedrine products in order to prevent from illegally transformation [5].

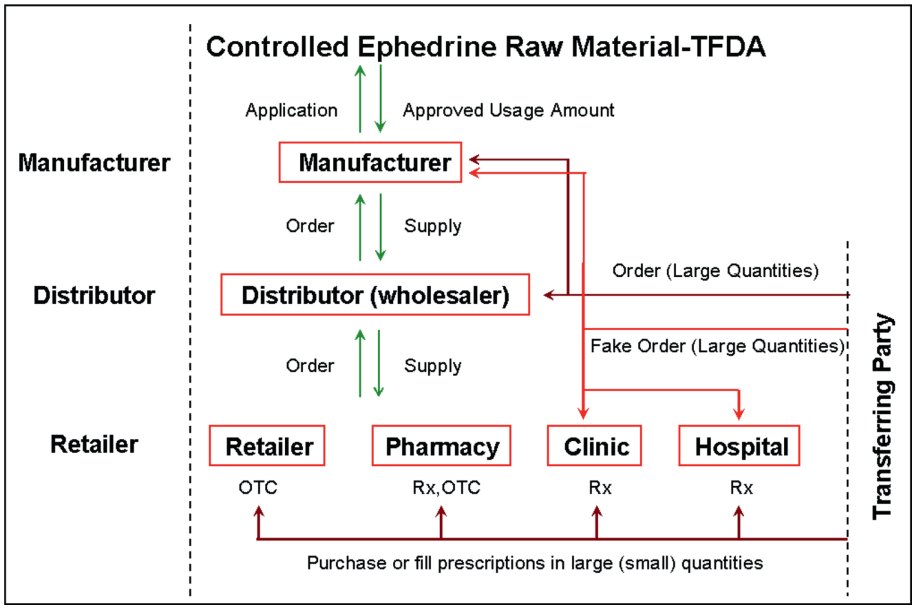

Fig. 1 – Possible ephedrine-related products circulation channel.

The new class of "behind the counter (BTC)" medication was created to control those OTC products containing ephedrine in order to prohibit citizens from acquiring ephedrine containing OTC products in community pharmacies [6]. The United States Drug Enforcement Administration (USDEA) even added the limited-sale policy to require the unit dose aluminum foil packaging for non-liquid products, sales with less than 3.6 g per day or no more than 9 g in total for 30 days, and to verify and record the corresponding consumers' identities: names and address in the community pharmacies [7,8].

Within European Union (EU), the French government forbids the sales of OTC products containing ephedrine. In England, OTC containing more than 1% ephedrine should be sold at community pharmacies and products with more than 720 mg of pseudoephedrine or 180 mg of ephedrine per pack are listed as prescription drugs. In Germany, those products containing over 720 mg pseudoephedrine are categorized as prescription drugs as well [9]. Cold medicines are limited to only 60 mg of pseudoephedrine per pack with no more than 12 units in total in Poland. Furthermore, anti-allergic products have to be combined with cetirizine in the formula, and no more than 120 mg per unit dose and less than 14 units in total per package [9].

Those cold and anti-allergic products containing ephedrine are categorized as controlled drugs in New Zealand. Each pack allows less than 1.8 g of pseudoephedrine, and these products should not to be retrieved without prescriptions. In Australia, those products containing pseudoephedrine are listed as non-prescription drugs and should be sold at community pharmacies. The customers should provide their identities with photo and the selling pharmacists have to record the customer's information through the online system to prevent from redundant buying [9].

To avoid pseudoephedrine being used as an ingredient in illegal drugs, Japan requires anyone who purchases large quantities (60 days' supply) or frequently (buying a total of over 60 days' worth in 7 days) should be registered and clarified if they are reselling the drugs, and their locations, dates, names of the items, amounts, reasons for selling, and further to verify the buyers' information (e.g., names, telephone numbers, addresses, characteristics and car license plate numbers). Moreover, the pharmacists are requested to notify the authorities or police agencies whenever they thought the buyer behaves suspiciously [10].

The regulations in China are in place for the management of ephedrine-related chemicals and their precursors. These products are listed as precursor chemicals under strict supervision to prevent their production, marketing, purchasing and supervision. The Chinese FDA is in charge of strengthening the management; implementing purchase permits regulations. These products of single ingredient ephedrine with small-packaging are sold as narcotics, and only national and regional wholesalers are authorized to sell these ephedrine products. In contrast, no retail sales for these products are allowed in China [11].

2.3. *Regulation strategy in Taiwan*

The current regulatory strategy in Taiwan focuses more on the manufacturers' obligations with stricter sales channels control and enhances more responsibilities toward those unreasonable end suppliers.

2.3.1. *Product*

The packaging of ephedrine related prescription drugs are required to use aluminum boxes. Those OTC products should be packaged not more than 7-day supplies. Syrups containing ephedrine and pseudoephedrine for cold medicines, painkillers or cough for "instructional use" are limited from one dose to up to 4000 mL and their packaging should not be altered at all, per item 2 and 3 of article 15 of Taiwan Regulations for Registration of Medicinal Products [12].

All these strategies are expected to increase the cost and difficulties for illegal producers to purchase these ephedrine-related products in large quantities. In addition, those purchases of ephedrine raw materials are strictly verified, and its whereabouts could be traced when necessary. Any suspicious activities will be reported to judicial and law enforcement agencies. If those ephedrine-related products are indeed used in the production of illegal drugs, the manufacturer's product license and/or plant permit will be relinquished according to Article 76 and 78 of the Pharmaceutical Affairs Act [13]. Further, tablets and capsules containing high dose of pseudoephedrine are considered to be re-categorized as the controlled drugs for better supervision, if it is necessary [14].

2.3.2. *Manufacture*

The manufacturers (as upstream) are required not to sell or supply these products to non-pharmacy, non-distributor and non-medical facilities per Article 49 of the Pharmaceutical Affairs Act [13]. The manufactures should keep and provide sales and distribution records. If not complied, the conduct might be recognized as a severe violation of Good Manufacturing Practice (GMP) regulations [15]. The manufactures will subsequently be fined according to the Item 1 and Item 2 of Article 57 of the Pharmaceutical Affairs Act [13]. If their products are found out for illegal drugs production, this will result in losing one or all products licenses. It is because this phenomenon was recognized as serious health hazards to the general public per Pharmaceutical Affairs Act [13]. Pharmacists (or assistant pharmacists) (including supervision pharmacists at manufacturers, and pharmacies) selling ephedrine-related products in abnormal large quantities shall be prosecuted, and reprimanded per items 2 and 6 of Article 21 of the Pharmacists Act [16].

2.3.3. *Wholesaler*

Pharmaceutical wholesalers who distribute these products from the industries to medical facilities are required to provide the details of buyers based on the corresponding manufacturers' sales records. As a result, the manufacturers or distributors shall not reject the distribution requests from competent regulatory agencies without good cause. Refusal to comply will result in disciplinary actions per Article 71 of the Pharmaceutical Affairs Act [13]. If the wholesalers sell straightly to the consumers or individuals, a violation of Article 49 of the Pharmaceutical Affairs Act [13], they will be punishable by Article 92 of the Pharmaceutical Affairs Act [13].

2.3.4. *Pharmacy and pharmacist*

Providing large quantities ephedrine-related products to individuals in pharmacies, a phenomenon recognized as wholesaling and not listed as in pharmacies business items, these pharmacies will get penalty per Pharmaceutical Affairs Act if they didn't have the business items changes pre-approved according to Item 1 of Article 27 of Pharmaceutical Affairs Act [13]. Selling prescription drugs without prescription by pharmacists is in violation of Article 50 of the Pharmaceutical Affairs Act and will be punished accordingly [13].

Pharmacists have to inquire about patients' symptoms and provide counseling in person for those "instructional drugs". The dosage of these products should not exceed 12 bottles, 12 soft tubes for one patient. The total purchased amount is limited up to 1200 tablets and not allowed to repetitive purchase within 6 months [17]. Pharmacists will violate the Pharmacists Act "sale or management of pharmaceuticals", and "explanations of instructions to the purchaser of drugs" whenever they exceed the reasonable dosages selling to individuals and will be reprimanded according to Article 21 of the Pharmacists Act [16]. If the supplier is not a pharmacist, he or she will be penalized with NT$ 60,000 to NT$ 300,000 fine according to Article 24 of the Pharmacists Act [16].

2.4. *Loopholes of regulation in Taiwan*

Those production permits with single ingredient of ephedrine-related products are mostly categorized as prescription drugs, where their ephedrine contents are mostly lower than 25 mg [18]. The contents of methyl-ephedrine products are mostly less than 30 mg while the contents of pseudo-ephedrine prescription drugs are mostly 30 mg, 60 mg or 120 mg.

Some episodes of misuses did occur that those ephedrine prescription drugs, either single ingredient or multiple ingredients, were used in the production of amphetamine and/or its analogs. Those sustained-release dosage forms containing 240 mg of ephedrine should be managed rigorously to prevent them from being used for the preparation of amphetamine and/or its analogs.

In fact, those ephedrine products are commonly used as weight-loss drugs by health professionals. This off-label indication practice makes it difficult for regulatory authority to monitor its official medical utilization. The judicially investigational data revealed only very few manufactures had their ephedrine-related products being used to produce amphetamine and/or its analogs. Though they usually claimed knowing nothing about those products' downstream usage, it does not make their appealing acceptable to the competent authority and the general public. It might be a good approach to immediately publish names of manufacturers with abnormal use of raw material of ephedrine to alert other peer manufacturers. US Risk Evaluation and Mitigation Strategies (REMS) for opioid products is another option. When manufacturers accept the product orders, they should put REMS into their GMP consideration accordingly to facilitate their risk self-management, self-diagnostics, self-assessment, and the social responsibilities.

Currently the risk assessment practice does exist in Taiwan's regulations. "Risk Analysis" is defined as the investigation data needed to effectively differentiate the "hazard" and to assess the risk levels in term 7, item 1, Article 98 of Standards for Medicament Factory Establishments [19]. "Post-Approval Risk Management Plan" is required for government authority approval of new drug application (NDA) term 3, item 1, Article 38-1 of Regulations for Registration of Medicinal Products [12]. It implicitly suggests that the manufacturers should actively introduce the risk management mechanism concept into NDA and daily operation for their ephedrine-related products, when necessary.

Successful illegal drugs combat involves both the supply and demand sides. Health agencies do not have the judicially investigative authorities and cannot timely and directly intervene against the transfer, abuse and production of illegal drugs. Therefore, the inter-organizational cooperation is the key to success to combat against illegal drugs. The ineffectiveness in the ephedrine-related products issue has much to do with the discoordination within different government authorities (judiciary, investigation and health). Take the judicial interventions of Drug Enforcement Administration in the United States as an example; they are more prone to collect information and to investigate the synthesis of illegal drugs because of the judicial system for this matter. Japan FDA, Ministry of Health, Labor and Welfare, has established a Compliance and Narcotics Division (CND) to supervise and provide guidance for illegally use of anesthetics and stimulants. Local CND Narcotic Agents, with the special judicial police authority, are responsible to execute criminal investigation about illegal drugs, monitor the sales channels, inspect periodically medical establishments, pharmacies and other pharmaceutical manufacturers, as well as offer the guidance, educational counseling and suggestions the regional stakeholders. Their experiences provide valuable and feasible practice for us to consider in our future strategy and action plan against the illegal use of ephedrine-related products in Taiwan.

3. Recommendation

Whenever ephedrine-related products are used for the production of amphetamine and/or its analogs, it causes detrimental outcomes to individuals and the whole society. We hereby suggest TFDA to take the following initiatives to better accomplish ephedrine-related products management:

1. Work closely with Bureau of Foreign Trade to create the special tax number with a pre-authorization letter from MOHW requirement for import/export of ephedrine-related products, stipulating export regulations and the C3 (inspection required) declaration requirement. The customs can thus proceed with inspections when importing or exporting these products. Before this special tax number initiative coming into effect, the government authorities can provide custom personnel with possible fraudulent tax numbers to raise their risk management alert with corresponding control level.

2. TFDA could adopt the European regulations and switch those ephedrine-related OTC products with more than certain amount per unit (for instance, pseudoephedrine over 60 mg) to prescription drugs. Furthermore, TFDA could request the medical facilities, pharmaceutical distributors to (1) only supply limited amount to patient (e.g., the total daily purchase quota for each person should be up to 3.6 g or 15 days' supply, or repeated purchase beyond 7-day gap), (2) keep the traceable information, e.g., names, addresses, for those consumer who exceed the expected quota and the records should be maintained for two years. For those medical institutions, pharmaceutical distributors and pharmacies with records of abnormal dosage, or over the reasonable dosages (e.g., off-label use), health authorities should elevate the inspection frequency to evaluate their reasonable utilization.
3. The applicant to use ephedrine-related raw materials for production should sign an affidavit stating its use for medical purpose. Those that have not signed the affidavit will be refused to obtain their ephedrine-related raw materials from TFDA. Should their products be ever transformed into amphetamine and/or its analogs, they will be responsible for further investigation. Any abnormal usage in raw materials should be reported to the Bureau of Investigation of Ministry of Justice (MOJ) and/or Criminal Investigation Bureau of Ministry of Internal Affairs.
4. Bureau of Medical Affairs in MOHW should establish a meaningful mechanism to investigate and monitor the off-label use of ephedrine for weight-loss purpose. The established mechanism for the medical institution should at least contain the standards for total volume control with clear conditions (e.g., normalized average use value per patient symptom per year, formula for abnormal curve range) based on geographic location and level of medical settings to control abnormal quantities from being used illegally. For physicians, they should be required to have legitimate reasons for off-label use at medical facilities and to put the information into patients' medical records. The health authorities should also establish an inspect mechanism to see if patient history is properly registered, and if necessary; inspect its reasonability of use.
5. Phenylephrine has replaced pseudoephedrine for weight-loss purpose as a control measure of ephedrine-related products issue internationally. However, phenylephrine is easily metabolized in the intestinal tract so that it is not well absorbed orally. With less anxiety side effect, using phenylephrine instead of pseudoephedrine might be another better choice.
6. Taiwan government agencies should conduct more rigorous and more frequent inspections on the manufacturers and put strict punishment to the violators for the purpose of effective management. Furthermore, all medical professionals should receive more education on the subject of legal responsibilities regulations. Those violators should be submitted for disciplinary actions according to Article 21 of the Pharmaceutical Affairs Act.
7. Fighting illegal drugs depends on the holistic organizational cooperation. Take the example of judicial intervention of US DEA; it might be necessary to integrate the judicial, police and health agencies for the investigation of ephedrine-related products being used for the production of illegal drugs in Taiwan. More specifically, we could learn from USA system that it has clearly defined and well assigned responsibility between FDA and DEA. The efforts and powers are thus integrated. We highly recommend an amendment of the Controlled Drugs Act to give the investigation responsibilities to the special judicial agencies in MOJ. This may also require amending the Organizational Law of MOJ. If Taiwan prefers the Japanese Narcotic Agent system, we recommend making an amendment of the Controlled Drugs Act toward another direction with the equipment of the special judicial police force organized by the MOHW as well as an amendment of MOHW Organizational Law. Both approaches should result in speeding up the TFDA re-organization and resolve the ephedrine-related products problem more effectively.

4. Conclusion

It is necessary to integrate the judicial, police and health agencies to prevent the production of illegal drugs from the ephedrine-related products in Taiwan. The efforts and regulatory control measures should be integrated to speed up the collaboration between different government authorities. It might be achieved through reorganization involving Taiwan Food and Drug Administration.

Acknowledgment

This study owes its thanks to the financial support to the DOH100-FDA-61403 project of FDA, Ministry of Health and Welfare (formerly known as FDA, Dept. of Health, Executive Yuan).

REFERENCES

[1] Executive Yuan. No. 1060019501 bulletin: schedules and items of controlled drugs. Taipei, Taiwan, Republic of China: Executive Yuan; 2013.
[2] Epoch Times (Taiwan). Pharmaceutical distributor sold cold medicine for illegal amphetamines manufacturing. Washington DC, USA: Epoch Times; August 30, 2011. Available at: http://www.epochtimes.com/gb/11/8/30/n3358715.htm [Accessed 25 October 2017].
[3] Formosa Television Station. Chairman of the pharmaceutical association involved in reselling cold medicine for amphetamines manufacturing. Taipei, Taiwan: FTV; August 31, 2011. Available at: https://www.youtube.com/watch?v=q63xSjJjVjU [Accessed 25 October 2017].
[4] Central News Agency. Two men arrested by police for illegally manufacturing amphetamine from cold medicine. Taipei, Taiwan: CNA; August 29, 2017. Available at: http://www.cna.com.tw/news/asoc/201708290311-1.aspx [Accessed 25 October 2017].
[5] United Nations. Report on the fifty-fourth session; resolution 54/8: commission on narcotic drugs, 2 December 2010 and 21–25 March 2011. New York, USA: United Nations; 2010.

[6] Palamar J. How ephedrine escaped regulation in the United States: a historical review of misuse and associated policy. Health Policy 2011;99:1–9.
[7] Drug Enforcement Administration. The combat methamphetamine epidemic act of 2005. Washington DC, USA: Drug Enforcement Administration; 2005.
[8] Drug Enforcement Administration. The combat methamphetamine enhancement act of 2010. Washington DC, USA: Drug Enforcement Administration; 2010.
[9] Association of the European Self-Medication Industry. AESGP ingredients dictionary 2016. Brussels, Belgium: AESGP; 2016. Available at: http://www.aesgp.eu/media/cms_page_media/68/AESGP%202016%20Ingredients%20Directory_FINAL.PDF [Accessed 25 October 2017].
[10] Ministry of Health, Labor and Welfare. The 0513 No. 1 official letter from narcotics policy supervisor of MOHLW to directors of health in prefectural governments: official letter from the drug and weapon division supervisor, organized crime policy department, metropolitan police department. Tokyo, Japan: Ministry of Health, Labor and Welfare; May 13 2011.
[11] Department of Health. Order No. 72. Peking, China: Department of Health; Apr. 7th, 2010.
[12] Ministry of Health. Regulations for registration of medicinal products. Taipei, Taiwan, Republic of China: Ministry of Health and Welfare; 2017.
[13] Office of the President. Pharmaceutical affairs act. Taipei, Taiwan, Republic of China: Office of the President; 2017.
[14] Two-Step Strategy for the Prevention of Respiratory and Cold Medicine Being Used to Produce Illegal Drugs. Taiwan Food and drug consumer newsletter, vol. 218; 2009. p. 2–3. Available at: https://www.fda.gov.tw/TC/PublishOtherEpaper.aspx?key=%E7%AC%AC218%E6%9C%9F [Accessed 25 October 2017].
[15] Department of Health. No. 0991100002 bulletin: manufacturers fail to provide transportation records of products containing pseudoephedrine, ephedrine or methylephedrine during GMP audit conducted by department of health shall be a sever violation act of GMP. Taipei, Taiwan, Republic of China: Department of Health; 2010.
[16] Office of the President. Pharmacists act. Taipei, Taiwan, Republic of China: Office of the President; 2014.
[17] Department of Health. Drug sample and gift regulations. Taipei, Taiwan, Republic of China: Department of Health; 2003.
[18] Taiwan Food and Drug Administration. Pharmaceutical license inquiry system. Taipei, Taiwan, Republic of China. Available at: https://www.fda.gov.tw/mlms/H0001.aspx. [Accessed 25 October 2017].
[19] Ministry of Health and Welfare. Standards for Medicament factory establishments. Taipei, Taiwan, Republic of China: Ministry of Health and Welfare; 2013.