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Review Article

Risk undermined in the bilateral pharmaceutical regulatory system in Taiwan

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ABSTRACT

The concept of Pharmacovigilance Planning and Risk Minimization Planning (PVP/RMP), initiated by the International Conference on Harmonization (ICH), addressed an important conceptual change from monitoring the safety of individual medicine to proactively conducting risk prevention for the minimization of medication error. However, the implementation of PVP/RMP is a challenge in societies like Taiwan where irrational medication and co-medication is prevalent. It is even more difficult in Taiwan where two regulatory bodies are governing pharmaceutical affairs, namely Taiwan Food and Drug Administration (TFDA) in charge of Western Medicine (WM) and the Department of Chinese Medicine and Pharmacy (DCMP) in charge of Traditional Chinese Medicine (TCM). There are thus dual-track drug approval panels, two GMP controls and two independent adverse drug event reporting systems. This rendered irrational co-medication of WM and TCM undetectable and the standard tools for monitoring pharmacovigilance inapplicable. The bilateral regulatory system is conceptually unscientific in accordance with PVP/RMP and unethical from humanity point of view. The first part of this review delivers (1) social aspects of polypharmacy in Taiwan; (2) regulatory aspects of pharmaceutical administration; (3) risks undermined in the bilateral regulatory system and (4) pharmacoepidemiology in relation to the risk of polypharmacy. As evidence-based medicine (EBM) forms the fundamental risk-benefit assessment on medication, the second part of this review delivers (1) the scientific aspects of the beauty and the odds of biological system that governs host–xenobiotics interaction; (2) conceptual evolution from product management (pharmacovigilance) to risk management (PVP/RMP); (3) non-biased due process is essential for risk-benefit assessment on medicinal products and (4) the opinion of the authors on system building for safe medication.

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1. Introduction

Pharmacovigilance Planning and Risk Minimization Planning (PVP/RMP), a theme of proactive system building on safe medication, represents important conceptual evolution from monitoring the safety of individual medicine (pharmacovigilance) to conducting risk prevention for the minimization of medication error (use of medicine). It was initiated by the International Conference on Harmonization (ICH) and becomes a global trend [1,2].

However, the implementation of PVP/RMP is a challenge in societies like Taiwan where irrational medication and co-medication is prevalent. It is even more difficult in Taiwan where the dual-track regulatory bodies are governing pharmaceutical affairs of western medicine (WM) and traditional Chinese medicine (TCM). Attempts in integrating WM and TCM into a sound uni-track regulatory body under Taiwan Food and Drug Administration (TFDA) failed when the Governmental Reformation Plan took place in year 2005.

Potential risk of irrational medication in Taiwan will first be described in this report from social and pharmaco-epidemiological aspects. Risk generated due to the complexity of product-oriented bilateral regulation and administration will be analyzed. How to implement a sound risk management on pharmaceuticals based on evidence-based risk-benefit assessment will be discussed.

To be specific, quality, safety and efficacy (QSE) are three criteria in drug approval for IND (investigational drugs) and NDA (new drug application) no matter they are synthetic, natural, biological or biotech generated origin. In practice, the approval panel is an integrative evaluation process of which the review committee is composed of a pool of QSE experts. As the products are different by nature, standards are set in different categories for products of different origin. In other words, pharmaceuticals are subjected to a uni-track review scheme while the review is executed based on different standards according to their nature.

TCM, as licensed drug, is logically subjected to the same approval panel. There is no point to single out TCM from other pharmaceuticals. However, sponsors in Taiwan can choose, at their own will, either administration body to apply for IND and NDA, as QSE criteria are different in the bilateral drug approval systems. Moreover, with two administration bodies independently in charge of TCM and drugs other than TCM, there are two quality assurance schemes, two post-marketing monitoring systems and two adverse drug reporting systems in Taiwan. Unknown risks are thus undermined both for consumers (health risk) and for the society (pharmaco-epidemiology), as there is no mechanism to exercise an integrative risk analysis. It is government's responsibility to establish a due process in order to exercise integrative risk analysis along the life cycle of all pharmaceuticals.

This report will then describe the humanity-based risk-benefit assessment on pharmaceuticals. The conceptual change initiated by ICH and the publication of PVP/RMP guidance thereof for system building of safe medication indicates that product management need to be transformed to

humanity-based risk management in modern era. With two independent pharmaceutical administration bodies it is impossible to exercise such risk management. It is the responsibility of lawmakers to seriously review current situation and take into consideration of system building for safe medication in order to keep abreast of the global trend on PVP/RMP.

1.1. Polypharmacy

Polypharmacy is widespread in the general public. Besides registered medicine, the population of complementary/alternative medicine (CAM) and TCM users is growing, especially in the aged and in patients with chronic disease [3,4]. As a considerable large portion of patients take CAM (including TCM) with registered medicines without notification to professionals, standard tools for monitoring of pharmacovigilance have its limitation. Safety threat thus emerges from various scientific and pharmacoepidemiological reports. Evaluation of clinical efficacy and adverse reactions caused by interactions of herbal remedy with conventional therapy becomes a critical issue [5,6].

1.2. Social aspects of irrational medication and co-medication in Taiwan

Taiwan is known for its outstanding national health insurance program which benefits 99% of the population. The welfare-like program rendered Taiwanese overusing the healthcare resources, indicated by the high physician's visit per person and the large number of drug items (both WM and TCM) per prescription [7,8]. Other than prescription drugs, patients took TCM in retail shop without notifying medical professionals. The imbalanced distribution of pharmacy service between hospitals, clinics and community pharmacies further reflects the lack of mechanisms for professional pharmacists to conduct pharmacovigilance monitoring on polypharmacy [9].

1.3. Regulatory aspects of pharmaceutical administration in Taiwan

CAM, including TCM, are marketed without license in most of the developed countries. Claims for therapeutic efficacy are thus prohibited or limited to authorized indications. TCM however are classified as licensed drugs in Taiwan. There are two regulatory bodies governing pharmaceutical affairs, namely Taiwan Food and Drug Administration (TFDA) in charge of WM and the Department of Chinese Medicine and Pharmacy (DCMP) in charge of TCM. There are thus two parallel drug approval panels in regulating clinical trials of investigational new drugs (IND) and new drug application (NDA), two GMP regulations and two adverse drug event reporting systems within the government [10].

The bilateral regulating system rendered standard tools for pharmacovigilance monitoring inapplicable, which is conceptually unscientific in accordance with evidence-based risk-benefit assessment for PVP/RMP in modern era. It led to the irrational co-medication undetectable and considered unethical from humanity point of view [11].

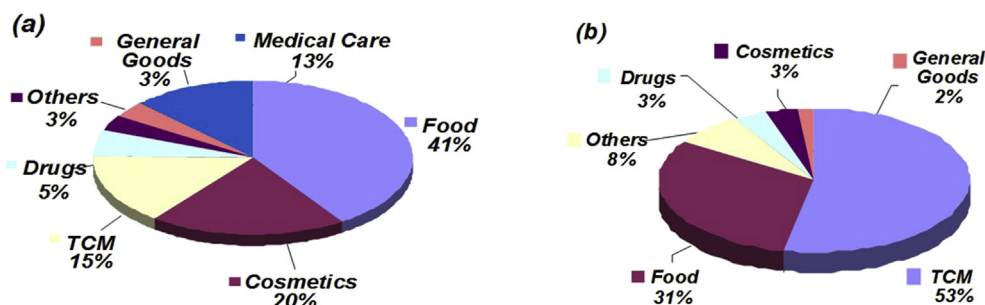


Fig. 1 – Identified illegal advertisement of medicinal products in year 2004 on cable TV (a) and on radio (b) in Taiwan.

1.4. Pharmacoepidemiology in relation to the risk of polypharmacy

Epidemiological features indicated that the prevalence and incidence rate of chronic kidney disease (CKD) in Taiwan are relatively high compared with other countries [12,13]. The incidence rate of end-stage renal disease (ESRD) of Taiwan ranked the top among the world prior to year 2009 [14]. Reports also indicated that herbal therapy was positively associated with CKD [12]. Safety issue in relation to polypharmacy becomes a challenge to the authority and the medical society.

With the prevalent use of TCM and CAM, inappropriate commercial advertisements in the media becomes a social problem. According to a report of survey study in Taiwan, the identified illegal advertisement of products with therapeutic claims on cable TV counts for 12% of total healthcare related advertisements (183 out of 1591 cases), of which 41% goes to food and CAM and 15% goes to TCM (Fig. 1a). The illegal advertisement rate is even higher on radio, with TCM ranked the top (53%) followed by CAM (31%) (Fig. 1b). Most of the advertisements are claims for weight reduction and for the treatment of erectile dysfunction while are lack of evidence [15].

2. Evidence-based medicine

Biological activity, i. e. the pharmacodynamic outcome, used to be major concern in conventional drug research and development. Pharmacokinetics (PK), the descriptor of drug–host interaction, is conducted at the later stage of drug

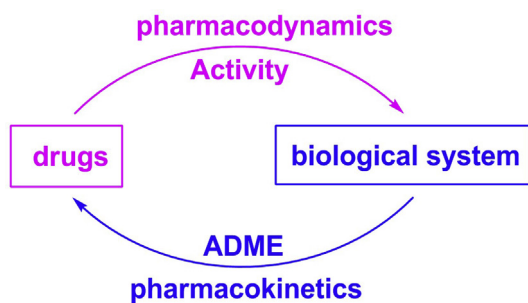


Fig. 2 – Integrative pharmacodynamic and pharmacokinetic outcome determines the efficacy of drug therapy.

development. However, the disposition of biological active substances in body system determines the success of these substances to become therapeutic agents. The failure in most cases is due to unsatisfactory PK and consequent toxicological outcome after xenobiotics enter the biological system (Fig. 2). As a consequence, the successful rate of bringing xenobiotics from preclinical to clinical stage was rather low, estimated to be 1/2000 [16–18].

2.1. Scientific aspects of partnership between xenobiotics and the host

The biological system, which forms the basis of xenobiotic–host interactions is full of mechanisms in manipulating drug action and its destination in the body. Mechanisms governing the xenobiotic–host interaction include absorption, distribution, metabolism and excretion (ADME, Fig. 3).

Transporters in biological system for delivering xenobiotics to target sites are associated with drug efficacy [19,20]. Examples include the competition of transporters for intestinal absorption, the interference in the rate and profile of metabolism, modification of drug distribution, change of renal clearance due to the competition of transporters for excretion in the kidney, and the occurrence of drug resistance due to the modification of ADME process [21].

Scientific evidences regarding to the sites and mechanisms of xenobiotic–host interaction are emerging. It is well documented that transporters in the intestine, liver, kidney and

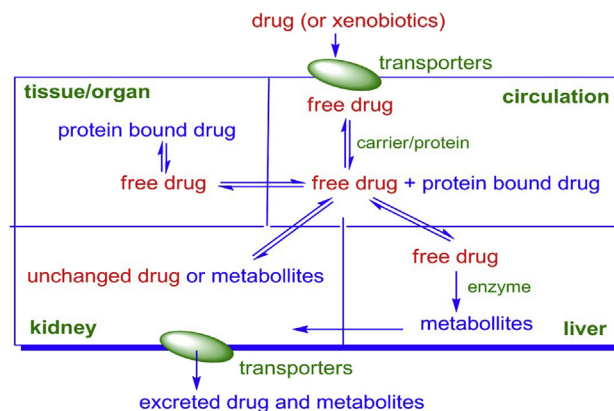


Fig. 3 – ADME determines the destination of xenobiotics in the biological system.

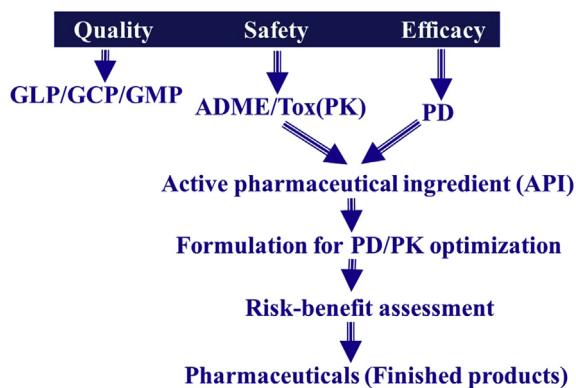


Fig. 4 – Illustration of risk-benefit assessment along drug approval process (Note: PK: Pharmacokinetics; PD: Pharmacodynamics; ADME/T: ADME and Toxicology).

brain are involved in the uptake and the efflux of chemical substances [22,23]. Transporters in the intestine for absorption and in the kidney for excretion demonstrated characteristics of broad substrate specificity, indicating the possibility of broad scope of drug-drug, drug-TCM and drug-food interactions. Evidence also supported the consequence of the involvement of transport proteins in the pharmacokinetic variability and the safety of drugs in human use [24]. The competition of renal transporter between drugs and food, for example, may change the bioavailability of drugs due to the change of renal clearance rate.

The metabolic system processing the biotransformation of xenobiotics provides another pitfalls for drug-drug and drug-food interaction. Reports indicated that hepatotoxicity and renal toxicity of xenobiotics are associated with the formation of reactive metabolites no matter they are from synthetic or herbal resources. Therefore partnership of xenobiotics with the body system forms the basis of EBM in

modern science and interaction between xenobiotics become key elements of risk-benefit assessment for justifying a xenobiotic to become a drug [25,26].

2.2. Risk-benefit assessment of pharmaceutical products

Drug approval is an integrative judgment process based on the risk-benefit assessment of quality, safety and efficacy of medicinal substances (Fig. 4). Evidence-based justification of drug-drug and drug-food interaction also becomes a standard procedure for safety evaluation of New Drug Application (NDA) by pharmaceutical regulatory bodies [27–30]. In order to increase the successful rate in new drug development, conventional sequential involvement of chemistry, pharmacodynamics (PD), safety/toxicity (T) and pharmacokinetics (ADME/PK) is evolved to an operation scheme of parallel PD/ADME/T screening (Fig. 5).

2.3. The theory of TCM therapy need to be correctly addressed

There are three key elements in Chinese Medicine regarding the theory of TCM therapy, namely (1) Yaw-Shi-Ton-Yuan (藥食同源); (2) Bien-Jen-Luin-Jhi (辨證論治) and (3) Juin-Chen-Tzuo-Shi (君臣佐使).

Yaw-Shi-Ton-Yuan (藥食同源) delivered important message that the body system does not differentiate food and medicinal herbs. They are all foreign (xenobiotics) to the body. Genseng for example is used as food as well as for treating disease. Bien-Jen-Luin-Jhi (辨證論治), the approach to TCM therapy by Chinese medical doctors, addresses the assessment of body condition (kinetics) prior to drug treatment (drug efficacy). This approach, in modern term of western therapy, is to measure pharmacokinetics in order to optimize the pharmacodynamics (efficacy) of TCM therapy. Juin-Chen-Tzuo-Shi (君臣佐使) using combination of herbs for therapy. It is conceptually and theoretically identical to the process of

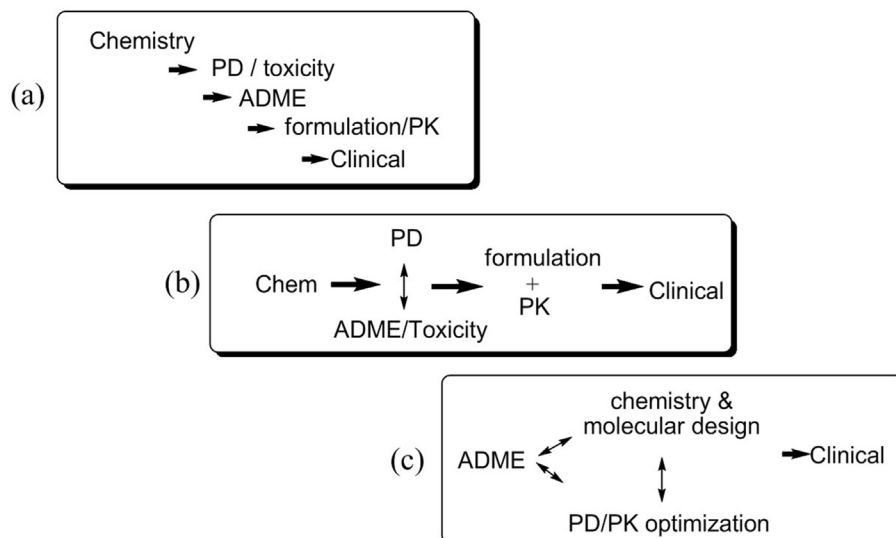


Fig. 5 – The strategic planning of drug development, guided by risk-benefit assessment based on evidence-based medicine, has evolved from (a) sequential involvement of PD, ADME/PK to (b) PD and ADME/PK abreast and to (c) system biology evaluation based on ADME.

API + Adjuvant + Delivery System + Vehicle
君 臣 佐 使

Fig. 6 – Both TCM and WM are combination products derived from formulation design.

formulation design toward PD/PK optimization in developing WM (Fig. 6) [31].

Chinese ancestors showed their wisdom both conceptually and in practice in using TCM for therapy, not only fulfilling the scientific norm but also being ethical and humanistic. To this author's opinion, the theory of TCM therapy is obviously misconducted by Taiwanese people, both in education and in practice of public policy. It needs to be correctly addressed in modern era for the sake of safe medication.

3. Conceptual evolution on medication

3.1. Pharmacovigilance

Pharmacovigilance Specification (PV) addresses the evidence-based justification of safely using individual drug throughout its life cycle from preclinical development (phase I, II and III clinical trials) and approval to post-market surveillance (phase IV).

However, genetic and cultural differences such as food and CAM (including TCM) intake are among factors that influence the therapeutic outcome of drug treatment. Therefore, safety evaluation of marketed drugs should be based on good quality of evidence from the growing population that took the drug after a reasonably long period of time. In order to overcome the fragmentation of information, pharmacovigilance requires comprehensive risk-benefit assessment based on the

accumulated data of the population using the individual pharmaceutical product [32]. This drives the move of Pharmacovigilance (PV) to Pharmacovigilance Planning (PVP).

3.2. From pharmacovigilance to pharmacovigilance planning

Partnership between xenobiotics and the body forms the beauty and the odds of medication, fundamentally judged as evidence-based medicine. Biological activity is thus not the only criteria in justification of medicinal substances for therapeutic use. Instead, the mainstream of pharmaceutical regulation has evolved from science-based product management (PV) to humanity-based risk management (PVP/RMP) (Fig. 7). The transition took almost thirty years.

Following the conceptual evolution, the Council for International Organizations of Medical Sciences (CIOMS) and ICH developed and published Topic ICH E2E Guidance in 2005 as an action to implement PVP/RMP. The guidance addresses the identification of all possible signals of risk in regard to drug use. Evidence based approaches to risk assessment such as genetic/racial and cultural factors (food and nutrition) are included in the Bridging Study Evaluation along drug approval panel, as indicated in Fig. 7. Pharmacoepidemiological studies thus become important for risk analysis [1,33–36]. This conceptual change, declared by the ICH, emphasized on risk prevention of medication, is already a global trend for system building of safe medication [37,38].

3.3. Pharmacovigilance of herbal medicines

Pharmacovigilance of herbal medicines started to call for attention in Europe and the US. It is suggested that systematic pharmacovigilance for building up reliable information as guidelines for the evaluation of safe and effective use of herbal medicines should be an essential issue in modern era [39]. Adverse Reactions from TCM therapy started to call for

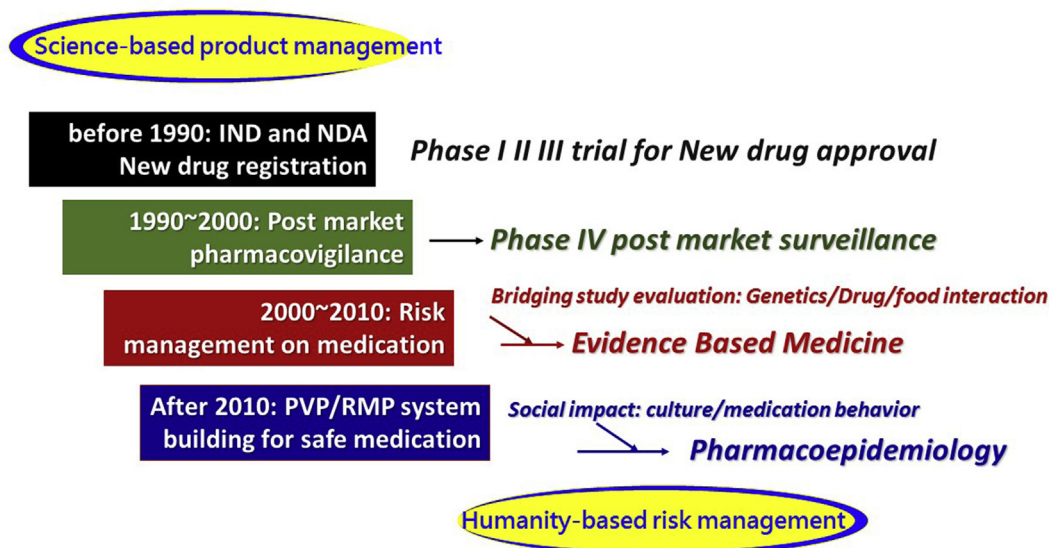


Fig. 7 – Illustration of ICH initiation of chronic transition from science-based product management (pharmacovigilance) to humanity-based risk management (PVP/RMP) on medication.

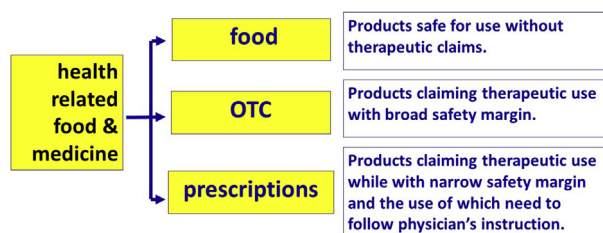


Fig. 8 – Humanity based classification of health related food and medicinal products.

attention [40,41]. Herb-drug interactions focusing on sites along ADME of drugs being effected calls for much attention of safe pharmacotherapy [42–44]. Interest in pharmacokinetic studies of drugs co-medicated with herbal remedies is increasing [45,46].

4. System building of safe medication in Taiwan

4.1. Ethical aspects on classification of health-related food and pharmaceuticals

Theoretically speaking, food and medicinal substances should be classified according to the risk measurement upon humanity concern. Risk-benefit assessment, in terms of quality, safety and efficacy, is the only justification for health related xenobiotics to become food and medicine (Fig. 8). The cognition that biological system can differentiate food and medicinal substances is against the scientific norm.

However, ordinary people in oriental society tend to classify health related products by their nature, i. e. product type such as food, nutraceuticals, WM and TCM (Fig. 9). The cognition came from the educational impact and the consequent conduction in public policy. Disregard the fact that WM is a formulation product, the majority of people in Taiwan simply differentiate WM and TCM by the thought that WM is a product consisted of single component while TCM is a combination. Disregard the complexity generated by the TCM

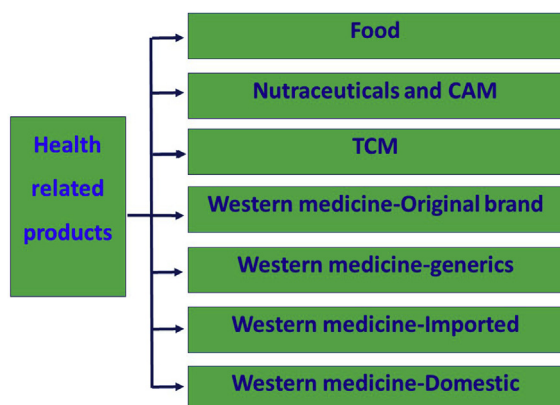


Fig. 9 – Classification of health related food and medicinal products according to product origin.

components, Taiwanese people simply believe, not logic though, that TCM is safe while WM is with toxicity.

4.2. Regulation and administration of western medicine in Taiwan

Upon modernization of pharmaceutical regulation toward global standard, laws such as PIC/S GMP, GLP, GCP, GMP of active pharmaceutical ingredient (API/GMP), Bioequivalence and Bioavailability (BA/BE) were implemented on WM by the Bureau of Pharmaceutical Affairs (Fig. 10) [33].

4.3. Regulation and administration of herbal medicine in Taiwan

Both WM and TCM are regulated by the Bureau of Pharmaceutical Affairs before 1995. Drug license is issued from this Bureau. After the lawmakers passed Pharmacy Law Article 103 in year 1996, TCM was regulated separately from WM by the Committee of Chinese Medicine and Pharmacy (CCMP).

Following Governmental Reformation Plan, the integration of all food and pharmaceutical affairs to the administration bodies of Taiwan Food and Drug Administration (TFDA) was the goal. Drafting the Organization Act of TFDA was initiated in year 2005 by this author, then the chief of the Bureau of Pharmaceutical Affairs. The Organization Act of TFDA was defined as the authority to govern all affairs regarding to food and medicinal products. However, political renounce was encountered. As a consequence, all food and medicinal products except TCM are regulated by TFDA since year 2009 and TCM was singled out and governed separately by the Department of Chinese Medicine and Pharmacy (DCMP).

According to the Organization Act of TFDA, TFDA is in charge of all affairs regarding to food and medicine (Article #1). Regardless of the fact that herbal medicine includes TCM, CAM and nutraceuticals, only CAM and nutraceuticals are governed by TFDA. However, drug license of TCM is issued. This is logically confusing and not convincible. As indicated with the number of license issued, TCM products grows drastically since 1995, the year that administration of TCM was separated from WM. It grows even faster after year 2009, when government reformation took place, and beyond (Table 1).

4.4. GDDP for implementing pharmacovigilance planning and risk minimization

From ethical point of view, humanity-based medication is an important concept to all the stakeholders of drug user. It should be justified by, and only by, the quality, safety and efficacy of medicinal substances, no matter they are from synthetic, biological, biotechnological or herbal resources. Without due process in control of risk prevention, the promotion of medicinal products claiming therapeutic use is non-ethical and unfair to consumers. It is also against the scientific cognition on evidence-based justification of medicine (Fig. 11) [47].

Good Dispensing Practice (GDP) addressed the safe delivery of medicines and medication information to patients. However, Risk exists in where pharmacy professionals are unable to reach. As such, stakeholders involved in product and

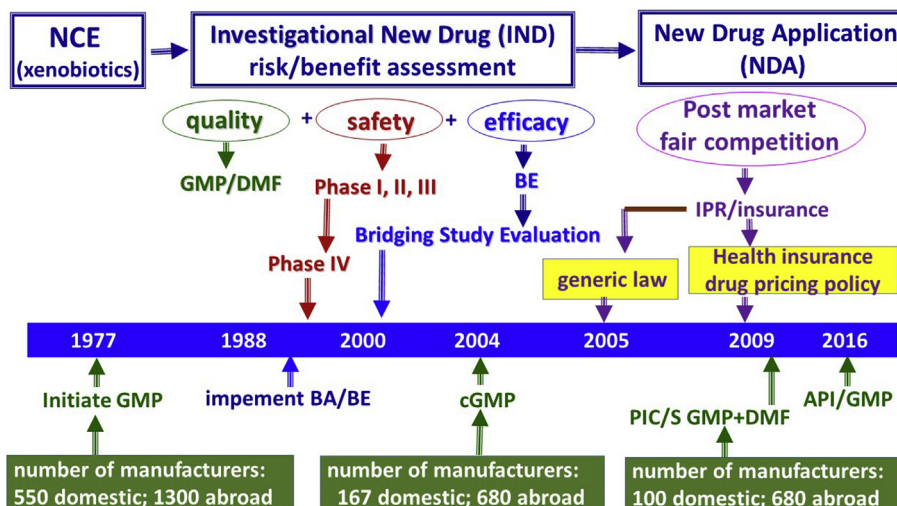


Fig. 10 – Summary of risk-benefit assessment on drug approval and post market surveillance on WM.

Table 1 – Summary of license of western medicine (WM) and TCM.

License number of the Year ^a		1995	2006	2011 ^b	2014 ^b	2017
WM	OTC	7152	7385	8164	7696	6727
	Prescriptions	14,718	14,235	16,883	16,199	15,299
	Total	21,870	21,620	25,047	23,895	22,026
TCM	OTC	4663	6444	–	–	8395
	Prescriptions	2394	4663	–	–	14,337
	Total	7057	11,107	–	–	22,732

^a Data listed are total licensed products in effect, provided by the authority.
^b Chronical data of TCM license number issued by DCMP is not available from the authority.

information delivery, namely product providers, medical professionals, the third party drug payers, media, consumers and policy makers in charge of food and drug administration, should also be responsible for the system building of safe medication. The concept of Good Dispensing and Delivery Practice (GDDP) is thus proposed. In this aspect, due process for the delivery of medicine and medication information is equally important in patient care (Fig. 12) [48].

Taiwan is lack of a due process for integrative and unbiased justification on safe medication. To this author's opinion, risk of polypharmacy came from conceptually misleading education on medication (behavior of drug use) and from public policy, as the separation of regulatory and administrative management on WM and TCM leads to the fragmentation of information in regard to medication risk.

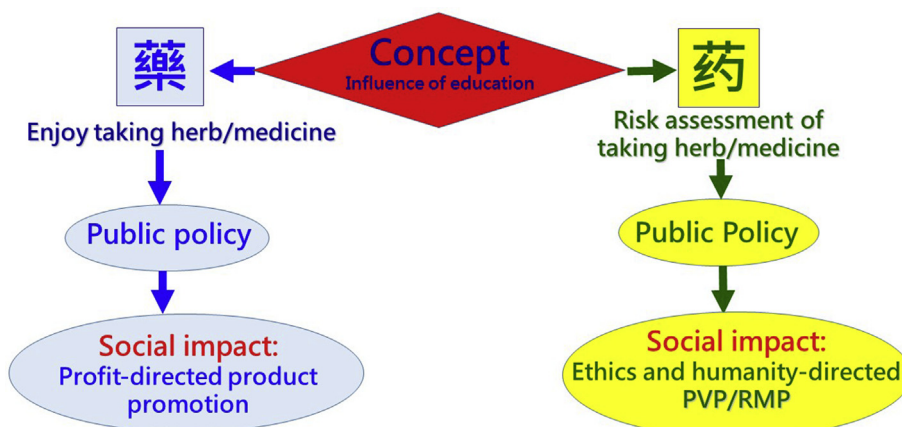


Fig. 11 – Conceptual discrepancy between product management and risk management and the consequences in social impact.

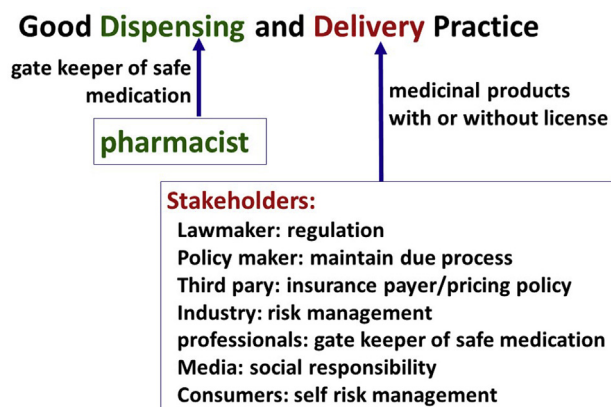


Fig. 12 – Social responsibility of stakeholders in medication management: Good Dispensing and Delivery Practice is essential for the system building of safe medication.

5. Conclusion

Risk of medication not only comes from registered drugs but also from irrational use and co-use of all types of products claiming therapeutic effect. Evidence-based justification on medicinal products is thus important for safe medication. The conceptual change from product-oriented pharmacovigilance to proactive pharmacovigilance planning for risk minimization is already a global trend. Use of medicinal products thus need to be evolved from pharmacovigilance of individual products to humanity-based integrative assessment of risk-benefit on medication.

Although challenging the culture in societies prevalent of irrational medication is most likely unwelcome, system building for safe medication need to be continuously addressed, proactively designed and pragmatically implemented by the authority. The bilateral administrative bodies in regulating WM and TCM in Taiwan is outdated in modern era, not only because it is against scientific norm but also ethically against humanity and thus need to be critically reviewed. Dissemination of opinions addressed in this article is to call for attention of the general public regarding the prevention of medication risk.

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