10

System Building for Safe Medication

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1. Introduction

This article aims to report (1) the scientific aspects of system biology that governs the mechanism of xenobiotics-host interaction; (2) the beauty and the odds of xenobiotics in the biological system; (3) integrative risk-benefit assessment on using xenobiotics for medication purpose; (4) global trend of conceptual change in risk management from product-oriented pharmacovigilance to proactive pharmacovigilance planning for risk minimization; (5) summary of public information regarding to potential risk underlying co-medication of licensed drugs with complementary/alternative medicine (CAM), traditional Chinese medicine (TCM) and nutraceuticals; (6) epidemiological aspects in co-medication of licensed drugs with herbal medicine; and (7) opinion on system building for safe medication in societies where irrational medication and co-medication is prevalent.

2. System biology

2.1 The biological system

The biological system is full of mechanisms in manipulating the action and the destination of xenobiotics, i. e. drugs and food, in the body. Mechanisms governing the xenobiotic-host interaction include absorption, distribution, metabolism and excretion (ADME, Fig. 1). Typical examples associated with xenobiotic-host interaction are the change of drug efficacy due to the competition of drugs and food in intestinal absorption, the interference of drugs or food in the rate and the profile of metabolism, modification of drug distribution by food or other drugs, the change of renal clearance due to the competition of food and drugs for excretion transporters in the kidney, and the occurrence of drug resistance due to the modification of ADME process (Wishart, 2007).

2.2 Evidence-based medicine

The biological activity, i. e. the pharmacodynamic outcome, is used to be the major concern in conventional drug research and development. Pharmacokinetic (PK) evaluation, the descriptor of drug-host interaction, is usually conducted at the later stage of drug development. However, the disposition of the biological active substances in the body system determines the success of these substances to become therapeutic agents. As a consequence, the successful rate of bringing chemical entities from preclinical to clinical stage was rather low, estimated to be 1/2000 (Nassar-1, Nassar-2, 2004). The failure in most cases is due to the unsatisfactory PK after the chemical entities enter the biological system (Fig. 2) (Grossman, 2009).

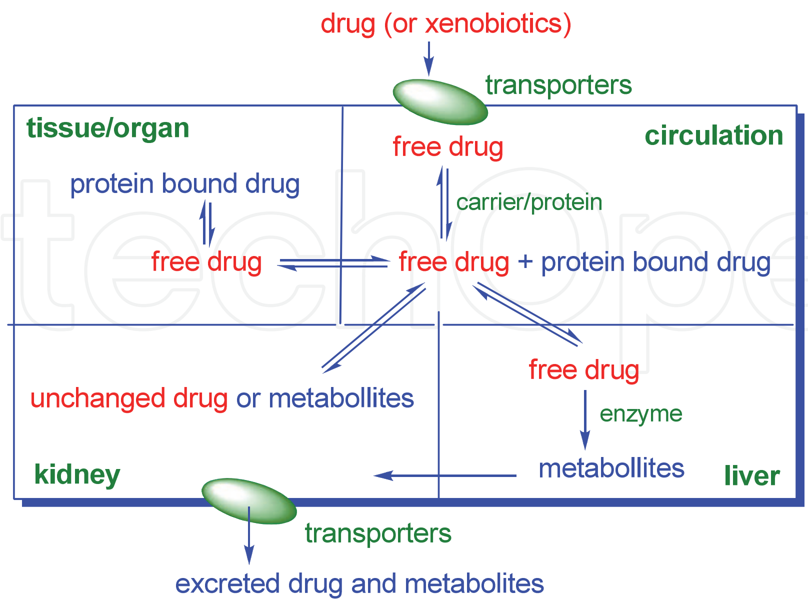

Fig. 1. ADME determines the destination of xenobiotics in biological system.

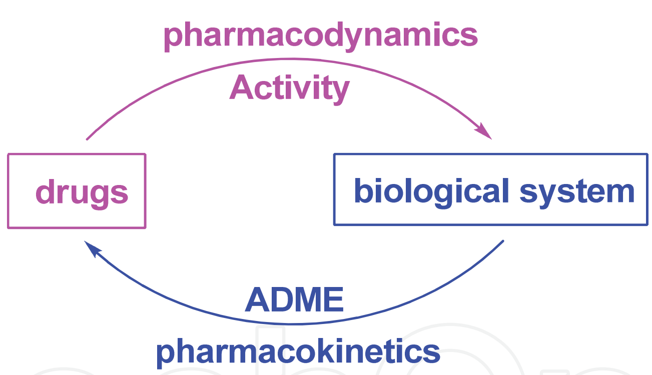

Fig. 2. Integrative pharmacodynamic and pharmacokinetic outcome determines the therapeutic efficacy of drugs.

3. The beauty and odds of xenobiotics in the biological system

Biological processing of xenobiotics via ADME determines the feasibility of medicinal substances to become effective therapeutic agents (Eddershaw et al., 2000; Ekins et al., 2010; Lombardo & Waters, 2011; Ruiz-Garcia et al., 2008). Factors affecting the fate of xenobiotics may exist anywhere along the ADME process and may lead to a change of well designed and documented pharmacokinetic profiles of registered pharmaceuticals (Harris et al., 2003; Yang C. Y. et al., 2006). Risk and benefit assessment is thus not only on the medicinal substances *per se*, but also on factors affecting the biological processing of these substances.

3.1 The sites and the mechanisms of xenobiotic–host Interaction

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 brain are involved in the uptake and the efflux of chemical substances like food and drugs (Brandsch et al., 2008; Oostendorp et al., 2009; Rubio-Aliaga & Daniel, 2008; Yang et al., 2006; Zhou, 2008). The pharmacological effect and the disposition of drugs are thus highly influenced by the function of transporters located in specific tissues (Ayrton & Morgan, 2008; Calcagno et al., 2007; Türk & Szakács, 2009; Yuan et al., 2008). Evidence also supported the consequence of the involvement of transport proteins in the pharmacokinetic variability and the safety of drugs in human use (Tsuji, 2006).

3.2 Drug-drug and drug-food interaction along biological processing of xenobiotics

Reports demonstrated that transporters in the intestine for absorption and in the kidney for excretion showed characteristics of broad substrate specificity, indicating the possibility of drug-drug and drug-food interactions. The pitfalls of transporter-mediated drug-drug, drug-food or drug-herbal interaction is thus an important issue to be elaborated for drug safety concern (Huang & Lesko, 2004; Pal & Mitra, 2006; Ward, 2008). Kidney, for example, is one of the important sites of drug-drug and drug-food interaction. The competition of renal transporter between drugs and food may change the bioavailability of drugs due to the change of renal clearance rate (Bachmakov et al, 2009; Kindla et al., 2009; Li et al., 2006; Tsuda et al., 2009; Wojcikowski, 2004). Thus a predictable ADME-toxicity modulation is important in the process along drug development (Szakács et al., 2008).

The metabolic system processing the biotransformation of xenobiotics provides another pitfalls for drug-drug and drug-food interaction (Tirona & Bailey, 2006). Reports indicated that hepatotoxicity (Brazier & Levine, 2003; Furbee et al., 2006; Holt & Ju, 2006; Schiano, 2003; Tang, 2007; Wang et al., 2006) and renal toxicity (Wojcikowski et al., 2004) of xenobiotics are associated with the formation of reactive metabolites no matter they are from synthetic or herbal resources (Venkatakrishnan & Obach, 2007; Zhou et al., 2007).

3.3 Risk-benefit assessment of pharmaceutical products

As potential risks in relation to the administration of xenobiotics are frequently reported, the biological activity is not the only criteria for the justification of medicinal substances for therapeutic use. The integrative judgment of medicinal substance-host interaction based on the quality, safety and efficacy is essential for risk-benefit assessment in drug approval. In order to increase the successful rate, strategy in new drug development is thus evolved from the conventional sequential involvement of chemistry, pharmacodynamics (PD), toxicity (tox) and pharmacokinetics (ADME/PK) (Fig. 3a) to parallel PD/PK assessment (Fig. 3b) for optimizing drug efficacy. Novel approaches are using biological ADME mechanism for new drug design at early stage of drug discovery (Fig. 3c) (Dingemanse & Appel-Dingemanse, 2007). Evidence-based justification of drug-drug and drug-food interaction also becomes a standard procedure for safety evaluation of new drug application by pharmaceutical regulatory bodies (Hartford et al., 2006; Zhang et al., 2008).

3.4 Pharmacovigilance

Genetic and culture differences such as food and nutritional intake are among the factors that influence the therapeutic outcome of drugs. Therefore, safety evaluation of marketed

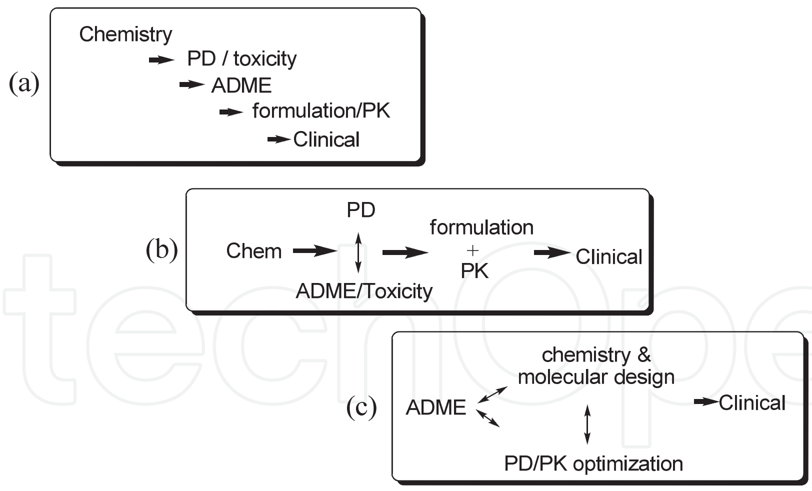

Fig. 3. The evolution of strategies in drug development from (a) sequential involvement of PD, ADME /PK to (b) PD and ADME /PK abreast and to (c) ADME for new drug design.

drugs should be based on good quality of evidence of the growing population that take the drug after a reasonably long period of time (Laupacis et al, 2002). 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 (McFarlance, 2002).

4. Potential risk from co-medication

4.1 Polypharmacy

Polypharmacy is widespread in the general population, especially in the elderly. Besides registered medicine, the population of CAM users is growing, especially in the aged and in patients with chronic disease (Chung et al., 2009; Desai & Grossberg, 2003; Kennedy, 2005; McKenna & Killoury, 2010; Miller et al., 2008; Nowack et al., 2009; Ohama et al., 2006; Ramage-Morin, 2009). The most prevalent use of CAM are for treating cardiovascular disease, pain healing, cancer adjuvant therapy and obesity (Izzo, 2005). According to a questionnaire-based survey research on CAM use, 55% of the 356 patients registered in hospital emergency department have tried at least one CAM therapy within the past 12 months, 17% have tried CAM for their presenting medical problem (Li et al., 2004).

A considerable large portion of patients take CAM with registered medicines without notification to professionals. Therefore, standard tools for regular monitoring of pharmacovigilance have its limitation. Safety threat as a result of drug-CAM interaction emerges from various scientific and pharmacoepidemiological reports (Anastasi et al., 2011; Balbino & Dias, 2010; Chiang et al., 2005; Cockayne et al., 2005; Sim & Levine, 2010; Smith et al., 2011; Tarirai et al., 2010). As it is not evidence-based, risk from polypharmacy especially from co-medication of prescribed drugs with CAM is inevitable. A UK perspective report raised an increasing awareness of herbal use and the need to develop pharmacovigilance practice (Barnes, 2003).

4.2 Social aspects in relation to the risk of medication and polypharmacy

Polypharmacy implies a potential risk of pharmacovigilance in societies where co-medication is prevalent. Taiwan for example is known for its outstanding national health insurance program which benefits 99% of the population. The welfare-like program rendered Taiwanese a potential overuse of the healthcare system, as indicated by the high physician's visit per person and the large number of drug items per prescription (Table 1) (Department of Health, 2008; Gau, 2007; Huang, & Lai, 2006; Hsu et al., 2004). Moreover, most of the prescriptions are massively dispensed in hospitals, with a released rate of 0.41%(year 2008) to community pharmacies on refills for patients with chronic disease (Bureau of National Health Insurance, Department of Health, 2011). The imbalanced distribution of pharmacy service between hospitals, clinics and community pharmacies further reflects the lack of mechanism for risk prevention on medication (Table 2).

	Taiwan	OECD countries
physician's visits (no. of visits/person/year)	15.2	5.9
Drug items per prescription	4.2	1.9
Drug expenditure to total national health insurance cost	25%	~15%

Table 1. Statistics of medication profile in Taiwan. Data of year 2008 are from National Health Insurance Database.

	Number of prescriptions	Number of pharmacists	Prescriptions dispensed /pharmacist/day
Medical Center	31,172,000	725	154
Regional Hospital	34,368,000	880	139
Local hospital	35,137,000	770	160
Clinics	217,052,000	8,404	91
Community Pharmacy	31,290,000	3,348	33

Table 2. Distribution of prescriptions to pharmacy for dispensing in Taiwan. Data of year 2008 are from National Health Insurance Database.

4.3 Regulatory aspects in relation to the risk of polypharmacy

CAM are marketed without license in most of the developed countries. Claims for therapeutic efficacy of CAM are thus prohibited or limited to authorized indications (World Health Organization, 2001 & 2004; Ziker, 2005). However, traditional Chinese medicine (TCM) are classified as licensed drugs in oriental societies. For example, TCM are separately registered from conventional pharmaceutical products via bilateral regulatory systems in Taiwan. Drug adverse events are managed via bilateral reporting systems as well. With the requirement of good manufacturing practice (GMP), the number of license issued to conventional medicine decreased drastically. The number of TCM license, on the other hand, increased with a significantly high growth rate (Table 3). The separation of regulatory and administrative management on conventional medicine and TCM leads to the fragmentation of information regarding to polypharmacy. Patients and consumers are thus facing an unknown risk from irrational co-medication.

	Conventional pharmaceutical products		TCM products	
year	prescription	over-the-counter	Prescription	over-the-counter
1995	14718	7152	2394	4663
Total in 1995	21,870		7,075	
2006	4235	1385	4663	6444
Total in 2006	5,620		11,107	

Table 3. Licenses issued for conventional pharmaceutical products and TCM in Taiwan.

4.4 Pharmaco-epidemiological aspects in relation to the risk of polypharmacy

Herbal medicine includes TCM, CAM and nutraceuticals. With the prevalence of CAM use, inappropriate commercial advertisements in the media are also prevalent. 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 nutraceuticals and 15% goes to TCM (Fig. 4a). The illegal advertisement rate is even higher on radio, with TCM ranked the top (53%) followed by nutraceuticals (31%) (Fig. 4b). Most of the advertisements are claims for weight reduction and for the treatment of erectile dysfunction while are lack of evidence.

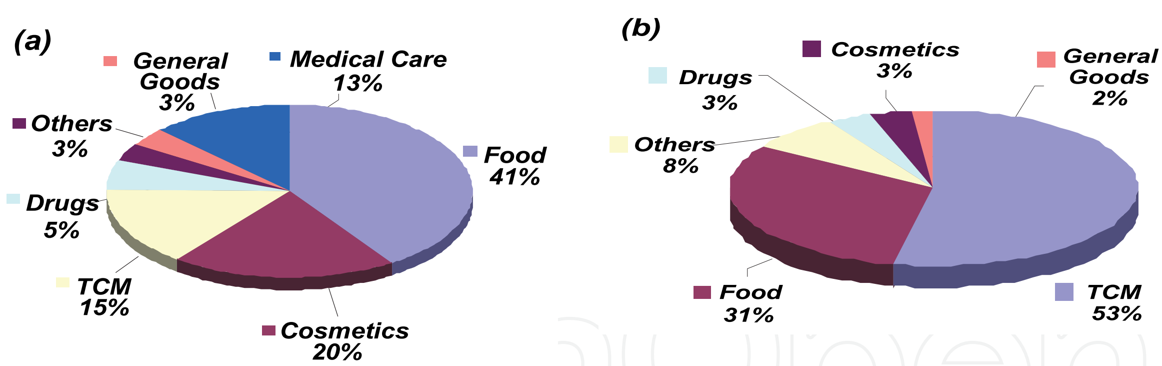

Fig. 4. Identified illegal advertisement of medicinal products in year 2004 on cable TV (a) and (b) radio in Taiwan (data are from Taiwan Drug Relief Foundation).

The incidence rate of end-stage renal disease (ESRD) of Taiwan ranked the top among the world (Fig. 5) (United States Renal Data System, 2006). The prevalence rate of ESRD in Taiwan raised from 1 per 2999 population in year 1991 to 1 per 498 population in 2006 (Fig. 6) (National Kidney Foundation, 2006). Reports indicated that herbal therapy was positively associated with chronic kidney disease (Bagnis et al., 2004; Chang et al., 2001; Chang et al., 2007; Guh et al., 2007; Nowack, 2008; Zhou et al., 2007). Safety issue in relation to polypharmacy becomes a challenge to the authority and the medical society.

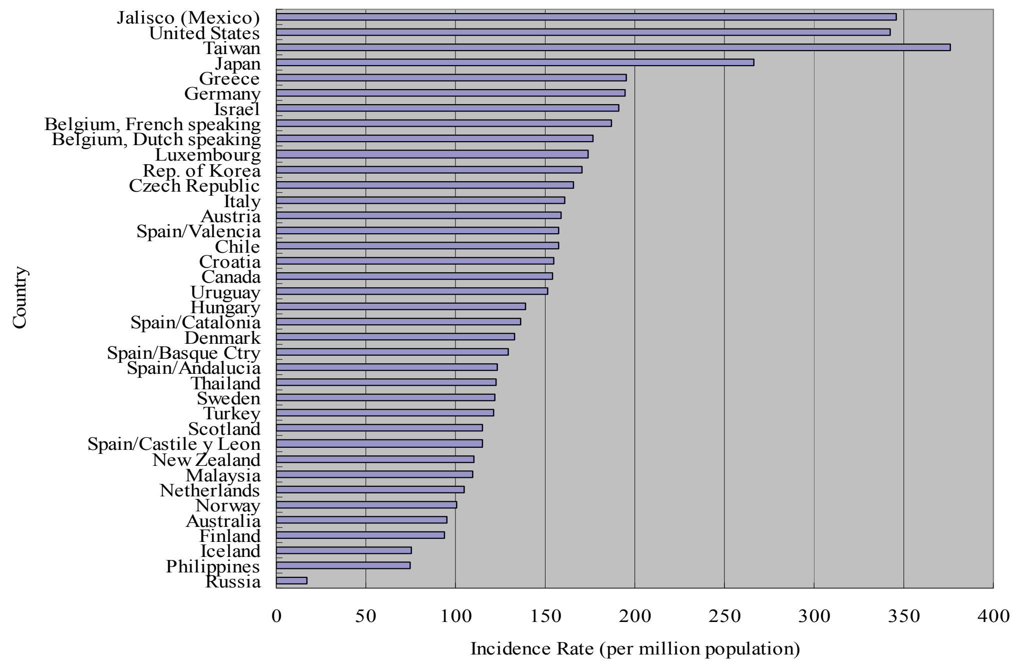

Fig. 5. The statistics of global incidence rate of end-stage renal disease (ESRD).

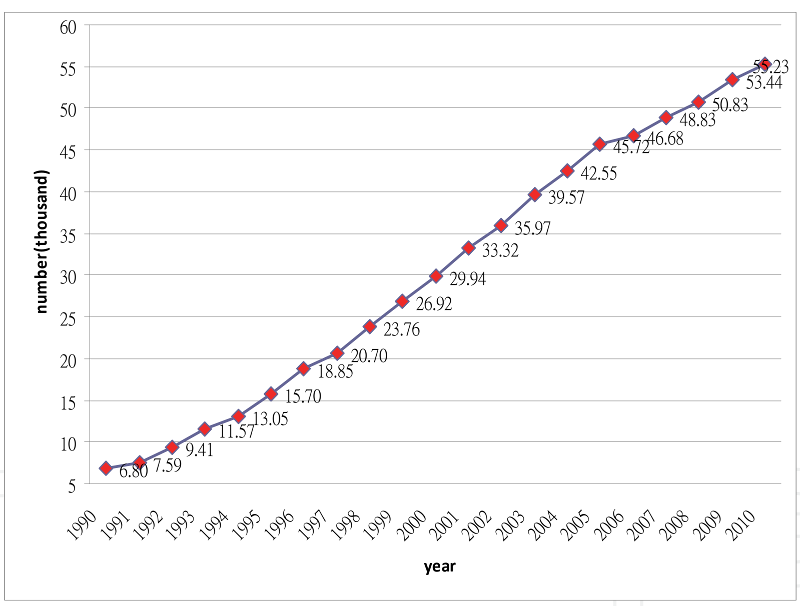

Fig. 6. The prevalence of end stage renal dialysis (ESRD) in Taiwan. Data are from the Bureau of National Health Insurance, Department of Health.

5. Risk management of medication

5.1 Global trend on risk management of pharmaceutical products

Two conceptual aspects regarding to risk management on medication were introduced by International Conference on Harmonization (ICH) (Bahri & Tsintis, 2005; Moseley, 2004; Tsintis & La Mache, 2004). Pharmacovigilance Specification (PV) addressed the evidence-based justification of drug safety throughout the life cycle of individual pharmaceutical product from preclinical development to post-market use. Pharmacovigilance Planning (PVP) emphasizes risk prevention and minimization of medication use (Callréus, T. 2006; Cappe et al., 2006).

5.2 From pharmacovigilance to pharmacovigilance planning

Following the conceptual initiation of PVP, 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 (International Conference on Harmonization, 2005). The guidance addresses the identification of all possible signals of risk regarding to drug use. Evidence-based approaches to risk assessment, such as genetic/racial and cultural factors (food and nutrition), are included. Pharmaco-epidemiological study becomes important for risk analysis (Fig. 7).

Fig. 7. The evolution of risk management of medication from product-oriented pharmacovigilance to risk management in pharmacovigilance planning.

5.3 System building for safe medication

The change from PV to PVP indicated the evolution from product-oriented risk management on individual medicine to a proactive risk prevention and minimization of medication. However, the risk management for pharmacovigilance initiated by ICH is essentially based on the refinement of safety-signal identification of registered pharmaceutical products. What is less addressed is the medicinal-type products without drug license. Risk prevention and minimization is thus difficult to be implemented in societies where patients tend to take conventional medicine and CAM without evidence-based justification in mind.

There is urgent need to call for public attention for the system building of safe medication. Risk and benefit assessment should be conducted on subjects who take all kinds of medicinal products via an un-biased integrative justification process. Humanity-based medication thus should be justified by the quality, safety and efficacy of medicines, no matter they are from synthetic, biological, biotechnological or herbal resources.

5.4 GDDP is essential for implementing pharmacovigilance planning

Following the guideline of Good Dispensing Practice (GDP), safe medication is fundamentally guaranteed for patients taking licensed pharmaceutical products. However, besides professional pharmacists, stakeholders involved in product and information delivery, namely product providers, medical professionals, the third party drug payers, media, patients and 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, good practice in the delivery of medicinal products as well as medication information is equally important to good dispensing practice (Fig. 8). This is especially important in societies where the due process of safe medication is not properly implemented by the authority. For example, due to the lack of a due process in the separation of prescription from dispensing in Taiwan, irrational co-medication is common. A study on risk factor analysis of co-medication of cisapride and erythromycin identified that the major risk came from the mal-prescription of medical professionals (Gau et al., 2007).

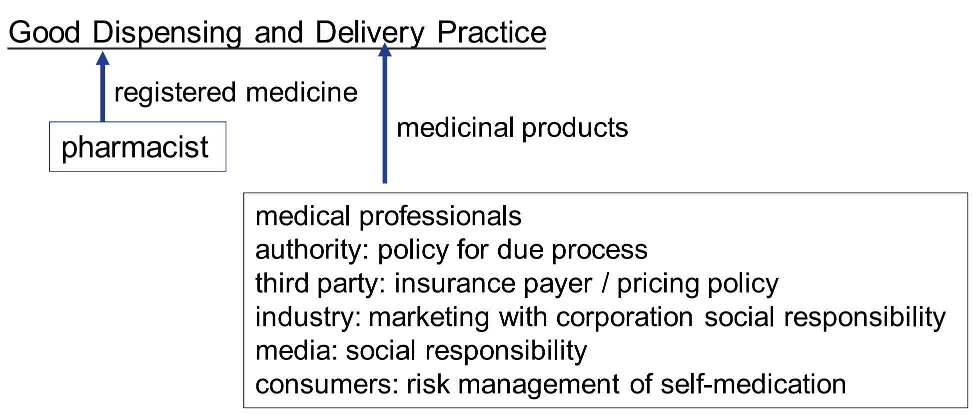

Fig. 8. Good Dispensing and Delivery Practice is essential for the system building of safe medication.

6. 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 medication is thus important for the system building of safe medication. The use of medicinal products needs to be evolved from pharmacovigilance of individual products to humanity-based integrative risk-benefit assessment for risk minimization. Although challenging the culture in societies prevalent of irrational medication and co-medication is most likely unwelcome, mechanism for consumer protection on system building for risk minimization need to be continuously addressed, proactively designed and pragmatically implemented.

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8. References

Anastasi, J. K., Chang, M. & Capili, B. (2011). Herbal Supplements: Talking with your Patients. *J. Nurse Pract.*, Vol.7, No.1, pp. 29-35.

Ayrton, A. & Morgan, P. (2008). Role of transport proteins in drug discovery and development: pharmaceutical perspective. *Xenobiotica*, Vol.38, No.7-8, pp. 676-708.

Bachmakov, I., Glaeser, H., Endress, B., Mörl, F., König, J. & Fromm M. F. (2009). Interaction of beta-blockers with the renal uptake transporter OCT2. *Diabetes Obes. Metab.*, Vol.11, No.11, pp. 1080-1083.

Bagnis, C. I., Deray, G., Baumelou, A., Le Quintrec, M. & Vanherweghem, J. L. (2004). Herbs and the kidney. *Am. J. Kidney Dis.*, Vol.44, No.1, pp. 1-11.

Bahri, P. & Tsintis, P. (2005). Pharmacovigilance-related topics at the level of the International Conference on Harmonisation (ICH). *Pharmacoepidemiol. Drug Saf.*, Vol.14, No.6, pp. 377-387.

Balbino, E. E. & Dias, M. F. (2010). Pharmacovigilance: A step towards the rational use of herbs and herbal *medicines. Brazilian J. Pharmacognosy*, Vol.20, No.6, pp. 992-1000.

Barnes, J. (2003). Pharmacovigilance of herbal medicines: A UK perspective. *Drug Saf.*, Vol.26, No.12, pp. 829-851.

Brandsch, M., Knütter, I. & Bosse-Doenecke E. (2008). Pharmaceutical and pharmacological importance of peptide transporters. *J. Pharm. Pharmacol.*, Vol.60, No.5, pp. 543-585.

Brazier, N. C. & Levine, M. A. (2003). Drug-herb interaction among commonly used conventional medicines: A compendium for health care professionals. *Am. J. Ther.*, Vol.10, No.3, pp. 163-169.

Bureau of National Health Insurance, Department of Health (2011). Available from: http://www.nhi.gov.tw/webdata/webdata.aspx?menu=&menu_id=&wd_id=&webdata_id=3812

Calcagno, A. M., Kim, I. W., Wu, C. P., Shukla, S. & Ambudkar, S. V. (2007). ABC drug transporters as molecular targets for the prevention of multidrug resistance and drug-drug interactions. *Curr. Drug Del.*, Vol.4, No.4, pp. 324-333.

Callréus, T. (2006). Use of the dose, time, susceptibility (DoTS) classification scheme for adverse drug reactions in pharmacovigilance planning. *Drug Saf.*, Vol.29, No.7, pp. 557-566.

Cappe, S., Blackburn, S., Rosch, S. & Tsintis, P. (2006). Proactive planning in pharmacovigilance. *Good Clin. Practice J.*, Vol.13, No.6, pp. 14-17.

Chang, C. H., Wang, Y. M., Yang, A. H. & Chiang, S. S. (2001). Rapidly progressive interstitial renal fibrosis associated with Chinese herbal medications. *Am. J. Nephrol.*, Vol.21, No.6, pp. 441-448.

Chang, C. H., Yang, C. M. & Yang, A. H. (2007). Renal diagnosis of chronic hemodialysis patients with urinary tract transitional cell carcinoma in Taiwan. *Cancer*, Vol.109, No.8, pp. 1487-1492.

Chiang, H. M., Fang, S. H., Wen, K. C., Hsiu, S. L.,Tsai, S. Y., Hou, Y. C., Chi, Y. C. & Chao, P, D. (2005). Life-threatening interaction between the root extract of Pueraria lobata and methotrexate in rats. *Toxicol. Appl. Pharmacol.*, Vol.209, No.3, pp. 263-268.

Chung, V. C., Lau, C. H., Yeoh, E. K. & Griffiths, S. M. (2009). Age, chronic non-communicable disease and choice of traditional Chinese and western medicine outpatient services in a Chinese population. *BMC Health Serv. Res.*, Vol.9, No.207.

Cockayne, N. L., Duguid, M. & Shenfield, G. M. (2005). Health professionals rarely record history of complementary and alternative medicines. *Br. J. Clin. Pharmacol.*, Vol.59, No.2, pp. 254-258.

Department of Health, Executive Yuan database (2010). Available from: http://www.doh.gov.tw/CHT2006/DM/DM2_2_p02.aspx?class_no=440&now_fod_list_no=11468&level_no=1&doc_no=77184

Desai, A. K. & Grossberg, G. T. (2003). Herbals and botanicals in geriatric psychiatry. *Am. J. Geriatr. Psychiatry*, Vol.11, No.5, pp. 498-506.

Dingemanse, J. & Appel-Dingemanse, S. (2007). Integrated pharmacokinetics and pharmacodynamics in drug development. *Clin. Pharmacokinet.*, Vol.46, No.9, pp. 713-737.

Eddershaw, P. J., Beresford, A. P. & Bayliss, M. K. (2000). ADME/PK as part of a rational approach to drug discovery. *Drug Discov. Today*, Vol.5, No.9, pp. 409-414.

Ekins, S., Honeycutt, J. D. & Metz, J. T. (2010). Evolving molecules using multi-objective optimization: Applying to ADME/Tox. *Drug Discov. Today*, Vol.15, No.11-12, pp. 451-460.

Furbee, R. B., Barlotta, K. S., Allen, M. K. & Holstege, C. P. (2006). Hepatotoxicity associated with herbal products. *Clin. Lab. Med.*, Vol.26, No.1, pp. 227-241.

Gau, C. S., Chang, I. S., Wu, F. L. L., Yu, H. T., Huang, Y. W., Chi, C. L., Chien, S. Y., Lin, K.M., Liu, M.Y., Wang, H.P. (2007). Usage of the claim database of national health insurance programme for analysis of cisapride-erythromycin co-medication in Taiwan. *Pharmacoepidemiol. Drug Saf.* Vol.16, No.1, pp. 86-95.

Grossman, I. (2009). ADME pharmacogenetics: Current practices and future outlook. *Expert Opin. Drug Metab. Toxicol.*, Vol.5, No.5, pp. 449-462.

Guh, J. Y., Chen, H. C., Tsai, J. F. & Chuang, L. Y. (2007). Herbal therapy is associated with the risk of CKD in adults not using analgesics in Taiwan. *Am. J. Kidney Dis.*, Vol.49, No.5, pp. 626-633.

Harris, R. Z., Jang, G. R. & Tsunoda, S. (2003). Dietary effects on drug metabolism and transport. *Clin. Pharmacokinet.*, Vol.42, No.13, pp. 1071-1088.

Hartford, C. G., Petchel, K. S., Mickail, H., PerezGutthann, S., McHale, M., Grana, J. M. & Marquez, P. (2006). Pharmacovigilance during the pre-approval phases: An evolving pharmaceutical industry model in response to ICH E2E, CIOMS VI, FDA and EMEA/CHMP risk-management guidelines. *Drug Saf.*, Vol.29, No.8, pp. 657-673.

Holt, M. P. & Ju, C. (2006). Mechanisms of drug-induced liver injury. AAPS J. Vol.8, No.6, pp. E48-E54.

Hsu, Y. C., Huang W. F. & Cheng S. H. (2004). Inappropriate prescribing of non-narcotic analgesics in Taiwan NHI ambulatory visits. *Chin. Pharm. J.*, Vol.56, No.36, pp. 111-120.

Huang, S. M. & Lesko, L. J. (2004). Drug-drug, drug-dietary supplement, and drug-citrus fruit and other food interactions: What have we learned? *J. Clin. Pharmacol.*, Vol.44, No.6, pp. 559-569.

Huang, W. F. & Lai, I. C. (2006). Potentially inappropriate prescribing for insomnia in elderly outpatients in Taiwan. *Int. J. Clin. Pharmacol. Ther.*, Vol.44, No.7, pp. 335-342.

International Conference on Harmonization. (2005). Guidance on E2E pharmacovigilance planning; availability. Notice. *Fed. Regist.* Vol.70, No.62, pp. 16827-16828.

Izzo A. A. (2005). Herb-drug interactions: An overview of the clinical evidence. *Fundam. Clin. Pharmacol.*, Vol.19, No.1, pp. 1-16.

Kennedy, J. (2005). Herb and supplement use in the US adult population. *Clin. Ther.*, Vol.27, No.11, pp. 1847-1858.

Kindla, J., Fromm, M. F. & König, J. (2009). In vitro evidence for the role of OATP and OCT uptake transporters in drug-drug interactions. *Expert Opin. Drug Metab. Toxicol.*, Vol.5, No.5, pp. 489-500.

Laupacis, A., Anderson, G. & O'Brien, B. (2002). Drug policy: making effective drugs available without bankrupting the healthcare system. *Healthc Pap,* Vol.3, No.1, pp. 12-30.

Li, J. Z., Quinn, J. V., McCulloch, C. E., Jacobs, B. P. & Chan, P. V. (2004). Patterns of complementary and alternative medicine use in ED patients and its association with health care utilization. *Am. J. Emerg. Med.*, Vol.22, No.3, pp. 187-191.

Li, M., Anderson, G. & Wang, J. (2006). Drug-drug interactions involving membrane transporters in the human kidney. *Expert Opin. Drug Metab. Toxicol.,* Vol.2, No.4, pp. 505-532.

Lombardo, F. & Waters, N. J. (2011). Drug design from the ADME/PK perspective: Does chemical intuition suffice in multifaceted drug discovery? *Curr. Top. Med. Chem.,* Vol.11, No.4, pp. 331-333.

McFarlance, A. (2002). Drug policy: the challenge is to overcome fragmentation. *Healthc Pap,* Vol.3, No.1, pp. 38-42.

McKenna, F. & Killoury, F. (2010). An investigation into the use of complementary and alternative medicine in an urban general practice. *Ir. Med. J.*, Vol.103, No.7, pp. 205-208.

Miller, M. F., Bellizzi, K. M., Sufian, M., Ambs, A. H., Goldstein, M. S., Ballard-Barbash, R. (2008). Dietary Supplement Use in Individuals Living with Cancer and Other Chronic Conditions: A Population-Based Study. *J. Am. Diet. Assoc.,* Vol.108, No.3, pp. 483-494.

Moseley, J. N. S. (2004). Risk management: A European regulatory perspective. *Drug Saf.*, Vol.27, No.8, 499-508.

Nassar, A. E. F., Kamel, A. M. & Clarimont, C. (2004). Improving the decision-making process in the structural modification of drug candidates: Enhancing metabolic stability. *Drug Discov. Today*, Vol.9, No.23, pp. 1020-1028.

Nassar, A. E. F., Kamel, A. M. & Clarimont, C. (2004). Improving the decision-making process in structural modification of drug candidates: Reducing toxicity. *Drug Discov. Today*, Vol.9, No.24, pp. 1055-1064.

Nowack, R. (2008). Herb-drug interactions in nephrology: Documented and theoretical. *Clin. Nephrol.,* Vol.69, No.5, pp. 319-325.

Nowack, R., Ballé, C., Birnkammer, F., Koch, W., Sessler, R. & Birck, R. (2009). Complementary and Alternative Medications Consumed by Renal Patients in Southern Germany. *J. Ren. Nutr.,* Vol.19, No.3, pp. 211-219.

Ohama, H., Ikeda, H. & Moriyama, H. (2006). Health foods and foods with health claims in Japan. *Toxicology*, Vol.221, No.1, pp. 95-111.

Oostendorp, R. L., Beijnen, J. H. & Schellens, J. H. M. (2009). The biological and clinical role of drug transporters at the intestinal barrier. *Cancer Treat. Rev.,* Vol.35, No.2, pp. 137-147.

Pal, D. & Mitra, A. K. (2006). MDR- and CYP3A4-mediated drug-herbal interactions. *Life Sci.*, Vol.78, No.18, pp. 2131-2145.

Ramage-Morin, P. L. (2009). Medication use among senior Canadians. *Health reports / Statistics Canada, Canadian Centre for Health Information,* Vol.20, No.1, pp. 37-44.

Rubio-Aliaga, I. & Daniel, H. (2008). Peptide transporters and their roles in physiological processes and drug disposition. *Xenobiotica*, Vol.38, No.78, pp. 1022-1042.

Ruiz-Garcia, A., Bermejo, M., Moss, A. & Casabo, V. G. (2008). Pharmacokinetics in drug discovery. *J. Pharm. Sci.,* Vol.97, No.2, pp. 654-690.

Schiano, T. D. (2003). Hepatotoxicity and complementary and alternative medicines. *Clin. Liver Dis.*, Vol.7, No.2, pp. 453-473.

Sim, S. N. & Levine, M. A. H. (2010). An evaluation of pharmacist and health food store retailer's knowledge regarding potentional drug interactions associated with St. John's wort. *Can. J. Clin. Pharmacol.,* Vol.17, No.1, pp. E57-E63.

Smith, C. A., Priest, R., Carmady, B., Bourchier, S. & Bensoussan, A. (2011). The ethics of traditional Chinese and western herbal medicine research: Views of researchers and human ethics committees in Australia. *Evid. Based Complement. Alternat. Med.,* Vol.2011, No.256915.

Szakács, G., Váradi, A., ÖzvegyLaczka, C. & Sarkadi, B. (2008). The role of ABC transporters in drug absorption, distribution, metabolism, excretion and toxicity (ADME-Tox). *Drug Discov. Today*, Vol.13, No.910, pp. 379-393.

Tang, W. (2007). Drug metabolite profiling and elucidation of drug-induced hepatotoxicity. *Expert Opin. Drug Metab. Toxicol.,* Vol.3, No.3, pp. 407-420.

Tarirai, C., Viljoen, A. M. & Hamman, J. H. (2010). Herb-drug pharmacokinetic interactions reviewed. *Expert Opin. Drug Metab. Toxicol.,* Vol.6, No.12, pp. 1515-1538.

Tirona, R. G. & Bailey, D. G. (2006). Herbal product-drug interactions mediated by induction. *Br. J. Clin. Pharmacol.*, Vol.61, No.6, pp. 677-681.

Tsintis, P. & La Mache, E. (2004). CIOMS and ICH initiatives in pharmacovigilance and risk management: overview and implications. *Drug Saf.*, Vol.27, No.8, pp. 509-517.

Tsuda, M., Terada, T., Ueba, M, Sato, T., Masuda, S., Katsura, T. & Inui, K. I. (2009). Involvement of human multidrug and toxin extrusion 1 in the drug interaction between cimetidine and metformin in renal epithelial cells. *J. Pharmacol. Exp. Ther.*, Vol.329, No.1, pp. 185-191.

Tsuji, A. (2006). Impact of transporter-mediated drug absorption, distribution, elimination and drug interactions in antimicrobial chemotherapy. *J. Infect. Chemother.*, Vol.12, No.5, pp. 241-250.

Türk, D. & Szakács, G. (2009). Relevance of multidrug resistance in the age of targeted therapy. *Curr. Opin.Drug Disc. Devel.,* Vol.12, No.2, pp. 246-252.

United States Renal Data System. (2006). Annual Data Report (ADR) Volume I: ATLAS of Chronic Kidney disease and end-stage renal disease in the United States, Available from http://www.usrds.org/

Venkatakrishnan, K. & Obach, R. S. (2007). Drug-drug Interactions via Mechanism-Based Cytochrome P450 Inactivation: Points to consider for risk assessment from In vitro data and clinical pharmacologic evaluation. *Curr. Drug Metab.*, Vol.8, No.5, pp. 449-462.

Wang, K., Mendy, A. J., Dai, G., He, L. & Wan, Y. J. Y. (2006). Retinoids activate the RXR/SXT-mediated pathway and induce the endogenous CYP3A4 activity in Huh7 human hepatoma cells. *Toxicol. Sci.*, Vol.92, No.1, pp. 51-60.

Ward, P. (2008). Importance of drug transporters in pharmacokinetics and drug safety. *Toxicol. Mech. Methods*, Vol.18, No.1, pp. 1-10.

Wishart, D. S. (2007). Improving early drug discovery through ADME modelling: An overview. *Drugs in R and D*, Vol.8, No.6, pp. 349-362.

Wojcikowski, K., Johnson, D. W. & Gobe G. (2004). Medicinal herbal extracts - Renal friend or foe? part one: The toxicities of medicinal herbs. *Nephrology*, Vol.9, No.5, pp. 313–318.

World Health Organization. (2001). Legal Status of Traditional medicine and Complementary/Alternative Medicine: a Worldwide Review. Geneva, document reference WHO/EDM/TRM/2001. 2.

World Health Organization. (2004). WHO guidelines for governments and consumers regarding the use of alternative therapies. *Pan Am. J. Public Health,* Vol.16, No.3, pp. 218-221.

Yang, C. Y., Chao, P. D. L., Hou. Y. C., Tsai, S. Y., Wen, K. C. & Hsiu, S. L. (2006). Marked decrease of cyclosporin bioavailability caused by coadministration of ginkgo and onion in rats. *Food Chem. Toxicol.*, Vol.44, No.9, pp. 1572-1578.

Yang, H. Y., Lin, J. L., Chen, K. H., Yu, C. C., Hsu, P. Y. & Lin, C. L. (2006). Aristolochic acid-related nephropathy associated with the popular Chinese herb Xi Xin. *J. Nephrol.*, Vol.19, No.1, pp. 111-114.

Yuan, H., Li, X., Wu, J., Li, J., Qu, X., Xu, W. & Tang, W. (2008). Strategies to overcome or circumvent P-Glycoprotein mediated multidrug resistance. *Curr. Med. Chem.*, Vol.15, No.5, pp. 470-476.

Zhang, L., Zhang, Y., Strong, J. M., Reynolds, K. S. & Huang, S. M. (2008). A regulatory viewpoint on transporter-based drug interactions. *Xenobiotica*, Vol.38, No.,78, pp. 709-724.

Zhou, S. F. (2008). Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. *Xenobiotica*, Vol.38, No.78, pp. 802-832.

Zhou, S. F., Xue, C. C., Yu, X. Q. & Wang, G. (2007). Metabolic activation of herbal and dietary constituents and its clinical and toxicological implications: An update. *Curr. Drug Metab.,* Vol.8, No.6, pp. 526-553.

Ziker, D. (2005). What lies beneath: an examination of the underpinnings of dietary supplement safety regulation? *Am. J. Law Med.*, Vol.31, No.23, pp. 269-284.

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