Journal of Food and Drug Analysis, Vol. 15, No. 4, 2007, Pages 377-386 藥物食品分析 第十五卷 第四期

From Pharmacovigilance to Pharmacovigilance Planning-- The System Building for Safe Medication

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ABSTRACT

The concept of pharmacovigilance planning (PVP) was initiated by the International Conference on Harmonization (ICH) in 2004 and followed by the publication of Topic ICH E2E Guideline. However, the implementation of PVP in societies like Taiwan where irrational medication or co-medication of conventional medicine with complementary/alternative medicine (CAM) is prevalent, became a challenge. This report aimed to (1) introduce the concept of PVP and the importance of evidence-based justification of medicinal products for risk prevention and minimization, (2) summarize the scientific evidence regarding the sites and mechanisms of drug–drug or drug-CAM interactions along the biological processing of xenobiotics and identify potential risks in relation to co-medication of conventional medicine with CAM by reviewing literatures, (3) employ public information to analyze potential risk underlying irrational medication of registered medicine, registered traditional Chinese medicine (TCM) and un-registered CAM in Taiwan, and (4) address the importance of conceptual change from individual product-oriented pharmacovigilance to a proactive system-based risk management of pharmacovigilance planning.

Key words: pharmacovigilance planning, conventional medicine, traditional Chinese medicine (TCM), complementary/alternative medicine (CAM), nutraceuticals, xenobiotics, co-medication, medication risk, safe medication

Two conceptual aspects regarding drug safety, the Pharmacovigilance Specification and the Pharmacovigilance Planning (PVP), were introduced by the International Conference on Harmonization (ICH)[(1)]. These initiatives addressed the risk management of medicines throughout their life cycle from preclinical development to post-market use[(2)]. Issues addressed in Pharmacovigilance Specification are evidence-based justification and post-market surveillance of individual drug safety[(3)], while PVP emphasized the concept of system building for safe medication.

Two major problems related to medication are emerging in societies like Taiwan where people tend to ignore the risk from irrational drug use. First, patients involved in the welfare-like National Health Insurance system exhibited a tendency of drug overuse. Second, the population using complementary/alternative medicines (CAM) are growing. Without conceptual understanding of the importance of evidence-based justification on drug use, patients tend to ignore the risk associated with co-administration of CAM with conventional registered medicine. There is urgent need to deliver the concept of patient's self involvement in safe medication by providing scientific information regarding the risk of medication. It is also important to call for public attention to the system building of an environment on knowledge-based medication.

The purpose of this report is to introduce the concept of PVP that ICH initiated and to address the importance of evidence-based medicine as humanistic approach to safe medication. Evidence regarding the sites and mechanisms of interactions between xenobiotics along biological processing of these substances, as well as potential risk related to co-medication of CAM and conventional medicine, will be summarized from peer-reviewed scientific reports. Pharmacoepidemiological aspects and potential risk underlying irrational medication of registered medicine, registered traditional Chinese medicine (TCM) and un-registered CAM in Taiwan will be discussed. The importance of conceptual change from product-oriented pharmacovigilance to a proactive pharmacovigilance planning will also be addressed.

Peer-reviewed scientific papers were retrieved from the database of PubMed Search and Retrieval System of U.S. National Library of Medicine and SCOPUS Abstract

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and Citation Database. Articles published from year 2000 to 2007 were retrieved for review. Keywords for search in the databases include [pharmacovigilance or evidence-based medicine] and drug interaction, [transporters or metabolizing enzyme or cytochrome P450] and drug interaction, [drug interaction or hepatotoxicity or nephrotoxicity] and [herbal or complementary or alternative or traditional Chinese medicine or nutraceuticals]. Public information regarding to the statistics of drug consumption, regulation, pharmacovigilance and pharmacoepidemiology in Taiwan are retrieved from the database of National Health Insurance Database (NHID), National Kidney Foundation ROC, National Reporting System of Adverse Drug Reactions in Taiwan, and the websites of the Department of Health, ROC.

I. *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 Guideline in 2005 as an action of implementing PVP[4]. It reflected a proactive thinking of the system building for safe medication. It also led to the emerging strategies for risk-management in the European Union, the USA and Japan, the three regions that intitiated the ICH.

With the concept of evidence-based medicine, the guideline addresses the identification of all possible risks regarding drug use[5,6]. All types of medicines are included in this guideline, while with major emphasis on existing registered medicine[7]. Evidence-based approaches to risk assessment such as epidemiological studies are also included in the implementation of PVP (Figure 1)[8-10].

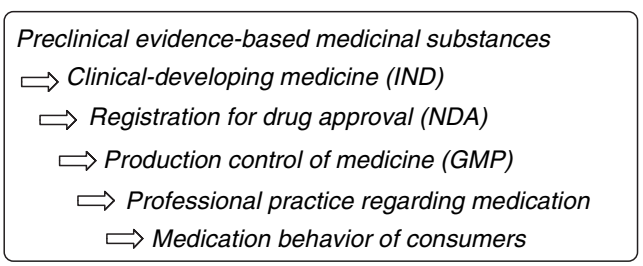

Figure 1. The life cycle and the pharmacovigilance checking points of medicines in relation to human use.

II. *Partnering of Medicine with the Body Forms the Concept of Evidence-based Medicine*

Biological processing of xenobiotics via absorption, distribution, metabolism and excretion (ADME) determines the feasibility of medicinal substances to become effective therapeutic agents[11-13]. Factors affecting the fate of xenobiotics may exist anywhere along the ADME processes and may lead to a change of well designed and documented pharmacokinetic profiles of registered pharmaceuticals[14-17]. 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. Accordingly, risk factors such as food-drug interaction and drug-drug interaction should be discussed and the evidence supporting such risks should be documented before the approval of therapeutic agents.

The concept of partnership of the body with therapeutic agents has been the fundamental theory of TCM therapy for hundreds of years. According to the theory of Bien-Tseng-Luen-Jee (辨證論治), risk and benefit assessment on therapeutic agents that human takes, no matter they are food or medicine (Iwao-Shih-Tung-Yuan, 藥食同源), determines the effectiveness of the therapy[18]. The theory of Chiung-Chen-Tsuo-Shih (君臣佐使) combination therapy, reflects a process of, in terms of modern pharmaceutical science, formulation design toward pharmacodynamic/pharmacokinetic (PD/PK) optimization (Figure 2). There is no discrepancy between TCM and modern pharmaceutical sciences in terms of pharmacovigilance.

According to the concept of pharmacovigilance, safety evaluation of marketed products should be based upon good quality evidence of the growing population taking the product after a reasonably long period of post marketing surveillance[19-20]. Therefore, information building for pharmacovigilance not only applies to pre-approved but also to marketed pharmaceutical products. The existing reporting of adverse drug reactions (ADR) on individual pharmaceutical product is thus suggested to be transformed from the passive reporting to a comprehensive proactive planning in order to overcome the fragmentation of information[21-25].

This risk management initiated by ICH is essentially based on the refinement of safety-signal identification of registered pharmaceutical products[26]. What was less addressed is the medication behavior of patients taking medicinal-type products, of which therapeutic effects are claimed while the registration for drug license is not required. As a result, patients' behavior of self-medication where phamacovigilance management is difficult to assess leads them to a situation of unknown risk. Therefore, the practice for risk minimization is difficult in societies where patients tend to take conventional medicine and CAM without evidence-based justification in mind. The PVP is also difficult to be implemented in societies like Taiwan where medicines are regulated in bilateral systems without cross references of information regarding patient's medication.

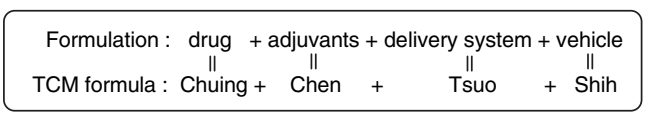

Figure 2. Chiung-Chen-Tsuo-Shih of TCM reflects a process of formulation design toward pharmacodynamic/pharmacokinetic (PD/PK) optimization.

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III. *Drug-Drug Interaction along Biological Processing of Xenobiotics*

As xenobiotics are subjected to biological processing of ADME, identification of the sites and the mechanisms of interaction between xenobiotics becomes important for the assessment of drug toxicity and its efficacy[27-35]. With the emerging evidence from system-based research, the disclosure of profiles on transporters and metabolic enzymes provides information regarding the sites and the mechanisms of ADME processing of the 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 interactions[36-42]. The transporter-directed approach for new drug design also becomes the trend for the modification or the optimization of pharmacokinetic profile of existing drugs[43-46]. As the metabolic systems process the biotransformtion of xenobiotics[47-54], reports indicated that hepatotoxicity[55-63] and renal toxicity[64-70] are associated with the formation of reactive metabolites no matter they are from synthetic or herbal resources.

On the other hand, the population of CAM users is growing[71,72], especially in the aged[73-75] and in patients with chronic disease[76,77]. The most prevalent use of CAM for therapeutic purpose are in treating cardiovascular disease[78-83], pain healing[84-87], cancer adjuvant therapy[88-94], and for obesity[95-98]. According to Li's report on a questionnaire-based survey research regarding CAM use by 356 patients registered in hospital emergency department, 55% of the patients have tried at least one CAM therapy within the past 12 months, 17% have tried CAM for their presenting medical problem. Those taking CAM had more visits to outpatient physicians than the patients without CAM therapy (7.8% vs 5.2%)[99]. A report of UK perspective on herbal safety demonstrated an increasing awareness to develop pharmacovigilance practices for herbal medicines[100].

As considerable proportions of patients are taken CAM with conventional medicines without notification to the professionals[101], standard tools for regular monitoring of pharmcovigilance thus have limitations while applied to investigating CAM[102,103]. Safety threat as a result of drug-CAM interaction emerges from various scientific and pharmacoepidemiological studies[104].

IV. *Medication Aspects in Taiwan*

High prevalence of physician's visit per person, large number of drug items per prescription, and high daily dispensing capacity per pharmacist made Taiwan of potential high risk of pharamcovigilance (Table 1)[105-107]. The imbalanced distribution of prescriptions to pharmacy for dispensing between hospitals, clinics and community pharmacies further reflects the lack of mechanism for risk prevention on medication (Table 2)[105].

V. *Regulatory Aspects in Taiwan*

Most CAMs are marketed without license in countries of the world. Claims for therapeutic efficacy are thus prohibited or limited to authorized indications[108-110]. However, pharmaceutical products in Taiwan are classified by the nature of the substances and are registered via bilateral systems. The Bureau of Pharmaceutical Affairs (BPA) conducts registration of conventional medicine and the Committee on Chinese Medicine and Pharmacy (CCMP) conducts the registration of TCM. Drug adverse events are managed via bilateral systems as well. Sponsors of pharmaceutical products of herbal origin may choose either route for product registration. For example, the alcoholic product containing herbal extracts might be registered in BPA as over-the-counters sold in pharmacy-only or registered in CCMP as herbal extracts sold in grocery stores.

With the implementation of good manufacturing practice (GMP), licenses issued by BPA decreased drastically for the past twelve years. TCM licenses on the other hand has increased at a significantly high growth rate since 1996 when CCMP started to conduct independent approval for TCM licenses (Table 3)[111]. According to Chang's report,

Table 1. Statistics of medication profile in Taiwan. Data of year 2003 are from National Health Insurance Database (NHID)

	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 2. Distribution of prescriptions to pharmacy for dispensing in Taiwan. Data of year 2003 are from National Health Insurance Database (NHID)

	No of prescriptions	No 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 3. Licenses of pharmaceuticals approved by BPA and CCMP

Year	Conventional prescriptions	Conventional over-the-counters	TCM prescriptions	TCM over-the-counter
1969~1995	14718	7152	2394	4663
1996~2006	4235	1385	4663	6444

Table 4. Statistics of ADR reporting in Taiwan and in comparison to that in the USA

	No of physician's visit[a]	No of ADR reporting cases[b]	Reporting rate (b/a)	ratio
Taiwan[a]	344,896,000	4629	0.00134%	1
USA[b]	1,746,294,000	422,889	0.024%	17.9

[a]2006; [b]2004.

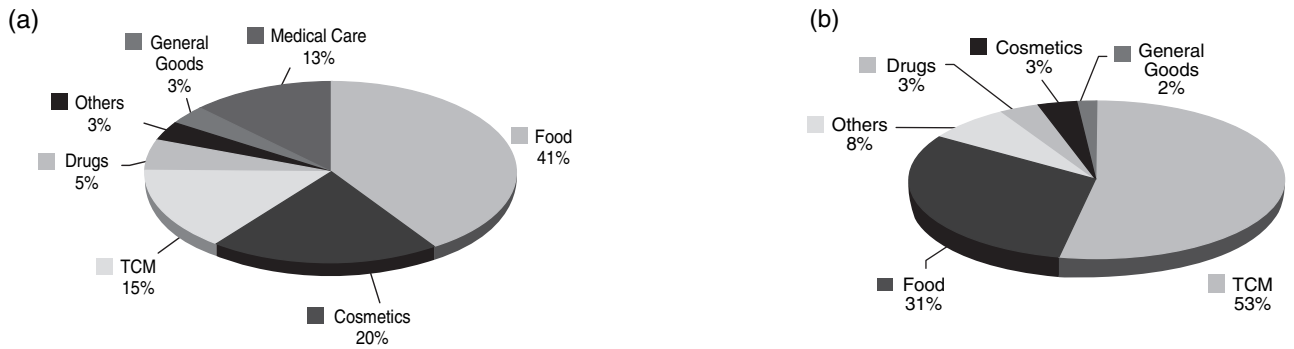

Figure 3. Identified illegal advertisement of medicinal-type products on (A) cable TV and (B) radio in Taiwan. The sampled monitoring study was conducted during August and December of year 2004.

half of the licensed TCM products are composed of more than 9 herbal components, and more than 60% of the products did not have claims for indication[111].

VI. *Pharmacoepidemiological Aspects in Taiwan*

It is commonly believed that TCM are safe and good for health. With claimed efficacy, it is convincing and encouraging to the consumers for TCM use regardless of the varied quality from doubtful sources. In order to avoid regulatory control, lots of TCM-containing products are marketed either as nutraceutical with broader claims of therapeutic use than that of the registered TCM or with indications claimed without approval. Therefore, inappropriate commercial advertisements in the media on food and medicines, especially TCM, are prevalent in Taiwan.

According to a survey study of cable TV and radio monitoring on health-related products conducted jointly by the Taiwan Drug Relief Foundation and the National Union of Pharmacists Association in year 2004, the illegal rate of advertisements on cable TV counts for 12% of total health related advertisements sampled for monitoring (183 out of 1591 cases). In terms of product nature, the illegal cases count for 41% and 15%, respectively, on food and TCM (Figure 3A). On the other hand, the illegal rate counts for 53% of total health related advertisements on radio, with TCM ranked at the top (53%), followed by food products (31%) (Figure 3B). Most of the advertisements are claims for weight reduction and for the treatment of erectile dysfunction while were lack of evidence[112].

As drug adverse reactions (ADRs) were estimated to represent the fourth to the sixth leading cause of death in the USA[113], ADR reporting becomes routine and requires pharmacovigilance practice. In comparison to the USA, Taiwanese patients have much less ADR reporting cases, with reporting rate 1/17.9 to that of the USA (Table 4)[114,115].

However, the incidence rate of end-stage renal disease (ESRD) in Taiwan ranked the top among the world (Figure 4)[116]. According to the report of National Kidney foundation ROC, the prevalence rate raised from 1 per 2999 population in year 1991 to 1 per 1054 population in year 1997, from 1 per 744 population in year 2000 to 1 per 498 population in 2006 (Figure 5)[117]. Reports of the pharmacoepidemiological studies demonstrated that analgesic use, as well as herbal therapy, was positively associated with chronic kidney disease[118,119] and urinary tract transitional cell carcinoma in Taiwan[120].

VII. *The Need for Pharmacovigilance Planning in Taiwan*

As the innovation of medicine could be as diversified as from synthetic, biological, biotechnological or natural resources, it is reasonable to address that humanity-based risk and benefit assessment rather than product-based

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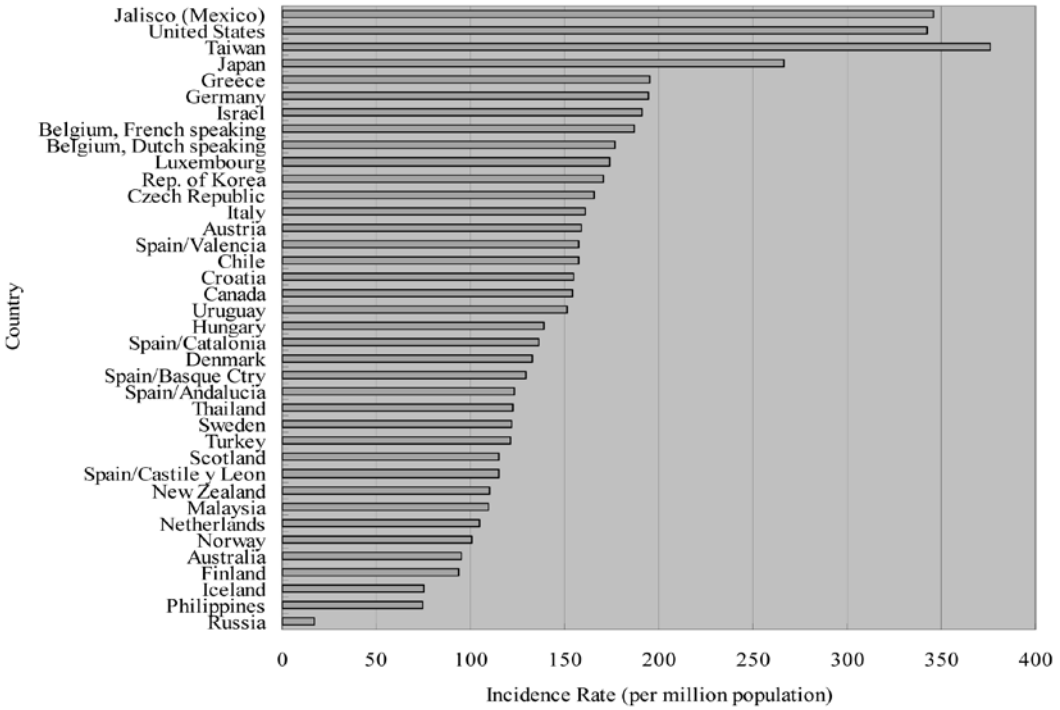

Figure 4. Comparison of the incidence rate of end stage renal dialysis (ESRD) in year 2004 among countries in the world. Data are from the website http://www.usrds.org/ of the United States Renal Data System (USRD).

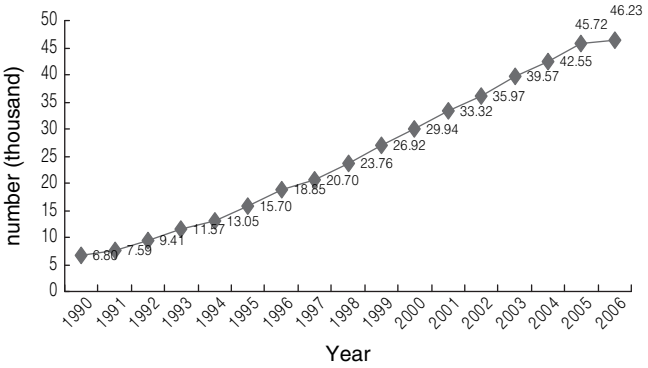

Figure 5. The prevalence of end stage renal dialysis (ESRD) in Taiwan. Data are from the web site http://www.kidney.org. tw/ of the National kidney foundation, ROC.

management should be the way for justification of the use of medicinal products, no matter that the products are for nutritional, therapeutic or healthcare reasons (Figure 6). Risk and benefit assessment of all medicinal products should thus be conducted via a unified process of integrated approach to evidence collection based on un-biased justification criteria[121]. Current bilateral systems for independent registration and regulation of conventional pharmaceutical products and TCM in Taiwan led to the fragmentation of evidences and no longer met the concept and the guideline of PVP. In order to move Taiwan toward international harmonization, a universal regulatory track should be designed and implemented based on an evidence-based justification process (Figure 7).

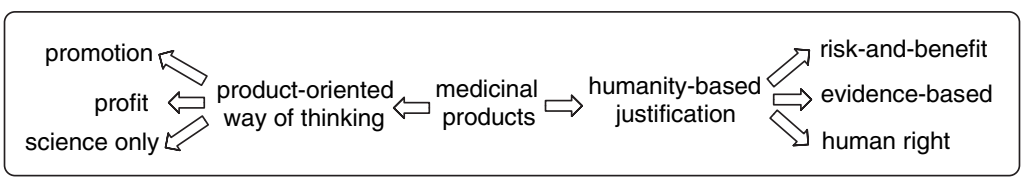

Figure 6. Conceptual difference of product-oriented pharmacovigilance and humanity-based risk justification on medication.

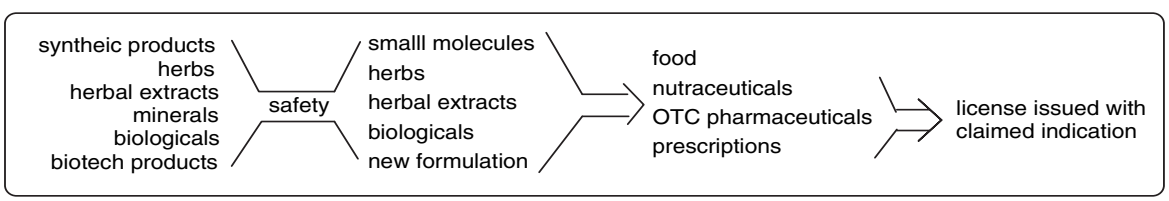

Figure 7. Uni-track of regulation on food and medicinal products is suggested. Evidence for safety assessment should be set on un-biased justification criteria, while standards of scientific evidence for efficacy assessment varies according to the nature of the products.

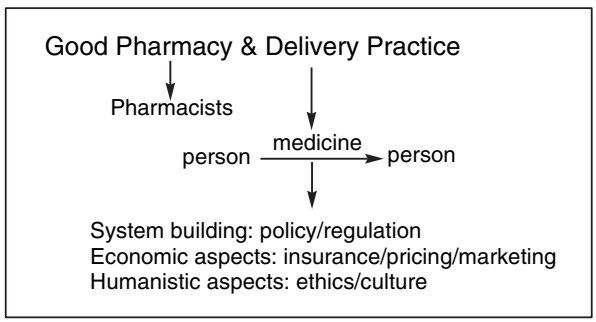

Figure 8. The system building for risk management of medicinal products is depicted as GPDP.

Although challenging the culture of irrational medication in societies like Taiwan is most likely unwelcome, mechanism for consumer protection by system building on risk minimization need to be continuously addressed, proactively designed and pragmatically implemented. Concept of Good Pharmacy and Delivery Practice (GPDP) rather than merely Good Pharmacy Practice (GPP) is thus proposed as a system building for risk management in Taiwan (Figure 8). All stakeholders involved in drug use, the product providers, professionals in medication service, patients, consumers, the third party medicinal product payers and, most importantly the policy makers should all be responsible for the implementation of PVP.

In conclusion, risk of medication not only comes from registered medicines but also from irrational use of all types of products claiming therapeutic efficacy. Product management no longer fulfills the concept of risk minimization on medication. The use of medicine need to be evolved from pharmcovigilance to pharmcovigilance planning for risk minimization. With humanistic and ethical concern, diversified approaches to the innovation of medicinal products should be followed by an universal risk-and-benefit assessment, regardless of its synthetic, biological, herbal or biotech origin. With un-biased criteria on requirement for quality, safety and efficacy, the establishment of a process of integrated evaluation of pharmcovigilance for all types of medicinal products becomes an important issue in order to move the society toward modernization and globalization.

ACKNOWLEDGEMENTS

The study was supported by the Department of Health (grant no. DOH95-TD-D-113-023).

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