

INTERNAL PROJECT OF CLRA 695
RISK MINIMIZATION STRATAGIES IN THE USA, EU, JAPAN: HOW DEVELOPING
COUNTRIES MAY BENEFIT

SUBMITTED
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DR. IRWIN G. MARTIN PhD
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BY
UDAY K SINGATHI
(E00946891)

DEDICATION

This research is completely dedicated to my parents, who gave me much support and encouragement during the course of my studies. My life in the USA could never have been possible without their love, affection, and support. I deeply express my love to my mother, Mrs. Premalatha Prabhakar, for her unending support and motivation during tough times. I am indebted to my brother, Mr. Rajesh Singathi, for his strong belief and hope in me and providing me the necessary assistance in all ways. I would also thank my friends and colleagues (Priyanka Tumuluru, Sunisha Chalasani, and Srikanth Maddali) who encouraged me during my stay at Eastern.

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ABSTRACT

Risk management strategies are the most essential elements for the drug safety profile. Developed countries like the USA, Europe, Canada and Japan are strengthening and updating their risk management plan every now and then. These countries have a systematic and well developed process of preventing drug risks in their respective markets. Developing countries like India, Pakistan, Sri Lanka and Bangladesh need to work on the improvement of their risk management processes. The risk management strategies in these countries are not as stringent and organized as the developed countries. An informal survey was conducted in rural parts in India to know the knowledge of risk management and drug risks among the pharmacists and patients. The observations of the survey have been described in detail and suggestions to improve the risk management have been proposed for developing countries and India in specific.

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1. INTRODUCTION

It is said that “No effective medicine is without risk but the benefits of a drug product have to outweigh the known risks”¹. Risk management is a process of estimating a drugs liability of risks and benefits, taking keen steps to minimize the known risks and ensure that the benefits of that drug outweigh the risks¹. Different drug regulatory agencies are undertaking different strategic programs to minimize the known risks through interventions such as medication guides, specialized education, communication plans, special monitoring, prescribing only under certain circumstances and assure the safe use of other elements^{1,2}. There has been an increased trend towards the establishment of risk minimization requirements for a class of drugs rather than an individual drug. The misuse, abuse and accidental overdose of some drugs had led to the concern to developing these strategies. The drug authorities have seriously started looking at the need to balance access to those drugs with the need to reduce abuse and drug misuse². Usually, drugs or drug classes, which come under risk minimization requirements, are subject to frequent changes. These strategies help in enhancing the communication with the patients about risks and in some cases they require registration of patients and educating the pharmacists about the risks of the drugs³.

Now, the question is, are all the drug authorities around the world following these Risk Management Strategies? Are these Risk Management Strategies really necessary? Not all the countries around the world are following these strategies though most of the developed countries have their own risk minimization strategies and developed different procedures. There are many

developing countries and under developed countries who do not have risk minimization strategies. These are mostly the non-ICH countries. The non-ICH countries include Australia, Brazil, South Africa and most of the Asian countries such as China, India, Pakistan, Sri Lanka and others.

Different countries have different means of managing or reducing the risk of marketed pharmaceuticals. The United States has FDA which monitors the risk management through the REMS program³. REMS have been effective from 2008 and since then there has been very good risk management for the drugs approved by FDA. In Europe, the risk management strategies have been monitored by European Medicines Agency (EMA). In Europe, a program similar to REMS has been into practice, known as Risk Management plans (RMP). This is a more elaborated version of the REMS in USA. In Japan, the Pharmaceuticals and Medical Devices Agency (PDMA) monitors the risk management strategies of their drugs and devices. Their management plan is more or less similar to the above practices in United States and Europe. This is known as Risk Minimization Plan (RMP). Other developed countries like Australia, Canada have similar plans to reduce or avoid the risks of a drug comparing the benefits of it.

The risk management strategies followed in most of the developed countries is very systematic and can be taken as an initiative to other developing countries. The outline of the strategies vary from one country or organization to another, but the overall functionality of the risk management strategies remain the same as to maintaining the benefit-risk balance. Countries are trying to collaborate with each other to improve the risk management strategies such as Europe and Japan. Other developing countries like China, India and Sri Lanka currently do not have an organized or systematic risk management system to decide whether the benefits of a drug outweigh the risks.

During the past years, numerous drugs have been withdrawn from the market due to safety concerns. Here, a question might arise to whether any of these drugs could have been rescued following high standard REMS. Drugs like Posicor™ (Mibefradil, generic drug) and Seldane, were removed from the market in 1998²⁵. The reason for their withdrawal was other drug interactions. Posicor, which was a blood pressure lowering drug, was found to be fatal with interaction with 26 other drugs. These drugs could have been saved by following good risk management strategies. Similarly, in Europe, an anti-diabetic drug known as Rosiglitazone has been withdrawn from the market as the post marketing studies revealed that the benefits of this drug no longer outweigh the risks. This drug was being used by thousands in Europe. This was evaluated due to stringent risk management strategies followed by EMEA.

In developing countries like India, many drugs have been withdrawn from the market. The reasons for the withdrawal are listed, but there aren't any risk management performed to justify the ban on these drugs. Phenformin, an anti-diabetic drug had been banned due to risk of lactic acidosis. Similarly, drugs like Gatifloxacin, Astemizole and Seldane have been removed from the market²⁶.

There are many other drugs which are being pulled off from the market for some or the other risk based reasons in India every year. These withdrawals are based on pharmacovigilance studies that are conducted to evaluate these drugs. There are millions of dollars being invested in research and development of these drugs which need to be handled systematically.

2. BACKGROUND

The Risk Management Strategies are followed by all the drug authorities around the world but different terminologies are used. In the United States, it is known as Risk Evaluation and Mitigation Strategies (REMS). REMS were earlier known as Risk Minimization action plans (Risk Maps) which was designed to minimize known risks for drug products⁴. The MHLW in Japan deals with a similar concept with potential risks, important identified risks and missing information known as Risk Management Plan (RMP)⁶. The European Medical Agency (EMA) has come up with a program known as European Risk Management Strategy (ERMS) which aims at providing measures that help in early detection of risks, minimization of risks and communication plans for drugs in the European countries throughout the lifecycle of the drug⁷.

2.1 Early Risk management strategy

The process of identifying a risk, analyzing it, creating an action plan to manage or avoid the risk is called risk management⁴. Risk management consists of four primary steps, risk detection, risk assessment, risk minimization and ways for risk communication. We are aware of risk management strategies in our day to day life. We experience this before we begin to do anything daily. For example, when a person has to cross a busy road, he looks on both the sides to wait for the vehicles to pass before he can cross the road to prevent the risk of being hit by a car. This is simple risk management that we are mostly unaware of.

Risk Management Plans in pharmaceutical industry needs to include the pre-approval stages of developing new medicines in submissions for approval⁵. This plan can be described as a set of

pharmacovigilance activities that characterize, identify, minimize or prevent the risks related to the drug or medicine and to communicate the concerned risks to health care providers, pharmacists and patients ⁵.

These risk strategies have been developed time and again by the concerned agencies throughout the world. The economy and development of a country plays a key role in their drug risk management. Many countries have learnt from the previous experiences of drug failures in market and their impact on patients. These lessons led to strengthening the infrastructure of risk management plans and upgrading their strategies. Today, most of the ICH following developed countries such as USA, Europe, Japan and Canada has stringent rules and regulations ⁵. But, developing countries like India, China, Sri Lanka and Pakistan have still a lot to work on their risk management strategies. In most of these countries, there isn't any department which exclusively overlooks the risk strategies like those in the developed countries. Proposals will be made to suggest risk minimization strategies for India keeping in mind the country's economy and this writer's experience working in India as a pharmacist.

3. METHODS

This paper will contain brief review of the risk minimizing processes in developed and developing countries. This will summary of the procedures and processes in the United States, Europe, Japan and developing countries, India in specific.

A. Summary of Risk Management Strategies in developed countries:

a) USA- REMS

b) EMEA-RMP

c) Japan-RMP

B. India- Specific risk management and pharmacy practice issues

Later, an informal survey conducted by the writer and the observations in India will be presented in detail. This informal survey was conducted in different pharmacy stores across Adilabad district in Andhra Pradesh. In this survey, the writer had taken the opinion and knowledge of nearly 45 pharmacists. These were either diploma holders (14) or holding a bachelor's degree in pharmacy (31). As a part of the survey, the writer had talks with pharmacists and also spent time making observations while they were attending the patients/customers. The writer had short talks with the patients/customers coming to these stores to collect their prescribed drugs and also taken their opinion and knowledge on the drug effects and medication guides. The observation from the interaction with pharmacists and patients/customers has been elaborated below with their respective charts.

The writer will then provide suggestions for improving the risk management systems in developing countries and India in particular. Two proposals will be made for this. The first

proposal will be suggestions for Indian risk management in particular and the second will be a proposal in general for developing countries in Asia.

4. RESULTS

4.1 Summary of Risk Management Strategies in developed countries:

4.1.1 US FDA

In 1960, FDA constituted a policy of complete disclosure, where the drug manufacturers had to provide all the information of their product's dose usage, effectiveness and side effects⁸. FDA also insisted on this mentioning these on the product labeling. Safety and effectiveness of a product form a crucial part of the drug licensing procedure. Controlled Substances Act (CSA) of 1970 was known as the beginning of the modern day risk management. This US federal drug policy CSA under which the prescribers, manufacturers, dispensers, product labeling, use, warning and distribution of drug products is regulated, brought in a new era of risk management by enforcing additional tools and risk indicators like letters to healthcare providers, pharmacists and also included boxed warnings^{8,9}.

Any drug approved by the FDA has to be marketed with a package insert along with the product. This package insert is the means of communication of the risks associated with its usage^{10, 11}. But, for some cases, the FDA and the manufacturers will have to go beyond the product labeling process with REMS. REM is to manage the risks of a product and to ensure that the benefits of the product outweigh the risks. FDA usually enforces REMS for a drug product or biological product with a primary goal to educate or inform the healthcare providers such as doctors and pharmacists as well as the patients. An applicant can also voluntarily submit a proposed REMS, without even being notified by FDA along with an original application or it can be a supplemental or amendment to original if it feels that REMS is necessary to ensure the benefits outweigh the risks. It is finally FDA that decides if the proposed REMS are required for that application. FDA can go ahead and also reject the proposed REMS application if it thinks

that is unnecessary and if it does not meet the FDAAA criteria. In such situations the applicant can as well undertake the alternative risk management measures that are outside of REMS ¹¹.

4.1.1.1 RiskMAPs

Before 2004, there were many drugs which were removed from market due to safety concerns, primarily; the risks of these drugs were outweighing their benefits ^{8, 11}. During this period the government started to work on developing different risk management concepts and their guidance. In March, 2005 RiskMAPs was outlined with three primary guidelines.

- 1) Developing a RiskMAP and its use
- 2) Risk assessment of a drug before marketing (Premarketing risk)
- 3) Reporting and communicating with the FDA to minimize the known risks^{10, 11}.

RiskMAPs was designed with the primary goal to minimize the known risks of a product while still preserving its benefits by following the guidance.

4.1.1.2 Risk Evaluation and Mitigation Strategy (REMS)

The Risk Evaluation and Mitigation Strategy has a primary goal to help the healthcare providers and patients to be aware of the known potential risks associated with the drug product and to work towards lessening the risk or eliminate the risk of a serious adverse reaction. The FDA, in 2008 made it a rule that any drug with potential risks need to come with a REMS plan. REMS are to make sure that the potential risks of a drug do not outweigh the benefits. The drug companies should come up with a strategic plan to manage the risks of the drug throughout its lifecycle^{8, 9}.

4.1.1.3 WHEN IS A REMS REQUIRED?

There may be numerous conditions to when REMS might be required. It can be a group of drugs with similar risk factor or medications with from the same drug class. Today many drug companies are submitting the REMS along with their NDA itself and allowing the FDA to decide if REMS is required for that particular drug⁹. Usually when a new drug is approved and there is a concern over the potential side effects or risks, FDA requires REMS to be submitted. It can also be submitted later if the sponsor becomes aware of new safety information in the post approval. FDA recommends REMS^{9, 11}.

The drug companies should also describe how the proposed REMS will be working, the objectives and goals from the time of drug approval to post marketing. But, from a sponsor's prospective; REMS implementation will be very expensive and time taking. The sponsor will have to hire more resources that will have to devote more time and efforts on the risk management, safety and regulatory activities of the drug. Usually the sponsors get very good assistance from FDA through the draft guidance and other links in their website to prepare for REMS¹².

4.1.1.4 Different elements of REMS

There are different elements of REMS that can be used by a sponsor which need to be appropriate. Below are elements proposed by the FDA based on the potential risk of the drug.

- A) Medication Guide
- B) Communication Plan
- C) EASU (Elements to Assure Safe Use)
- D) Implementation Plan

E) Timetable for submission of assessments^{13, 16}

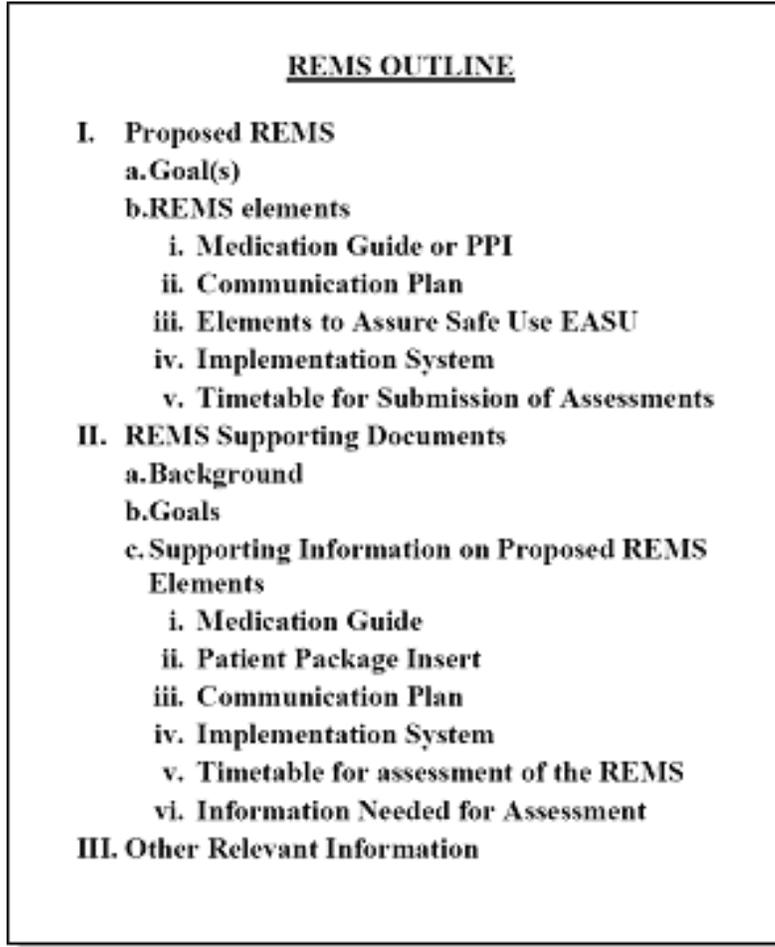


Figure1: REMS outline taken from Ref 8.

4.1.1.4a Medication Guide

According to the Code of Federal Regulation, 21 CFR 208, medication guide is required by law and draft guidance has been added to the FDA website to help the sponsors, healthcare providers and patients understand its essence. Medication guide is the most commonly used REMS tool for checking potential risks¹³.

Medication Guides are paper handouts that contain FDA approved information which is helpful to the patient to understand the potential risks of a particular drug to prevent adverse

events. The medication guide has information like what the drug exactly is, how to use that drug and what risks are involved in taking that drug. Along with the medication guides, we may also find the consumer guides which contain even more detailed information of the drug usage compare to medication guide¹⁴.

4.1.1.4b Communication Plan

It is a description of the company's plan to educate healthcare professionals on the safe use of the product to support implementation of the REMS¹⁴. The tools for a communication plan include

- a. Letters to health care providers
- b. Information about serious hazard and risks of a potential drug passed on to the providers.
- c. Seeking help of professional societies to disseminate the information.
- d. Explain the healthcare providers about safety and management protocols and encourage them to implement them^{16, 17}.

4.1.1.4c Elements to Assure Safe Use (ETASU)

FDA requires these when the drug is inherently hazardous or is intentionally abused¹⁵. This is required where PPI and communication plan are not expected to evaluate the risk factors for the drug³. FDA needs to approve drugs only in presence of such elements. Attestations (legal statement that one has met the thresholds and all of the requirements of an act), enrollment forms, training materials, patient education, safety protocols, medical monitoring procedures, and data collection forms may be included as ETASU¹⁷.

Training of prescribers/pharmacies/hospitals, patient monitoring, evidence of patient safety, drug dispensary restrictions, periodic re-certification and re-enrollment may be also included under ETASU^{16, 17}. Patient enrollment and collection of information like clinical outcomes, compliance data safety information, clinical and lab data may be important.

4.1.1.4d Implementation systems

These systems monitor and evaluate the implementation of ETASU and suggest the improvement methods for implementation. Process of distribution of applicable products by certified distributors to certified pharmacies and appropriate patients may be included as a part of these systems. A database with all certifications, conducting periodic audits to assure ETASU compliance and trustworthiness of distribution systems are the elements of REMS^{17, 18}.

4.1.1.4e Timetable for submission of assessment

Risk assessments for NDA's and BLA's should be submitted to FDA on a periodic basis in REMS. Minimum frequency of 3 assessment submissions is required for every 18, 36 and 84 months but the frequency varies depending upon the risk factors¹⁶. Three statements about period of interval between submissions and the next approximate submittal date should be notified not less than 60 days from each submission date. This periodic submission may be amended upon request or only after a 36 month assessment^{16, 17}.

4.1.2 European Medicines Agency (EMA)

At the time of authorization, a product is authorized based on the positive indications provided for the existing demographics keeping in mind the benefit and risk balance of the

product technically. A drug or product's safety information during the time of authorization is very limited due to numerous factors such as clinical trials done on relatively small population, local ethnicity, restricted age group and other demographic issues that persist during that time⁶. Though there are multiple risks attached to a product, there is a very small scope to identify the potential risks of that product during initial authorization. The actual risks are identified with necessary pharmacovigilance planning along with characterizing the safety profile of the drug from the pre and post authorized study data. When the pre-authorization or initial authorization is sought, not all potential or actual risks would have been identified. There may be other demographic population such as pregnant, children, elderly people, lactating women, people of different ethnicity with whom the drug risk is greater or the results of that drug are different^{6,7}.

While assessing a drug's profile there are a few important things to be kept in mind such classification of known and unknown risks of a drug, pharmacovigilance planning to identify new risk factors, implementation of risk mitigation strategies^{7, 19}. A drug or a medicinal product with a desired pharmacological activity will definitely have some undesired risk factors. But, its difference on target population may vary with disease prevalence and its severity. Keeping these strategies in mind a drug might have different versions of risk minimization procedures for a particular region, though there will be core RMP overall regardless of where it is being used.¹⁹

4.1.2.1 Overview of the EU-RMP structure

According to the EU-RMP (Risk Management Plan) template, the following template is categorized into Parts and Modules. The RMP consists of 7 standard parts and which are subdivided into modules which are tailored in such a way that more modules can be added or removed accordingly.²⁰

P1: Product information

This part of RMP contains the general information of a drug/medicinal product such as active drug substance in the product and the therapeutic group that it belongs to. It also holds the administrative RMP information of the parts and modules covered and the dosage, indication, strength and the forms used and also the number of medicinal products in that application.^{19,20}

P2: Safety specifications

This part of the template is again categorized into 8 different Modules. This part of RMP will form the basis for future pharmacovigilance planning and also risk minimizing strategies. Safety specifications provide the safety information of known

M1: Epidemiology of the drug indication and the target population

M2: Non-clinical section of safety specification

M3: Exposure to clinical trials

M4: Populations that were missed for clinical trials

M5: Post authorization studies

M6: Additional requirements from EMA for safety specifications

Under this module there are a few specific topics that are taken into consideration.

- Potential to be harmed with overdoses.
- Transmission of infectious diseases.
- Misuse for illegal purposes.
- Chances of medication errors or wrong medication/dose/patient.
- Possibility of off-label use.
- Particular pediatric issues²¹.

M7: Identified risks and potential risks

EU has categorized a few drug products as Advanced Therapy Medicinal Products (ATMPs) for human use. These comprise of drug products related to gene therapy and somatic cell therapy. Keeping in mind the importance and the risk factors of these kinds of drug products, the Module 7 in this case needs to be replaced with Identified and potential risks for ATMPs. Apart from these, this module also highlights other possible risks like food-drug interaction and drug-drug interaction, newly identified safety concerns from recent post authorization studies and safety implications^{7,21}.

M8: Overall summary of the safety specifications.

This module deals with the safety concerns related to the active substance, formulations to be used, route of administration, target population.

P3: Pharmacovigilance plan

This provides the structured plan for the identification of ne safety concerns of the drug product, its risk factors and the importance of missing information that needs to be sought. This part of RMP provides the information of routine and additional pharmacovigilance activities that need to be done.

P4: Planning for post-authorization studies

P5: Evaluation of the need for risk minimization

P6: RMP

P7: Summary of the RMP

Clinical and non-clinical brief overview and summary of all the above modules need to be provided. The risk management plan should be treated as a scientific document and strictly not used for promotional or commercial purposes^{19, 20}.

European Medicines Agency sees benefits of interaction with Japanese regulators. There has been an increase in the interaction between the developed countries for the betterment of drug safety and to avoid duplication of the work done. Over the past 3 years there has been constant increase in the interaction between Japan regulatory authorities and the European Medicines Agency in information exchange, regulatory education and better awareness²².

4.1.3 PMDA (Pharmaceuticals and Medical Devices Agency)

Japan can be also listed as a developed country. Their risk minimization is not as specific as EMEA or not as perfect as REMS by FDA. But, still they have implemented a different method which is also effective as are the other developed countries. The risk management plan used in Japan is known as the Risk Minimization Plan (RMP)^{22, 23}. RMP is the minimization activities that are done to lessen the potential known risk of the drug and to maintain the appropriate balance between the risks and benefits of the drug that were observed during the approval process and also the post marketing. RMP guidelines deal with the identified risks, important potential risks and other missing information which were identified during the approval process and also the post marketing studies²⁴.

In Japan, the sponsor is called a MAH (Marketing Authorization Holders). The MAH should make sure to add new implementation plan of risk/benefit assessment. The RMP should be developed at the time of approval following the E2E guidelines and the MAH is supposed to

outline the safety specifications at the time of application. If there are any safety issues that were identified after the application, the MAH is supposed to update the RMP for the review ^{22, 24}.

When can a RMP be applied?

- ❖ When a new dosage or additional indication is added to a new drug application at the time of approval.
- ❖ When a new drug combination is proposed at the time of approval review.
- ❖ When safety specification is submitted newly for re-examination at the time of approval.
- ❖ When safety specification is submitted newly for re-examination at the time of post marketing phase.
- ❖ When applying for a generic drug and its reference drug has already developed an additional potential risk activity²³.

According to the PMDA, keeping in mind the above conditions, before the sponsor submits a PMS or a basic plan for post marketing surveillance, it will have to include RMP which will contain the Pharmacovigilance Plan and the Risk Management Plan as recommended.

4.1.3.1 Risk Minimization Plan

Based on the identified Safety Specifications, MAHs should develop a Risk Management Plan to promote the safe use of a drug and also check the risk to benefit balance. Keeping the Safety Specifications in mind, additional actions should be developed and a clear description should be provided of how these actions were taken and the methods used. The contents of the Risk management Plan are assessed at the time of approval review process and any additional actions are necessary are recommended ^{23, 24}.

Below are a few considerations that a Risk Management Plan must follow:

- Identified risk population
- Demographics of patients being treated with the drug
- Potential risk of the drug
- Seriousness of the complications
- Seriousness of the disease
- Severity of the ADRs
- The impact of Adverse Drug Reactions on the benefit-risk balance.
- Safety measures and marketing strategies overseas.
- The differences in the safety profile of the drug in Japan compared to overseas.
- Effect of the Risk Minimization Plan (RMP).

All the above risk management activities need to be detailed considerably before reporting to the PDMA. The Risk Management Plan has to be developed and kept updated depending on the post marketing situations so that there is a good benefit-risk balance ²².

4.1.3.2 Pharmacovigilance Plan

Pharmacovigilance plan can be either routine pharmacovigilance plan or additional pharmacovigilance plan. This is referred to as ICH E2E guidelines and these pharmacovigilance activities are developed at the approval review and post marketing based on the Safety Specifications which primarily include important identified risks, important potential risks and important missing information²³. The PDMA usually recommends this plan to generic drugs which have additional pharmacological activities from the original drugs, follow on biologics and new drugs at the time of approval submissions. This plan is also recommended when a new safety concern has been identified during post marketing^{23, 24}.

4.2 Developing countries (India)

The drug regulatory authority in India is Central Drugs Standard Control Organization (CDSCO) which regulates the approval or new drugs to the marketing of any medicine in India. CDSCO lays down the rules and regulations for the pharmaceutical industry in India. They have subdivisions for every state which monitor the drug approval to marketing process for their respective states. The Indian pharmaceutical industry is growing at the rate of 12-14% per annum. More new drugs, vacancies and new routes of administration are coming up in the market every year. It is estimated that every year around 20,000-30,000 applications for New Chemical Entities (NCE) are being received by CDSCO. India is a country with a vast population, different ethnic variations, different medicinal practices and various disease prevalence patterns.

What could be the risk minimization strategies followed by India, a country with second highest population and a large pharmaceutical market? After a lot of research and from the writer's knowledge of pharmacy, the writer noticed that the risk minimization strategies are at its juvenile stage in this country. The risk management in India mainly concentrates on the adverse reactions monitoring. As a part of the risk management program, CDSCO has coordinators at different ADR monitoring centers (AMCs) in Zonal and sub-zonal offices. This is definitely an excellent strategy for gathering adverse events from all parts. Adverse drug reporting is a strong ICH procedure followed all throughout the world by both the developed and developing countries^{27, 28}.

In India, any person who has either a diploma or a bachelor's degree in pharmacy is eligible to open up a pharmacy outlet. There are a few thousand pharmacists graduating every

year in India. This might be one of the reasons why you can find a pharmacy outlet almost every few yards in a town. Every small clinic has an attached pharmacy with numerous generic non-generic and other drugs. Nowadays even tiny villages with a population of a couple of hundreds of people also have a pharmacy outlet.

4.2.1 Pharmacy practice in India

The literacy rate India is known to be 74.04% in 2011 but it is difficult for a layman to understand the drug by its name and dosages or understand a medicine that he has been prescribed. The issues that the writer feels that the pharmacy practice in India is facing include the following.

4.2.2 Lack of Risk managing infrastructure

Unlike developed countries such as USA, Europe and Japan, India does not have a planned and organized infrastructure that manages the risk minimizing strategies. Developed countries have an organization exclusively monitoring this domain, which makes the administration run smoothly with different checkpoints to monitor risk. Techniques like medication guides, communication plans and post marketing studies do not exist in most of the developing countries like India, Pakistan, Sri Lanka, etc. Processes such as REMS or RMP which could lay rules and regulations for minimizing the risks of drugs could be more effective. No pharmaceutical company in India or other developing countries would come forward voluntarily to market their drugs with package inserts or medication guides. A process is required to decide which medicine needs risk minimizing activities.

4.2.3 Use of Medication Guide (PPI)

Medication guides used in developed countries like USA and Japan have proved to be the first and the best risk minimization strategy. They have been effective in carrying the risk information of a drug and thus bringing awareness about that particular drug and so, minimizing the risk. In India, only a few drug manufacturers follow the practice of using a medication guide, mostly pediatric drugs. Sometimes, drugs in the form of gel or solution have medication guides with minimal information of its therapeutic dosage, effects of over dosage and its side effects which can be barely seen. Compact drugs like tablets and capsules are available in sheets which have the therapeutic ingredients printed on it with minimal content of dosage information. Pharmacists were trained to explain the use of a medication guide but hardly anyone follows it. Most importantly, it is the patients who ignore the medication guide and treat it as an unwanted waste paper ²⁹.

4.2.4 Communication Plan

There is no such Communication Plan program in India. Here the manufacturer is least bothered to give any detailed description of the risks of his product to the providers and the providers are also least bothered. Everything here is done for commercial motive of give and take. It is usually not the manufacturer that would directly communicate with providers but the middlemen with a role 'Medical Representatives' who would do knowledge transfer regarding the new drugs in the market to the providers. These middlemen were not very qualified as necessitated in law which affects the reliability of the information they provide. Providers in countries like India would ignore the risk factors and risk assessment strategies in many circumstances as they would treat their profession as a business but not a 'Profession' in its

virtual terms. These medical representatives are usually brokers who are basically behind increasing the sales of the drug product without passing on the risk information. The representatives preferentially request the providers to prescribe their drug in return for financial favors. Even if a communication plan was set up between the manufacturers and providers in one or the other way, the purpose was served in very rare circumstances.

4.2.5 Unqualified Pharmacists

As the writer mentioned earlier, in a small town in India, you will not be surprised to find at least 20 pharmacy stores. But according to IPA (Indian Pharmaceutical Association) and CDSCO, only a person with either a diploma or a bachelor's degree is a qualified pharmacist. But in most of the developing countries, you hardly see this happening. . Firstly about 70% of pharmacists in countries like India were under qualified for their designations. These are students who had just passed grade VIII or IX and are behind the counter selling medicines. Definitely, these students will have no clue about a medication guide or can they explain the risks or side effects of a drug. Prescription provided by the providers when taken to a pharmacy was handed over an under qualified pharmacist who would only sometimes provide the medication prescribed by the pharmacists. But, in most of the cases they would give the patients with drugs with other brand names or different dosage forms ³⁰. There would be some worst conditions of patients being given expired drugs too which may be less efficacious with side effects. Pharmacists lack knowledge on the benefits and side-effects of the drug due to which they fail to explain its importance to patients. There were many instances of drug-poisoning due to improper information provided by the pharmacists to the patients which wouldn't come into lime light. Pediatrics attain utmost importance in this scenario as the pharmacists would provide the patients

an over dosage/high potency medication which lead to child abnormalities³¹. Most of the patients are also unaware of side effects of a medicine and the dosages leave alone the medication guides. The so called pharmacists are at times reluctant to look into a prescription and simply give a medication that they know. There is a drug controller for every zone who is supposed to supervise these, but practically nothing has been done to change these situations.

Loopholes that the writer observed as a pharmacist:

- No higher authority or organizing infrastructure to manage the risk-benefit ratio of a new drug in market.
- Risk management plan only concentrating on ADRs and not focusing on other strategies to minimize risks of drugs.
- No proper communication plan program. Communication gap between the manufacturers and the health care providers leading to primary focus on financial benefits rather than treatment of patients.
- Prescription errors leading to pharmacists giving the wrong medicines.
- Unqualified pharmacists who do not know the principals of pharmacy leading to administering wrong medicines.
- Pharmacists who are unaware of the risks and benefits of a drug.
- Pharmacists ignorant of knowing the risks of a new drug in market and reluctant to know its facts through medication guide.
- Communication gap between the pharmacist and the patient.
- Medicines given to patients without prescription.
- Low literacy rate in suburban and rural areas.

5. DISCUSSION

5.1 US System

The simplest and best risk minimization strategies followed throughout the world in my opinion would be the REMS by FDA. REMS are to manage the risks of a product and to ensure that the benefits of the product outweigh the risks. FDA usually enforces REMS for a drug product or biological product with a primary goal to educate or inform the healthcare providers such as doctors and pharmacists as well as the patients¹¹. The primary elements of REMS are

- A) Medication Guide
- B) Communication Plan
- C) EASU (Elements to Assure Safe Use)
- D) Implementation Plan
- E) Timetable for submission of assessments^{13, 16}

5.2 EU System

Out of all the risk management strategies discussed, EU-RMP is the most detailed infrastructure. This would also mean that these strategies will be more effective to minimize the risks of a drug. But keeping the economy and infrastructure of developing countries, I would not suggest the EU-RMP system in these countries. For developing countries to implement this infrastructure they need put in loads of funds initially and they will also need to hire more number of employees. But, in my opinion EU-RMP would be the best risk management organization which would prevent the risks of a drug to a great extent.

5.3 India specific issues

After working as a pharmacist and also doing a survey in India for 2 months (May & June, 2011) in a place called Bellampally in the state of Andhra Pradesh, India, the writer was able to gather a little information regarding the knowledge of package inserts, medication guides and the communication by doctors, pharmacists and patients. A detailed description of the below mentioned issues is given in the results section.

- ❖ Lack of Risk managing infrastructure
- ❖ Use of Medication Guide (PPI)
- ❖ No Communication Plan
- ❖ Unqualified Pharmacists

Apart from these, author conducted informal surveys on the pharmacist's knowledge of medication guides, their interaction with the patients, their knowledge on the side effects of a drug and the patient's knowledge on package inserts and medication guides.

5.3.1 Pharmacist's interaction/knowledge

Compared to other developed countries, Indian literacy rate is very low. Practically speaking, most of the people find it difficult to understand English. Almost all the drugs in India, be it generic or non-generic drugs are marketed and labeled in English, which cannot be understood by a layman. The difficulty here is, there are nearly 30-40 regional languages in India and it would be very impractical for the government to implement these languages in their regions. So the easiest and practically possible method here would be to improve the communication between the pharmacists and patients and also providers and patients. In observations, author had the opportunity to interact with 45 pharmacists, most of whom own

pharmacies there. After spending considerable time with them, author had come to the below conclusion.

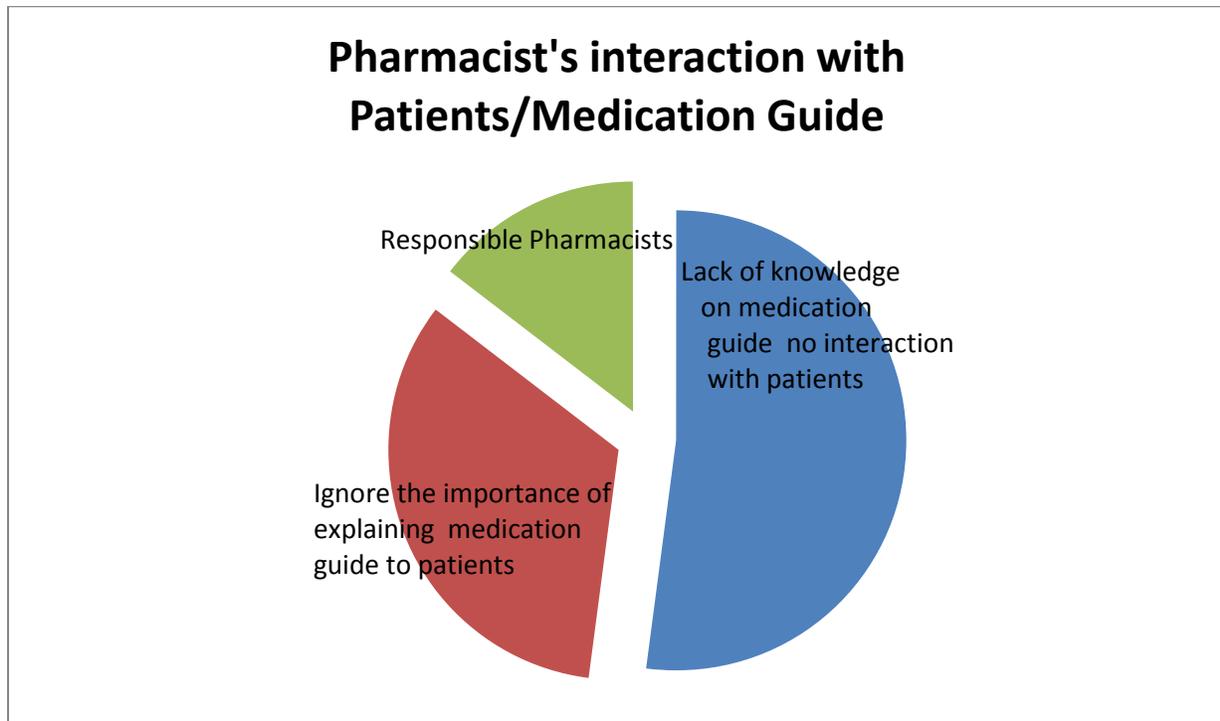


Figure 2: Pharmacist's interaction with Patients/Medication guide

- It was only business that they were doing there and not really professional.
- Out of 45 pharmacists, 22 of them did not know what a medication guide was and they did not do any interaction with the customers/patients.
- As they did not know what exactly a medication guide was they did not bother to read it nor did they know the risk of that drug.
- Next, there were 12 of them who were aware of the medication guides or package inserts knew the essence of them. But, unfortunately these neither read them nor could they understand the medication guides of package guides. They ignored them and failed to explain the risks of a drug to the patient/customer.

- Fortunately, there were 11 out of 45 pharmacists who followed the profession. They spent ample time to know about a drug through package inserts or medication guides or through internet. They were successfully able to convey the risk impacts of a drug and also take a follow up of their experience. This was a great challenge for these pharmacists as most of the patients or customers were village people who hardly knew how to read and write.

5.3.2 Patient knowledge on drug risk

At the same time, I started doing an informal survey on patients who came to collect their medicines at the pharmacies on their knowledge of drug risk, medication guides and package inserts. Surprisingly, there were a few hundred people who did not want to know the drug risk or side effects of a drug. Out of all, I could take the opinion of 184 patients/customers. The below chart depicts the percentage of people in different categories.

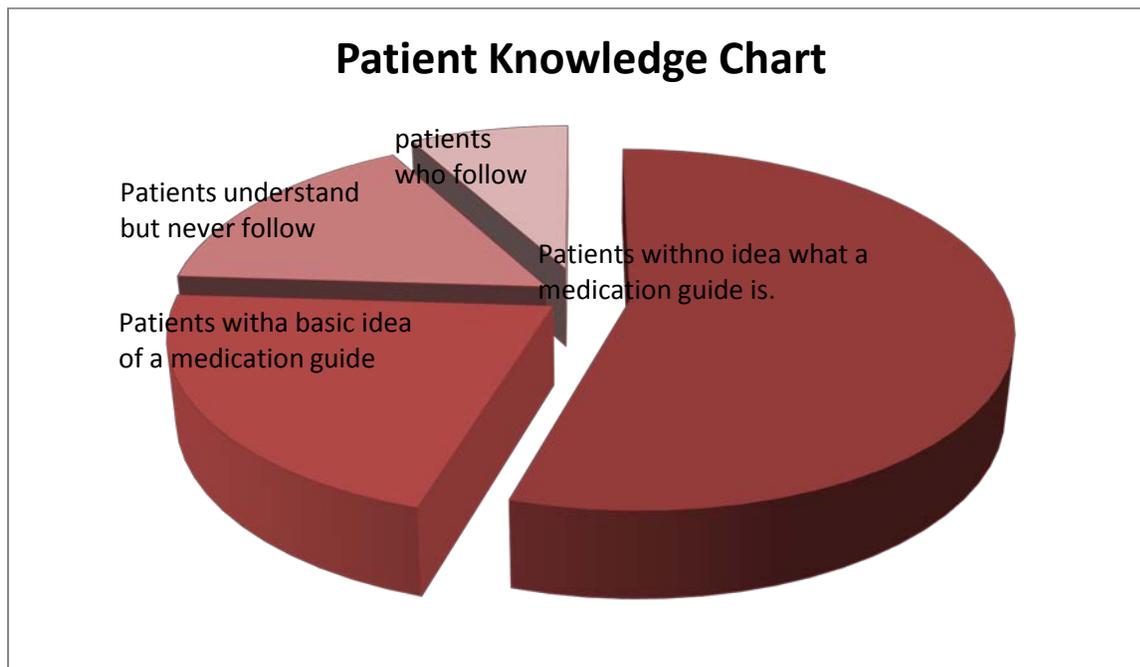


Figure 3: Patient Knowledge Chart

- ❖ Out of the 184 people that I surveyed, nearly 55%, that is 101 people had no idea of package inserts and what a medication guide in a drug were. Most of them thought that it was a piece of advertisement for that drug. A few of them did not know that a drug would have risks or side effects and most of them were not bothered to know what they were. Unfortunately, most of them were hardly educated.
- ❖ Nearly 21%, that is 51 people had a basic idea that a drug could have risk factors and side effects and knew what a package insert or medication guide contained. But, unfortunately, they did not want to communicate with the pharmacists or the providers about the risks. They just believed the drug would do whatever it is supposed to do.
- ❖ The next category was educated people which came up to 16% that are 23 out of 184 people. They knew that a medicine can have risk factors and side effects but did not bother to know them. I requested them to read a medication guide and asked the pharmacist to explain them the risks or side effects. They fortunately understood what exactly was in the packages and medication guides and also were able to follow the pharmacists.
- ❖ Finally, I had 13 people who were educated too and they did have lots of knowledge on risks, side effects, package inserts and they did follow medication guides that they came across. They were also curious to know more about the medicines that they were prescribed and kept themselves updated.

5.3.3 Healthcare Provider's (Physician) knowledge on drug risk

Below are few highlights and concerns of what I had observed. I would just like to compare the communication plan that is been implemented in the US.

- ✚ In India, you will hardly find any Letters to health care providers, basically doctors from the manufacturing companies to educate them about the risks of a new drug into market.
- ✚ There are no protocols set for the healthcare providers to learn about the safety management.
- ✚ No information about serious hazards or potential risk of drugs is passed on to the providers.
- ✚ If there are any hazards that come to the notice of a provider, it is hardly brought to the notice of the manufacturer.
- ✚ There are ‘medical representatives’ who are hired by the drug manufacturing companies to market their product. These people seriously don’t have sufficient knowledge on the drug they market and only lure the providers to prescribe their product with something in return of the favor.
- ✚ Overall, there is no communication plan, which would have helped to pass on the risk information from the manufacturer to the providers to the patients. So, there is no continuation in this chain.

5.3.4 Proposals

Based on the above research for the improvement of Risk minimizing strategies in developing countries, India in particular, two proposals will be suggested.

5.3.4.1 Proposal 1:

- ❖ First and the foremost, India needs to develop an infrastructure exclusively for risk minimization strategies in the country. Keeping in mind the economy of developing countries such as India, Pakistan, Srilanka and Bangladesh, I suggest them to follow a

FDA monitored REMS kind of system for risk minimization in their own countries. This system is simpler and less sophisticated than EU-RMP and Japan-RMP as well as suits the financial considerations of these countries. This way at least a few of the above mentioned drugs could be protected if Indian drug authorities would follow few risk management strategies similar to those of United States, Europe and Japan. This is an easy step to implement in developing countries.

- ❖ This system should be given the authority to decide whether a New Drug Application should be accompanied with a detailed risk minimization plan. This might take a little while to implement but not hard.
- ❖ In this system, I would also like to suggest an element similar to medication guide to be made available in English as well as the regional languages to improvise the patient education. This is really necessary and easy to implement.
- ❖ Since the literacy rate in developing countries is comparatively low, strong rules should be imposed such that it is the duty of the pharmacist as well as the provider to educate the patients of the risk factors of a particular drug. This might be a hard task but can be implemented up to certain extent.
- ❖ Pharmacists along with the providers should maintain the records of the patients who are being administered with a drug that has a Risk minimization plan. This step can be a great challenge, but if implemented, it would make a large difference.
- ❖ A follow-up of the adverse events for these drugs needs to be recorded and reported. This is already being practiced in most places so easy to implement.

- ❖ Knowledge transfer sessions should be organized by the manufacturers to the providers regarding the risk factors of any drug with risk minimization plan. This is a bit hard to organize but not impossible to implement.
- ❖ A detailed description of the pharmacologic factors of the drug with an RMP should be provided in a possibly efficient way to the providers to make them aware of all the risk factors of a particular drug before being prescribed to the patients.
- ❖ Need for strong post marketing studies, especially for the drugs which have a RMP so that the adverse effects can be effectively monitored. This is hard to implement but should be implemented.
- ❖ Rules should be framed such that only eligible, qualified pharmacists work in a pharmacy.
- ❖ Changes should be made in the education system of a pharmacist which should include basic training on the understanding of a medication guide and package inserts which will be practically helpful during their practice. This is easy to be implemented in the education system of pharmacy practice.
- ❖ A pharmacist should be well trained to educate a patient about the potential risks and side effects of a drug. This would thus decrease the communication gap between a pharmacist and a patient and the betterment of risk minimization strategies.
- ❖ Government should bring in awareness programs among the people regarding the importance of the risk minimization plans implemented. This will be the toughest plan for the government, as it would be difficult to take pass the message to a common man.

5.3.4.2 Proposal 2

I would also like to propose another system which would suit the financial status of all the developing countries especially Asian countries. Most of the Asian countries are developing countries with Japan and Singapore being the notable exception. My suggestion would be that all the Asian countries can plan to come on a single platform and develop a new risk minimization system for all the Asian countries similar to the EU-RMP. The EU-RMP has all the European countries under one system which monitors their risk management plan. Similarly, developing countries like India, China, Pakistan, Sri Lanka, Korean countries, Bangladesh, Nepal and other countries along with the developed countries like Japan and Singapore can plan for an Asian Risk management Plan (ARMP). The benefits of the system can be,

- As most of the countries are still developing and a few still under developed this would help them financially. They need not invest large amounts to start a new infrastructure.
- Developing countries will have a great opportunity to work with Japan which is far more ahead in terms of risk management. The suggested Asian Risk Management Plan (ARMP) can have its headquarters in Japan which will also help Japan and the developing countries.
- The ARMP can be more detailed and a single organization can frame the rules and regulations of the system.
- This will also improve the drug trade between these countries and this way the under developed countries can benefit with new medicines coming to their market.
- There will also be a bigger scope for post marketing studies on larger population and with different ethnic groups. This process would further reduce the risk properties of a drug.

The 2nd proposal is very hard to be practically possible, but it can also be very effective if it can be implemented. It might be time taking and needs lot of ground work to be done, but still it all worth it.

6. CONCLUSION

Developing countries along with India could improve their drug safety if the above suggestions were implemented. These were just my opinion and not intending to criticize any organization. The writer only thinks that the drug safety systems in these countries could improve if there were less political interference. Most of the countries do not have a standard risk management plan. The writer thinks that ICH should intervene and recommend the concerned governments to start working on developing systems for risk minimization.

7. REFERENCES

1. RxList Inc. (2007) Medication Guides for certain prescription products. RxList, The internet drug index Retrieved on February 11,2011 from <http://www.rxlist.com/script/main/art.asp?articlekey=81665>
2. Impact of Risk Evaluation and Mitigation Strategies. The FDA amendments act of 2007 Retrieved on February 11, 2011 from <http://www.ashpadvantage.com/fdaaa/fdaaa-spring-newsletter.pdf>
3. EMEA (2007). European risk management strategy. European medicines agency. Retrieved on January 19,2011 from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010971.pdf
4. TCS n.d, Role of IT in managing adverse drug events. Tata consultancy services. Retrieved on January 18,20011 from http://www.tcs.com/SiteCollectionDocuments/White%20Papers/Role_of_IT_in_Managing_Adverse_Drug_Events.pdf
5. Impact of Risk Evaluation and Mitigation Strategies. The FDA amendments act of 2007 Retrieved on February 11, 2011 from <http://www.ashpadvantage.com/fdaaa/fdaaa-winter-newsletter.pdf>
6. Dr. Annalisa Rubino & Dr. Thomas Goedecke n.d, Risk management; safety specifications. European medicines agency. Retrieved on February 2, 2011 from http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/09/WC500096198.pdf

7. EMEA (2012). European risk management strategy. European medicines agency. Retrieved on January 19,2011 from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf
8. History of Risk evaluation and mitigation strategies, ParagonRx . Retrieved on January 21, 2011 from <http://www.paragonrx.com/rems-hub/rems-history/>
9. Leiderman, D. (2008) Risk Management of Pharmaceutical Products at FDA – A Historical Perspective
10. USFDA (2012), Drug safety and availability, U.S. Food and drug administration. Retrieved on February 2, 2011 from www.fda.gov/Drugs/DrugSafety
11. Risk Evaluation and Mitigation Strategy Assessments (June 7, 2012), Social Science Methodologies to Assess Goals Related to Knowledge, U.S. Food and drug administration. Retrieved on January 21, 2011 from <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301966.pdf>
12. Smith, D., Willy, M., Karwoski, C., Winterstein, A. (2011, August). Generalizability of Risk Evaluation and Mitigation Strategies Effectiveness Evaluations. Poster presented at 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, Illinois.
13. Medication Guide, Retrieved on August 14, 2012 from <http://www.lunesta.com/Lunesta-Patient-Medication-Guide.pdf>
14. Karen Collins-Lenoir, (June 2009), REMS performance assessments. The common element to REMS.

15. Federal policy REMS. Retrieved on August 14, 2012 from
<http://www.aspmn.org/conference/documents/stanton-stmarie-brown-barnes-remsfinal.pdf>
16. Risk evaluation and mitigation strategy, Ortho McNeil-Janssen pharmaceutical, Inc.
Retrieved on August 22, 2012 from
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020634s053,020635s058,021721s021REMS.pdf
17. Gary Slatko, (5th Oct 2009), FDA's Draft Risk Evaluation and Mitigation Strategy (REMS) Guidance – A Preliminary Review (Part II).
18. CSAVES, REMS elements, Controlled substance authentication verification & education system. Retrieved on August 23, 2012 from <http://www.csaves.org/remselements.aspx>
19. FDA (2012), Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. Food & drug administration.
Retrieved on August 3, 2012 from
<http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301966.pdf>
20. Smith, D., Willy, M., Karwoski, C., Winterstein, A. (2011, August). Generalizability of Risk Evaluation and Mitigation Strategies Effectiveness Evaluations. Poster presented at 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, Illinois.
21. Webgate N.D, Public laws & docid. Webgate. Retrieved on September 3, 2012 from
http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf

22. PMDA (2012), Risk management plan guidance, Pharmaceuticals and medical devices agency. Retrieved on September 13, 2012 from
http://www.pmda.go.jp/english/service/pdf/mhlw/PFSB-SD_Notification120411-1.pdf
23. MHLW (n.d), Risk management plan, Pharmaceutical and food bureau, Ministry of health, labour & welfare. Retrieved on September 14, 2012 from
http://www.pmda.go.jp/english/service/pdf/mhlw/20110802_RMP.pdf
24. GMP (2012), Japan: Risk management plan, GMP publishing. Retrieved on September 20, 2012 from <http://www.gmp-publishing.com/en/gmp-news/gmp-aktuell/japan-risk-management-plan-draft-guidance.html>
25. DFE (2008), Medication dangers, Dr.Fostersessentials. Retrieved on September 20, 2012 from <http://www.drfostersessentials.com/store/warnings-recalls.php>
26. Medindia (n.d), Banned drugs / drugs banned in India / list of banned drugs, medindia, network for health. Retrieved on September 21, 2012 from
<http://www.medindia.net/patients/patientinfo/drugs-banned-in-india.htm>
27. CDSCO (n.d), Pharmacovigilance program of India, Central drugs standard control organization. Retrieved on September 24, 2012 from
http://www.cdsc.nic.in/pharmacovigilance_intro.htm#Risk
28. CDSCO (n.d), Risk management, Central drugs standard control organization. Retrieved on September 24, 2012 from
http://www.cdsc.nic.in/pharmacovigilance_intro.htm#Risk%20Management
29. Personal observation by author as a pharmacist at Sri Sai Medicals, Adilabad, India on 06/06/2011.

30. Personal observation by author as a pharmacist at Care Pharmacy, Hyderabad, India on 08/16/2011.
31. Personal observation by author as patient's relative in Lalitha Nursing Home, Warangal, India on 03/30/2012.

