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An analysis of legal warnings after drug approval in Thailand

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ABSTRACT

Drug risk management has many tools for minimizing risk and black-boxed warnings (BBWs) are one of those tools. Some serious adverse drug reactions (ADRs) emerge only after a drug is marketed and used in a larger population. In Thailand, additional legal warnings after drug approval, in the form of black-boxed warnings, may be applied. Review of their characteristics can assist in the development of effective risk mitigation. This study was a cross sectional review of all legal warnings imposed in Thailand after drug approval (2003–2012). Any boxed warnings for biological products and revised warnings which were not related to safety were excluded. Nine legal warnings were evaluated. Seven related to drugs classes and two to individual drugs. The warnings involved four main types of predictable ADRs: drug–disease interactions, side effects, overdose and drug–drug interactions. The average time from first ADRs reported to legal warnings implementation was 12 years. The triggers were from both safety signals in Thailand and regulatory measures in other countries outside Thailand.

1. Introduction

Drug risk management (DRM) is the overall and continuing process of minimizing risk throughout the life cycle of a product to optimize its benefit and risk balance (McEwen, 2004). According to the United States' Code of Federal Regulation (CFR), the serious risks which led to death or serious injury are to be displayed in new warnings or added in black box warnings (BBWs) (Willy and Li, 2004). The 21CFR 201.57 in part states: "Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal data toxicity may also be the basis of a boxed warning in the absence of clinical data" (Willy and Li, 2004).

Adverse drug reactions (ADRs) surveillance is essential for DRM after approval as it enables the detection of significant ADRs in the post marketing surveillance phase. In the first study to describe additional or non-routine risk minimization measures (ARMMs) in 225 risk management plans submitted to the United Kingdom regulatory authority, the most common types of risk requiring an ARMM were ADRs (39%) (Keddie, 2013).

In order to ensure drug safety, various methods such as change of drug labeling, black box warnings, written communication to healthcare professionals, restriction of supply and withdrawal from the market have been used to manage a drug's risk (Ehrenpreis et al., 2012).

BBWs describe serious ADRs and potential safety hazards (Wang et al., 2010). After an adverse reaction has led to death or serious injury, it is added to the prescribing information (Murphy and Roberts, 2006). Most often, they were added in the post marketing phase, in response to spontaneous events in the population. In the USA, 8.2% of drugs had acquired one or more box warnings for safety reasons after drug marketing (Lasser et al., 2002).

Another study analyzing drug labeling changes and the prevalence of BBWs found that around 11% of all safety related labeling actions of the US Food and Drug Administration (US FDA) were BBWs. A total of 174 black-box changes were made in the 3 year period 2004–2006, of which 97 (55.7%) were revisions in BBWs (Cook et al., 2009).

Mostly serious ADRs were reported after drug approval. BBWs can be the effective tools to manage drugs risk and make awareness to prescribers and patients. There was not enough space for details or guidelines in BBWs but serious risks were primarily displayed for approval (Wagner et al., 2006). Zarowitz found that ADRs, monitoring requirements, drug–drug interactions, drug–disease interactions, drug–laboratory test interactions are the criteria focused on in BBWs. Zarowitz also emphasizes the need for special training of health care professionals about BBWs, especially in nursing and aged care facilities (Zarowitz, 2008).

In an paper analyzing all drugs prescribed from ten US Health Maintenance Organizations during a 30 month period of study,

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around 40% of patients received at least one medicine with a BBWs that could potentially apply to them (Wagner et al., 2006). In a study which aimed to find whether current US FDA boxed-warning drugs were included in eight on line standard reference resources (e.g. DRUGDEX, Facts and Comparisons and PDR), only 32% were covered in all eight (Cheng et al., 2010). The sensitivity of these on line information sites (= number of true BBW on a site ÷ total number of BBW × 100) was as low as 42% (this was with on line PDR) (Cheng et al., 2010).

Yong et al. identified new BBWs for which the US FDA issued a press release, talk paper or Public Health Advisory ($n = 52$) and examined subsequent mentions ($n = 551$) in top ten US newspapers, 5 most viewed television networks and a news wire service (Associated Press) (Yong et al., 2009). They defined six core messages (which were brand name, generic name, treatment indication, reason for BBW, clinical recommendations for patients and recommendation for patients to discuss with their healthcare practitioners). US FDA documents included a median of 5 of the 6; the media studied included a median of 3 of 6 (Yong et al., 2009).

Knowledge about the mechanisms of ADRs and their risk factors is essential for the preparation of new BBWs. The basic classification for ADRs comprises type A (augmented) reactions and type B (bizarre or idiosyncratic) reactions. Type A reactions or predictable adverse reactions are those in which the adverse reaction occurs with a dose relationship to the administered drug and usually reflects the known pharmacologic actions and pharmacokinetics of the drug. Predictable ADRs are observed in patients without known predisposing factors and include toxicity, side effects, secondary drug effects, and drug interactions.

Type B reactions are unpredictable and unrelated to the known pharmacology of the drug. The reactions are frequently more severe and potentially fatal. The mechanisms of action are influenced by immunological and genetic factors (Khan and Solensky, 2010). Unpredictable serious ADRs have been one of the most important types added in new BBWs.

The current drug surveillance system in Thailand has been established for more than 20 years. A legal warning (black-boxed warning) may sometimes be mandatorily applied at approval in Thailand. In addition, the Drug Safety Advisory Subcommittee of the Thai Food and Drug Administration (Thai FDA) is assigned to decide the significance of various safety signals and give recommendations to add or revise the legal warnings after a drug's authorization. The Drug Safety Advisory Subcommittee reports to the Drug Committee which makes the final recommendations to the Thai FDA. This study aimed to identify the criteria or category of risks in legal warnings in Thailand in the post marketing phase. The specific characteristics of warnings after drugs approval were evaluated. Additionally, the triggers of legal warnings were also assessed.

2. Methods

The study was a cross sectional review of legal warnings which were recommended by the Drug Safety Advisory Subcommittee of the Thai FDA and implemented in Thailand after drug authorization. The study period was from January 2003 to June 2012. The study setting was at the Thai FDA, Ministry of Public Health, Thailand. The sources of information were the minutes of the Drug Safety Advisory Subcommittee and the Drug Committee.

The review was designed to trace and document the characteristics of all the legal warnings. The analysis was done from the stage when the subcommittee was alerted by any type of safety signals until the legal warning was required. A classification of ADRs in two main classifications of ADRs (predictable and unpredictable ADRs) was the initial framework for the review. Legal warnings for biological products and revisions of warnings which were not related to safety were not included in this study. The time between the first ADRs of any sort reported in Thailand for that drug or a member of the drug class and legal warning implementation was analyzed.

3. Results

During January 2003 to June 2012, nine legal warnings were revised or added for safety reasons. Most triggers of actions came from safety signals arising in Thailand or actions by other regulatory authorities outside Thailand. One legal warning followed a Market Authorization Holder's request (Table 1).

Seven drug classes and two individual drugs (sulfasalazine and nimesulide) were the subjects of warnings. The warnings for some individual members of some of the drug classes had additional warnings added to the class specific warning. For four of the seven warnings about classes of drugs, the warning mentioned only predictable (type A) ADRs.

Concerning predictable ADRs, four main subtypes were found to be the basis for legal warnings in this study; (1) drug–disease interactions, (2) side effects, (3) overdose or toxicity and (4) drug–drug interactions. Potential for liver toxicity in patients with liver disease was the most common drug–disease interactions and adverse effects when taken in pregnancy and lactation were the most common side effects included in the warnings.

All the legal warnings included mention of unpredictable (type B) ADRs in addition to predictable effects. A warning that a drug was unsafe in patients with asthma, atrophic rhinitis conditions or a history of allergy to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) was added to all conventional NSAIDs. Warnings about allergic reactions were required for all in the oral and topical fluoroquinolone classes, sulfonamides and all selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) drugs (Table 2).

The average time between the first report in Thailand of any ADRs of any sort to a drug or a member of the drug class and implementation of a legal warning was 12 years. The longest time was found with phenylbutazone (27 years) and the shortest with pioglitazone (2 years). Legal warnings for conventional NSAIDs and selective COX-2 inhibitors were revised twice during the study period.

4. Discussion

Our findings showed that the change of safety information by other regulatory authorities outside Thailand had triggered most of the considerations of legal warnings. The primary criterion for warnings about predictable ADRs was drug–disease interactions, such as in hepatic or renal failure patients or other high-risk patients. Murphy and Roberts reported that high-risk patients were the most frequent subjects of additional box warnings in the US (46.11%) (Murphy and Roberts, 2006).

The results revealed that potential liver toxicity was the most often specified criterion in the legal warnings, being included in more than half of all warnings in Thailand. This is consistent with a previous study reporting that hepatic failure was the most common topic of additional warnings after drugs were marketed (19%) and that, hepatic reactions were amongst the top five safety reasons for withdrawals from the market (26.2%) (Fung et al., 2001).

Stevens–Johnson syndrome caused by ciprofloxacin triggered a box warning for the fluoroquinolone drug class in Thailand. Such an uncommon reaction was not established at the time of the drug's registration. Other factors may be related to such a serious

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