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Risk Management Policy and Black-Box Warnings

A Qualitative Analysis of US FDA Proceedings

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Abstract

Background: The US FDA increasingly applies risk management to drug safety policy. Little is known about the process by which the FDA approves labelling changes. Although advisory committees can recommend any of the risk management tools, including the use of 'black-box warnings', it is unknown whether they deliberate on these questions or how they apply the principles of risk minimization or management during their considerations of drug licensing.

Objective: To examine the process by which risk management is considered by the FDA, including the role of FDA advisory committees. We also aimed to identify and describe drug labelling changes and additions, including the prevalence of black-box warnings.

Methods: We electronically obtained publicly available information regarding drug approvals, drug revisions and advisory committee meetings over 3 years (2004–6) from the FDA. Data in the form of meeting transcripts and full histories of labelling changes were collected on drugs discussed by advisory committees. We then searched and qualitatively analysed the meeting transcripts to identify themes in the discussion. We also created a database of all prescription drug labelling changes for 3 years and examined which drugs have had the most changes. We describe the risk management consideration process and report the frequency and characteristics of labelling changes. Excerpts from the transcripts are selected to illustrate both typical and atypical features of the discussion.

Findings: A total of 174 black-box changes were made in the 3-year period of our study, of which 77 were new black-box warnings and 97 were revisions in black-box warnings. Of 77 new black-box warning additions, only 11 drugs were discussed by the advisory committees. Of the 17 most frequently revised drug labels in these 3 years, two were discussed in the advisory committee meetings. Advisory meeting discussions revealed confusion about black-box warnings and emphasized potential consequences of the warnings rather than their content.

Conclusion: The safety labelling of drugs on the market is changed often. Panels of advisors consider only a few drugs, rarely discuss the labelling requirements, and display confusion about applying black-box warnings. The creation and application of black-box warnings on prescription medications should receive closer attention from the FDA and its advisors.

Background

The US FDA increasingly implements risk management to address safety concerns of prescription drugs[1,2] but does so with insufficient data and limited tools for communicating risk information.[3] The provisions of risk management plans may allow a drug with significant safety risks to reach or remain on the market. Adverse events in medical care are often related to drugs, including those from medication errors and adverse drug reactions.[4-6] In consultation with the FDA, manufacturers remove about one drug per year from the market due to safety concerns. Between 1978 and 2003, 25 drugs were removed from the market for safety reasons, and from 1990 to 2002, 11 drugs were approved under special safety requirements.[7] The current system for collecting data and monitoring adverse drug events in the US has many limitations.[8-11] FDA surveillance relies upon spontaneous and voluntary reporting; therefore, it likely underestimates the frequency of adverse events.[12,13] Since the early 1990s, the FDA has accelerated its regulatory review times for prescription drugs, thereby shortening the premarketing surveillance period for adverse events.[14,15]

'Black-Box Warnings': A Type of Risk Management

A bolded, boxed warning on prescription drug package inserts called the 'black-box warning' may be required for FDA approval and licensing.[16] According to the US code, a black-box warning may be added to the labelling if clinical or animal toxicity data indicate the possibility of death or serious injury.[17] The black-box warnings recommend precautions for prescribers, but also provide guidance to all health providers and patients who use the drug.[18] More often, black-box warnings are added later, in the post-marketing phase, in response to spontaneous events in the population.[17] Of 548 new drugs approved between 1975 and 1999, 8% later required a new black-box warning, and 3% were eventually withdrawn from the market.[19] Some drugs stay on the market with dozens of labelling modifications; for example, restrictions on the drug isotretinoin, sold as Accutane® since 1982, have changed several times.[20,21] Roche Pharmaceuticals withdrew the Accutane product from the US market in June 2009, citing costly lawsuits, but generic isotretenoin will continue to be available, and the risk management plan may be transferred to another sponsor.[22]

The existing variation in labels worldwide raises safety concerns. A comparison of warnings in the US and Germany found important differences in labels for the same drug in one-third of cases, often from the same manufacturer.[23] Only in one case in 2 years did the two countries change labels at the same time for the same reason. A comparison of the warnings on painkillers in the US and Europe found various differences that cast doubt on the scientific basis of regulatory decisions in both systems.[24] A study of package inserts in 26 countries also found variations in warnings.[25] These findings may indicate that the limitations of the regulatory process dilute the relationship between labelling and scientific evidence. In fact, one study suggests that regulatory bodies should be more transparent because information supporting decisions is often not released to the public.[26]

The Role of US FDA Advisory Committees in Risk Management

The US federal bureaucracy has long used expert advisory committees, which were formalized

in 1972 in part to protect the public interest.[27] FDA advisory committees can help reconcile complicated and highly technical questions of safety and efficacy.[28] Drug manufacturers have supported the use of advisory committees because they can help resolve disputes with agency staff.[29] However, the advisory process has been subject to controversy regarding committee membership and balance, consistency of process and transparency, and the politics of science.[30-33] In July 2008, the FDA asked an advisory committee whether antiepileptic drugs should carry a new black-box warning about the risk of suicide.[34] The committee voted in favour of a new warning, but opposed the addition of a black-box warning as it was regarded as overly discouraging of prescriptions.[35] Although advisory committees can recommend any of the risk management tools, for example educational campaigns, pharmacist or patient registries, special packaging and warning labels, as well as black-box warnings, it is unknown whether they deliberate on these questions or how they apply the principles of risk minimization or management during their considerations of drug licensing.

This paper examines the process by which risk management plans are considered by the FDA, including the role of FDA advisory committees. Using data from 3 recent years of licensing decisions, we identify and describe drug labelling changes and additions, including the prevalence of black-box warnings.

Methods

We conducted an archival study of government documents and data in order to examine the FDA process for the approval of labelling changes.[36] The data for this retrospective study were collected electronically from the FDA. We began data collection in 2007 and selected the three most recent and complete years of data available at that time (2004–6), as going back any further in time would not reveal the current trends in drug labelling. We created two databases: one of all FDA safety-related actions over 3 years and one of drugs discussed by advisory committees over the same 3 years. The first database was extracted from the FDA MedWatch website (http://www.fda.gov/medwatch/safety.htm), which provides monthly reports of safety-related modifications to labels. This monthly report does not include new approvals, but only changes to safety-related sections of existing labels: black-box warnings, contraindications, other warnings, precautions, adverse reactions, patient package insert or medication guide. Our extracted data includes the date, the generic name of the drug, sponsor name, section modified and other information.

For the database of drugs discussed by advisory committees, meta-data were collected for Center for Drug Evaluation and Research Advisory Committee meetings over 3 years, from 2004 to 2006, from the briefing information, summary minutes and transcripts (wherever best available). We coded for new drug applications or license revisiting, and also looked for the inclusion of new black-box warnings. Additional data on this list of drugs were collected from the Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). We collected and recorded from this website a summary of each drug's approval history, together with specific approval history details, when available. We recorded available information about the licensing history of each drug discussed by committee during those years.

We identified 47 drugs approved by the FDA after advisory committee meetings, and searched the full transcripts of the meetings for discussion of black-box warnings or risk management plans, using the following key terms: 'risk', 'risk management', 'black box', 'boxed warning' and 'safety'. In addition, we identified the drugs with the most label changes that were discussed by FDA advisory committees. We selected the drugs with seven or more labelling changes in the drug history (with or without a black-box warning) and searched the committee transcripts for discussions of these drugs. One author (RG) conducted the keyword searches, which were verified by another author (DC); this search yielded few hits, therefore all transcript pages were scrutinized. We conducted qualitative analysis of the advisory committee transcripts.[37] Two authors, RG and DC, independently examined all the transcript passages

that were extracted, and identified themes in the discussions relevant to safety warnings and risk management. We describe the risk management consideration process and report the frequency and characteristics of labelling changes. As is standard in qualitative research, excerpts from the transcripts are selected to illustrate recurrent as well as deviant features of the discussion.[38]

Results

Black-Box Warnings and Other Label Changes

Our search yielded 1569 cases of FDA action in 3 years. From the data on 1569 drug labelling changes, a total of 174 black-box warning changes were made in the 3-year study period (table I). Of these, 77 were new black-box warnings added to the label. We searched for these 77 drugs with new black-box warnings in the database of drugs discussed in advisory committee meetings that we had compiled and found that 11 (14%) of these drugs were discussed in advisory committee meetings. The remaining 97 changes were revisions to existing black-box warnings. Only three (3%) of these revisions were discussed in the advisory committee meetings. Of the 11 drugs discussed in the advisory committees as candidates for new black-box warnings, 8 drugs were covered in a single 2004 meeting on the risks of antidepressants to children.[39]

Drugs with frequent (seven or more) safety-related labelling changes during this 3-year period are listed in table II. These include changes to the black-box warning, precautions, warnings, contraindications and adverse reaction sections of the drug label. There were 17 drugs with frequent labelling changes. Six drugs had black-box warnings and only two were discussed by the advisory committees.

Table I. Total drug labelling actions in 3 years (2004–6)

Action	Number
Total labelling actions (addition or revision)	1569
All actions related to black-box warnings	174
New black-box warnings added	77
New black boxes discussed by advisory committee	11
Other actions discussed by advisory committee	3

Advisory Committee Discussions

We identified 106 individual drugs that were discussed in advisory committee meetings from 2004 through 2006 (table III). More general discussions of classes of drugs were not included in this analysis. In addition, some meetings considered several drugs together. The data on meeting outcomes led us to categorize the meetings into six categories:

- new applications not approved;
- new applications approved with black-box warning;
- new and approved with no black-box warning;
- revised labelling approved with black-box warning;
- revised but making no black-box warning changes (may leave black-box warning in place if present);
- revised labelling having no black-box warning.

Of the 31 new drugs discussed in the advisory committee meetings, 14 were approved by the FDA, of which 4 were subsequently given black-box warnings. Of the 75 revised drug applications, 14 were given a new black-box warning. In the remaining 20 (31%) revised drugs, changes were usually made to other sections of labels, such as for precautions, adverse effects, warnings and contraindications. Thus, of the total 106 drugs discussed in the advisory committee meetings, 18 (4 new drug applications and 14 revised drug applications [17%]) experienced black-box-related label changes.

We researched the overall history of labelling changes for all the drugs discussed by advisory committees over the 3-year study period and identified the drugs with the most label changes (some of the changes occurring before or after the 3-year study period) that were discussed by the committees, as well as those with a history of frequent changes but without a black-box warning. The four drugs discussed by committees during 2004–6 with the highest total number of label changes but without black-box warnings were Mevacor® (lovastatin), Pravachol (pravastatin),

Table II. Drugs with the most frequent label changes in 3 years (2004–6)

Trade name	Generic name	No. of label changes	'Black-box warning'	Discussed in advisory committee meeting
Zofran®	Ondansetron	10	No	No
Cipro®	Ciprofloxacin	9	No	No
Levaquin®	Levofloxacin	9	No	No
Paxil®	Paroxetine	9	Yes	Yes
Effexor XR®	Venlafaxine	9	Yes	No
Premarin® [a]	Estrogens	9	Yes	No
Vfend®	Voriconazole	9	No	No
Cordarone®	Amiodarone	9	No	No
Taxotere®	Docetaxel	8	Yes	No
Minocin®	Minocycline	8	No	No
Abilify®	Aripiprazole	7	Yes	No
Not applicable	Potassium chloride	7	No	No
Effexor®	Venlafaxine	7	Yes	Yes
Gleevec®	Imatinib	7	No	No
Nexium®	Esomeprazole	7	No	No
Zantac®	Ranitidine	7	No	No
Lexiva®	Fosamprenavir	7	No	No

a Regular Premarin® tablets of various strengths, which share one approval history.

Diprivan (propofol) and Xenical® (orlistat). Mevacor® has had 35 labelling revisions throughout its history. The transcripts of these advisory discussions for these four drugs were searched for terms such as 'black box' or 'boxed warnings' and it was found that none of these committee meetings included discussion of adding a black-box warning to these drugs.

The analysis of advisory committee transcripts for mention of applying black-box warnings revealed limited discussions and some confusion. For the ten newly proposed drugs that were approved with no black-box warnings, we found discussions of black-box warnings evident in advisory committee proceedings for only one drug (Daytrana® [transdermal methylphenidate]). All 14 drugs already on the market that were revisited by FDA advisory committees and given new black-box warnings received much discussion around black-box warnings, usually in support of the warning proposed by the manufacturer. Discussion tended to focus on the consequences of adding a black-box warning rather than the data or information that needed to be included in the warning. For example, the advisors considering the drug Ketek® (telithromycin, an anti-infective for community-acquired pneumonia) were polled on the contents of a proposed black-box warning; however, as they considered what risks to include, the transcripts contained expressions of confusion and apprehension, and one doctor stated, ''I don't know what a black box really means and I don't worry about too many of them''.[40] Interestingly, an advisor at another meeting was concerned about the effect a black-box warning might have on Medicaid state formularies, possibly making the drug unavailable by discouraging its inclusion in the formulary.[41]

Table III. Drugs discussed in Center for Drug Evaluation and Research Advisory Committee Meetings over 3 years (2004–6)

Individual drugs discussed	106
New applications	31
not approved	17
approved with black-box warning	4
approved, no black-box warning	10
Applications for revised labelling	75
not approved	41
approved with black-box warning	14
approved, no black-box warning changes	20

Advisors considering Daytrana® for attention-deficit hyperactivity disorder, which was among new drugs in this study that were approved by the FDA with no black-box warnings, seemed to agree on a warning of some kind and were concerned with the impact a black-box warning would have on direct-to-consumer advertising.[42] The package insert for Daytrana® approved on 6 April 2006 included a warnings section but no special bolded black-box warning. A drug for dementia, Exelon® (rivastigmine; 1.5, 3.0, 4.5 and 6.0 mg capsules), was revisited by the advisors and given no black-box warning; in fact, an advisor argued that Exelon® was needed because the black-box warning on other drugs has limited available treatments for certain patients.[43] A meeting about Provigil® (modafinil; tablets) provoked discussion of whether the black-box warning was simply a statement of risk or if "it was a risk-benefit consideration".[44]

Discussion

Health and safety regulations in the US and some other countries are called 'risk regulations' because they attempt to reduce exposure to possible harm.[45-48] Risk analysis continues to become more important in US policy, but the methodology is imperfect and requires subjective nonscientific decisions that consider value judgements and policy priorities.[49,50] The quality of the epidemiological evidence base for medication risk management varies widely at present.[51] There has been little evaluation of the evidence in support of a particular strategy or the effectiveness of different risk management strategies. One alternative to risk management is the precautionary principle, which anticipates 'harm' rather than 'risk' and therefore places a larger burden of proving safety on the manufacturers and distributors of new chemicals, compounds and therapies.[52,53]

Risk management at the FDA is a way to keep potentially harmful, but necessary, drugs on the market while maximizing drug safety. One of the most frequently used risk management strategies is the black-box warning. Black-box warnings in the US are often unheeded or misunderstood. A number of studies have shown that providers are often unsure about the implications of the black-box warnings, and may often prescribe against them.[17,54,55] Prescribers may be responding to unclear directions on labels and/or making carefully calculated decisions to prescribe a drug with risks.[56] Moreover, prescribers of approved drugs are allowed to deviate from the labelling and commonly prescribe for off-label uses.[57-59] The addition of a black-box warning to a drug label might reduce prescriptions and increase caution, as it did with antidepressants for adolescents in 2004.[60] Manufacturers cannot use the less detailed 'reminder' type of advertisement for these drugs because boxed warning information must be included.[61] Warnings seem to hurt sales and may play a role in litigation.[62] The black-box warning might also trigger other safety checks; recently, the state of California began special additional scrutiny of hospital use of drugs with black-box warnings, but this process has unexpectedly revealed additional confusion about warnings in clinical practice.[63] The language of the warning may be unclear to providers or to patients,[64,65] and the black-box warning rarely makes it onto any special straightforward sticker or instruction for consumers.[66]

Given the confusion about, and the potential impact of black-box warnings, one could expect that the evidence base for the warnings might be discussed in detail and with confidence by advisory committees. Only a limited number of drugs are scrutinized by advisory committees each year and, among those in this study, many surely did not warrant black-box warnings because they are of lesser risk. Yet the meeting transcripts elicit the prospect of missed opportunities for fully-evaluated, stronger safety measures, because in the rare discussions of warnings the advisors appeared perplexed about when the measure might be appropriate, and seemed to require further information. Moreover, in the 3-year period of this study, among the top 17 drugs with seven or more labelling changes, only 2 drugs were discussed in the advisory committee meetings. Also, of the 17 more frequently amended drugs, only 6 drugs presently have black-box warnings. As these drug labels are revised frequently by adding more precautions, adverse reactions, warnings and

contraindications, perhaps they should be considered in terms of adding a black-box warning.

In 1999, the FDA began to implement a policy of risk management-based decision making for drugs, in consideration of risks and benefits to patients.[67] The Prescription Drug User Fee Act reauthorization of 2002 (PDUFA III) required the agency to produce risk management guidelines. Final 'risk minimization guidances' issued in March 2005 explain that the FDA goal of risk management is 3-fold: (i) premarketing risk assessment; (ii) risk minimization action plans (RiskMAPs); and (iii) pharmacovigilance.[68] In 2005, the agency announced that a permanent Drug Safety Board would monitor any postmarketing problems.[69] The FDA now encourages drug manufacturers to present risk management plans with new drug applications; manufacturer-created plans may help a drug receive approval and may expedite the process.[70] The FDA Amendments Act of 2007 provides more resources for drug safety, including increased postmarketing enforcement and improvement of the adverse events reporting system.[71,72] Under the new law, RiskMAPs became risk evaluation and mitigation strategies (REMS).[62] The FDA can now order manufacturers of any drug to provide REMS, either with new applications or within 180 days.[73] Internal discussions between manufacturers and the FDA are rarely available for public scrutiny.

Limitations

This study reveals the challenges of collecting data from the FDA websites and documents. The lack of meta-data presents many hurdles in conducting simple identification and coding. For example, many of the advisory committee meetings are posted without summary minutes and without these, hundreds of pages of raw transcript must be read to discover the content of the meeting. Also, information on some of the drug histories, such as modified indications, package revisions, control supplements, efficacy supplements, manufacturing change or additions, new dosage regimens and over-the-counter switches is not to be found. Among the 1569 labelling changes, some may have been simple typographical corrections but others may have been quite substantial. Some of these may have been made under the 'Changes Being Effected' (CBE) rule (in place since 1982 and recently amended) by which manufacturers can apply for fast-tracked label changes upon learning new information, but the distinction between CBE and regular applications is not noted in Medwatch.[74]

Moreover, the current label is often not available and/or past labels are not available for comparison; therefore, comparisons of lengthy package inserts can be overly labour-intensive. For some drugs, the FDA website does not provide a copy of the label at all, but, in some instances, the manufacturer's website provided a current label. For two drugs in our list, AeroBid® (flunisolide) and Maxair® (pirbuterol), changes were mentioned in the drug approval history but were not mentioned in the MedWatch data. In addition, we focused on 3 specific calendar years, but the approval process takes longer and there may be some lag-times involved, such as advisory meetings before the study resulting in label changes during the study. Until 2007, the FDA had to negotiate label changes with manufacturers, which may also lengthen the time between agency proceedings and any changes. Lastly, these 3 years may or may not be representative of the process at present because drug safety was receiving considerable attention during this time; for example, with the drug rofecoxib (Vioxx®), which was withdrawn on 30 September 2004.[75] Nevertheless, the salience of drug safety could also lead to expectations of increasingly careful discussions of warnings at advisory committee meetings, which was not our finding in this study.

Conclusion

Drug safety policy involves the challenge of finding consensus among the multiple stakeholders.[76,77] Our study further reveals that the black-box warning component of risk management is applied inconsistently, usually postmarket and usually without much input from expert advisors. The most serious FDA warning entails much confusion. Thus, the creation and

application of black-box warnings on prescription medications should receive closer attention from the FDA and its advisors. We suggest that the FDA should establish criteria for creating different categories of warnings, and should educate FDA panels about these criteria. The study results provoke further questions about the transparency of the process and the evidence base for risk management strategies for drug safety. Another improvement would be clear guidance about whether advisory panels should address unresolved scientific questions or should make recommendations coloured by speculation about unintended consequences from policy. Post-marketing surveillance efforts should include evaluation of compliance with black-box warnings. Managing risk does not necessarily reduce vulnerability.[78] Clinicians should be aware that a policy rooted in risk management and minimization, but with some *ad hoc* features, may leave patients vulnerable to harm.

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