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Level of Evidence Associated with FDA Safety Communications with Drug Labeling Changes: 2010-2014

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Abstract

Purpose: Approximately 800,000 safety reports are submitted to the FDA annually, however, only significant issues generate drug safety communications (DSC). The purpose of this study was to determine the type of clinical evidence used to warrant a change in drug labeling for drugs with DSC between January 1, 2010 and December 31, 2014. **Methods:** Selected data was obtained from the FDA website. The primary endpoint of the study was the frequency of the types of clinical evidence used in FDA communications, as reported through the FDA DSC. Results were evaluated via descriptive statistics, and chi-squared for nominal data. **Results:** A total of 2521 drug safety labeling changes were identified and 99 (3.9%) of safety communications met the inclusion criteria. The majority of the labeling changes were associated with single agents (83.8%). The three most frequently reported labeling changes were warnings (68.7%), precautions (58.6%), and patient package insert/medication guide (23.2%). Case reports resulted in the greatest number of documented literature types ($n = 791$), followed by randomized controlled trials ($n = 76$), and case control/cohort studies ($n = 74$). Significantly more evidence for DSCs were classified as Level of Evidence B (LOE B, 68.6%), compared to LOE A (17.1%), and LOE C (14.1%) ($p = 0.007$). **Conclusions:** The majority of drug labeling change initiators was associated with LOE equivalent to B. Practitioners should evaluate data associated with labeling changes to determine how to interpret the information for their patients.

Keywords: Safety, Drug safety communication, level of evidence

Introduction

The Food and Drug Administration is tasked with protecting the public health from safety risks associated with medications and other products.¹ Clinical trial information is extensively reviewed prior to market approval and postmarketing safety reports are used to ensure that harm is not disproportionately reflected in patient outcomes. New drugs are approved on the market faster now than ever before. The number of drugs that were approved in 2014 doubled the number approved in 2008.^{2,3} The FDA is able to approve drugs with more efficiency due to updated conditions and regulations that mandate drug companies conduct follow up studies after approval of their drug.⁴ New information can emerge about the safety of a drug as a result of postmarketing surveillance studies and voluntary MedWatch safety reports.

Approximately 800,000 safety reports are submitted to the FDA yearly.⁵ Clinically significant safety information is conveyed to the public through written communications, broadcasts, webinars, conference calls, various forms of electronic social media, and the FDA website.⁶ Drug Safety Communications (DSC) are electronic documents used to communicate important safety information to the public.⁷ This format was established in early 2010 to improve the clarity of communications from FDA to the public. DSCs commonly consists of a summary of the safety issue, nature of the risk, established benefits of the particular drug or drug class, recommendations for health care providers and patients, and a summary of the data reviewed by the FDA.⁶ DSCs can result from labeling target populations in which the drug should be used, adverse effects, drug-drug interactions, contraindications, warnings and precautions, and patient package inserts or medication guides.⁶ These safety alerts are intended to inform patients, as well as, assist healthcare providers make the most informed decisions regarding drug therapy. No information exists to document that patients read these reviews.

DSCs use clinical evidence to justify changes that are made on drug labels. However, the level of clinical evidence associated with each communication is not standardized and can vary

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(e.g., single adverse drug reactions to controlled clinical trial).⁸ Unfortunately, drug safety communications that result from preliminary information may cause patients to discontinue needed medications or alter the way in which the medication may be taken that is not consistent with the way in which the drug was prescribed. In addition, physicians may opt to discontinue needed therapy, depending on the risk associated with continuing therapy.⁹ Premature warnings could result in unnecessary reluctance among physicians to prescribe a particular drug. On the other hand, safety alerts can prevent adverse effects and negative health outcomes among high-risk patients. Therefore, to provide optimal patient care and to avoid unsubstantiated changes in therapy, it is essential to be able to determine the clinical evidence associated with labeling changes and to determine how that information should be used in defined patient populations.¹⁰

Lester et al evaluated safety-related drug label changes in 2010.¹¹ In this study, spontaneous reports were associated with 52% and 55% of label changes and anti-infectives and cardiovascular drugs were among the drug classes most frequently affected. The label change initiator was most commonly associated with adverse reactions, precautions, and warnings.¹¹ These findings are consistent with a previous study in which over half of the adverse events were associated with spontaneous reports and 25% were associated with information from clinical trials.¹²

Currently, there is a lack of published literature that describes the level of evidence associated with labeling changes that are reported via FDA DSCs. The purpose of this retrospective study was to determine the type of clinical evidence used to warrant a change in drug labeling for drugs with FDA drug safety communications from January 1, 2010 to December 31, 2014.

Methods

This study was a retrospective data analysis evaluating FDA DSCs and the level of evidence used to warrant drug label changes. FDA DSCs posted from January 1, 2010 to December 31, 2014 were analyzed in this study. The primary endpoint was the frequency of types of clinical evidence used in the FDA drug safety communications as reported in the communication. Secondary endpoints were the type of drug labeling changes made (e.g. boxed warning, contraindication, warnings, precautions, dosage administration, drug interactions, adverse events, patient package insert/medication guide, pregnancy category, other changes).

All FDA drug safety communications from 2010 to 2014 involving a label change were included in the study. Updates to safety communications were included if the update consisted of a label change. Updated safety communications

that met the inclusion criteria were recorded in the year that the original labeling change was made. Safety communications for over-the-counter (OTC), blood, and tissue products were excluded. On-going safety communications that had not yet resulted in a label change were also excluded. Radiopharmaceuticals, contrast agents, and other products that were not recognized by American Hospital Formulary Service (AHFS) were not included in the study.

Selected data was obtained from the Drug Safety and Availability section of the FDA website (<http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm>).¹³ Drug communication entries included the following information: safety announcement, additional information for patients and healthcare professionals, and the data summary. Data was sorted by date of the FDA communication and extracted from this website between April and June of 2015.

The data was compiled and sorted into an Excel spreadsheet. The initial draft of the spreadsheet was pilot tested with five products to determine which variables needed to be included in the spreadsheet. The data was manually evaluated to include the following information: date of the safety communication, AHFS classification, drug or drug class involved, type of label change (e.g. boxed warnings, contraindications, warnings, precautions, dosage administration, drug interactions, adverse reactions, patient package insert/medication guide, pregnancy category, and other changes), the level of evidence, type of study/evidence used to support the change, whether the data was published, and if the safety communication was ongoing. The type of label change was extracted from the safety announcement component. When the safety announcement was unclear as to the rationale of the label change, the package insert was consulted for recent changes. If two drugs in the same safety alert had different AHFS categories, the merged category was included in the data analysis. Addition of a medication guide was recorded as changes to the medication guide. The data summary section provided the information related to the type of evidence used to support the label change. If literature type could not be determined from the drug safety communication, the manuscript abstracts were searched through PubMed to determine the type of study for appropriate classification. Consensus between investigators was maintained when PubMed searches were completed.

Level of evidence (LOE) was determined based on the criteria from the American College of Cardiology and American Heart Association (ACC/AHA) guidelines.¹⁴ The evidence was classified by Levels A – C. Level A evidence consisted of data from multiple ($n \geq 2$) randomized clinical trials (RCTs) or a

single meta-analysis (MA). A single randomized clinical trial, non-randomized studies (e.g. cohort studies, case-control studies), or any registry or database evaluations (e.g. FDA Adverse Event Reporting System) were classified as Level B evidence. Level C evidence included any expert opinions, case studies, or case reports. Spontaneous case reports were included as Level C evidence. Communications that did not include any evidence or include the types of evidence used were automatically recorded as Level C evidence. If more than one type of evidence was cited in the safety communication, then the highest level of evidence was documented.

Pooled-analysis were classified as meta-analyses. If the FDA drug safety communication indicated "several" case reports were documented and did not include the exact number of case reports, then the Merriam-Webster's definition of "several" to be "more than 2" was used to assign a value of 3 in the spreadsheet.¹⁵ Clinical evidence was recorded as published if the communication stated it was published or the article was found to be published through the reference listed.

Results were evaluated by descriptive and inferential statistics. Descriptive statistics were used to quantify the following data: number of FDA safety communications issued per year was calculated, mean number of clinical literature by literature type (e.g. tallied number of: meta-analysis, randomized controlled clinical trials, registries, cohorts, case series, and case reports). Pearson Chi-square test was used to evaluate nominal data (e.g., associations between LOE and year of labeling change, type of labeling change, publication status, AHFS class, number of single agents and drug classes, etc). Proportions or cross-tabulations of frequency data were also conducted. Analysis was performed using SPSS version 19 (Armonk, NY).

Results

A total of 2,521 label changes were identified between years 2010 and 2014. However, only 142 data safety communications were evaluated and 99 met the criteria for the study. Forty-three of the DSCs were excluded because of their OTC status (n=6), communication did not result in a label change (n=35) or the product was not in the AHFS (n=2). The largest amount of exclusions was in 2012 (n=10), followed by 2011 (n=9), and 2010 and 2013 (n=8, respectively). See Figure 1.

The following DSCs were included, as reflected by the year: 2010 (n=20), 2011 (n=33), 2012, 2013 (n=19), and 2014 (n=8). The 75 drugs and 12 drug classes within the safety communications were from 21 AHFS classifications. The top three most common classifications were central nervous system drugs, anti-infective agents, and cardiovascular drugs

and consisted of 21, 18, and 9 communications, respectively. Of the 99 communications 16 (16.2%) were in reference to an entire drug class (see table 1). The three most common changes were in the categories of warnings, precautions, or patient package insert/medication guide which were found in 68 (68.7%), 58 (58.6%), and 23 (23.2%) communications, respectively. Only 17 (17.2%) communications lead to changes to boxed warnings.

Drug safety communications were most commonly associated with level B evidence. There were 17 communications classified as level A, 68 communications categorized as level B, and 14 communications were level C. The most abundant source of evidence was case reports, which had a total of 791 entries. Registries consisted of 41 queries that lead to 38 changes. In total, 42 communications referenced evidence that was published within the literature (see table 2).

Differences between LOE of the single agents used in the DSC was compared for the level of evidence and no significant differences were identified for single agents and LOE involved for the DSCs; (P=0.497). However, a significant difference between LOE and AHFS drug classes was observed (p=0.007). Of the top three drug classes, the percentage of DSCs in the central nervous system drugs classified with LOE A, B, and C was 17.6%, 26.5%, and 0%, respectively. In the anti-infective agent class, the percentage of DSCs classified as LOE A, B, and C, were 11.8%, 19.1%, and 21.4%, respectively. The percentage of DSCs identified in cardiovascular drugs as LOE A, B, and C was 17.6%, 26.5%, and 0%, respectively (see tables 1 and 2).

The percentage of unpublished data with LOE A, B, and C evidence was 47.1%, 52.9%, and 92.9%, respectively, compared to the same LOE type in the published data set (52.9%, 47.1%, and 7.1%, respectively). Therefore, a statistically significant inverse relationship between publication and LOE ($p = 0.002$) was observed which indicated that published reports were associated with fewer robust literature classifications, with the exception of LOE A (Table 3). No statistically significant associations between published reports and label classifications (e.g., boxed warnings, contraindications, warnings, precautions, dosage administration, patient package insert/medication guide, pregnancy, or other) were observed. However, fewer DSCs that provided information on drug-drug interactions were published compared to those label changes that were not associated with drug-drug interactions (11.9% vs. 88.1%; $p=0.048$). Similarly, significantly fewer label changes for adverse events were published compared to other label change categories (2.4% vs. 97.6%; $p=0.016$) (Table 3).

Discussion

The majority of evidence used to warrant a change in drug labeling for drugs that had FDA safety communications over the five-year period was associated with Level B evidence. Central nervous system, anti-infective, and cardiovascular drugs were associated with the largest number of FDA DSCs with labeling changes. In addition, the warnings section of the package insert was more frequently associated with changes.

Rackham et al. evaluated the evidence supporting FDA alerts for drugs with adverse cardiovascular events. Nine drug safety communications were included in the review and the strength of evidence was ranked according to Level of evidence A, B, C, and U (unrated). Of the nine, only one safety alert was classified as level A evidence with the majority of evidence being presented as cohorts, case controls, case reports/case series, expert opinions or anecdotal evidence.¹⁰

Studies and other important patient-related information have the ability to impact regulatory decisions regarding drug products. All of them may not be associated with the best clinical evidence. Moore et al. evaluated safety warnings in 2009 and found that adverse event reports by either drug manufacturers or through the MedWatch program influenced the majority of the FDA's new regulatory actions and new boxed warnings, 57% and 76% respectively. Clinical studies only represented 26 of the 135 changes (19%), but only two were derived from statistically significant differences and one was based on a single study case.⁴

The clinical impact of FDA communications on patient care has been evaluated. Clinical care was significantly impacted as antipsychotic and antidepressant communications were associated with a decrease use in non-targeted populations and an increase in suicides among children following the antidepressant advisories.¹⁶

Our study demonstrates that the level of evidence that prompts FDA drug safety communications is not consistent with the rigor of controlled clinical trials. However, controlled clinical trials are not the best way to evaluate adverse drug reactions associated with drug products. This study confirms that LOE B is associated more frequently with labeling changes. Previous studies have evaluated drug safety label changes over short periods of time compared to our comparison over a 5-year period. Furthermore, to our knowledge this is the only study that evaluated the association between label changes and LOE used in corresponding safety communications. In addition, the current study evaluated drug safety communications, the information that is most readily available to health care professionals and the public regarding safety topics that are deemed most important by the FDA. Despite

this, no significance was found between type of label change initiator and LOE. There was also no significant difference between the LOE of the clinical information and 5-year period associated with the study. A relationship was found between AHFS class and LOE, but it was not determined if one classification tended to have better evidence compared to another. Lastly, an inverse relationship was observed between publication and LOE which seems to indicate that safety concerns with more publications tended to be less likely to have a drug safety communication. Spontaneous reporting appears to be the most common literature type associated with label changes. Although spontaneous communications are useful in helping practitioners hypothesize important information about drug products, they are limited in their ability to determine the magnitude of clinical impact the label change initiator may have. In addition, underreporting and insufficient clinical information limits the usefulness of this type of literature.¹⁹

The clinical impact of drug safety communications may be far reaching and unpredictable. Communications for targeted populations may have an exaggerated effect on other subpopulations. There may be a large decrease in utilization that may inappropriately impact patients. As a result, practitioners need to be able to determine the risk:benefit profile in their patients in order to recommend appropriate therapeutic strategies in light of FDA safety communications.

The study contained several limitations. The quality of the data (e.g., meta-analysis, controlled clinical trials) used for each therapeutic classification was not analyzed. Furthermore, our assessment did not take into account the quantity of evidence presented under categories B or C. The sample size of this study is small and therefore limits the number of relationships that can be discerned from the data. When a communication was in reference to two or more drugs, but not a drug class, all drugs and evidence were combined as a single entry. This method prevented proper association between evidence and its corresponding drug. The method in which data was tabulated restricted the number of tests that could be performed. This prevented stratification of data within a set to determine if associations could be made between subgroups and factors such as LOE. If it was not possible to determine the type of data used to impose a labeling change, then it was automatically assigned to level C. This may have had a small impact on the findings. Selection bias could be introduced based on how the investigators chose to interpret a communication in light of the inclusion criteria. An effort was made to minimize such bias through active communication between investigators in order to maintain consensus. Communications had varying depths and information was provided in a different format than other communications

within the same year. Although the investigators could have contacted the FDA to determine whether or not additional information was used to initiate safety alerts, the purpose of the study was to evaluate drug safety communications and investigators deemed additional probing of the FDA was unwarranted. These communications are those that the FDA deems as most important. In addition, pooled analysis was considered meta-analyses; however, due to the small size of these analyses (n=9; 0.9%), it is unlikely that this assessment affected the results.

Conclusion

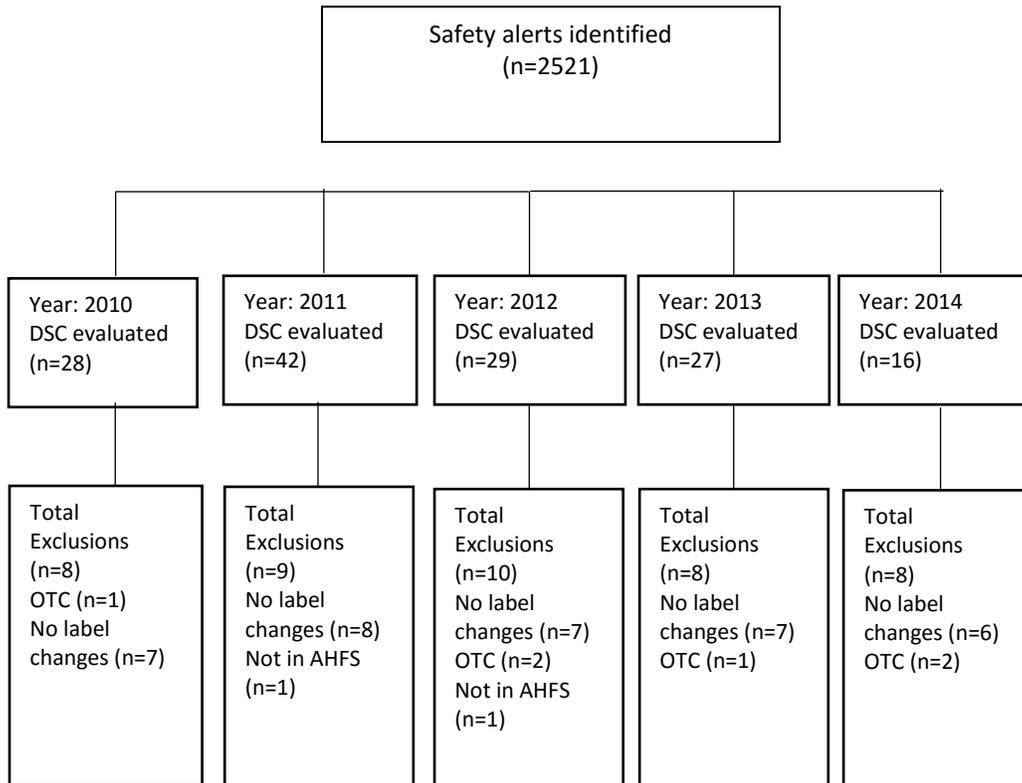
Drug safety communications are released to the public for safety information that will most frequently impact patient care. However, only a fraction of the drug labeling changes prompt a drug safety communication. This analysis revealed that the majority of literature associated with labeling changes resulted from Level of Evidence B (i.e., single, randomized trial, non-randomized studies, and registry or database evaluations). In addition, the most frequent type of drug labeling changes was due to warnings, precautions, and patient package insert/medication guide; however, no statistically significant differences were observed between type of drug labeling changes and level of evidence. Although the level of evidence associated with labeling changes was not considered the most robust literature type available, practitioners need to be able to evaluate this type of data to determine the potential impact in their patient population. Additional studies are warranted to determine the quality of the evidence of all drug labeling changes to determine the level of evidence associated with each.

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Figure 1: Inclusion/Exclusion Flow Chart



DSC-drug safety communication; OTC-over the counter; AHFS-American Hospital Formulary Service

Table 1: Frequency of Safety Communication Characteristics^a

Characteristic	Frequency (%)
Year	
2010	20 (20.2)
2011	33 (33.3)
2012	19 (19.2)
2013	19 (19.2)
2014	8 (8.1)
Single agent	83 (83.8)
Drug Class	16 (16.2)
AHFS drug classification	
Anorexigenic agent	1 (1.0)
Bone resorption inhibitors	2.0 (2.0)
Immunosuppressive Agents	8 (8.1)
Local anesthetics	1 (1.0)
Other Misc. Therapeutic Agents	2 (2.0)
5-Alpha Reductase Inhibitors	1 (1.0)
Anti-Infective Agents	18 (18.2)
Antidotes	1 (1.0)
Antineoplastic Agents	6 (6.0)
Autonomic Drugs	5 (5.1)
Blood Formation and Coagulation	6 (6.1)
Cardiovascular Drugs	9 (9.1)
Central Nervous System Drugs	21 (21.2)
Electrolytic, caloric, and water balance	1 (1.0)
Expectorants and Cough Preparations	2 (2.0)
Gastrointestinal Drugs	6 (6.1)
Gold Compounds	2 (2.0)
Hormones	4 (4.0)
Anti-infective agents, Cardiovascular drugs	1 (1.0)
Diagnostic agent, Cardiovascular drugs	1 (1.0)
Immunosuppressive agents, Antineoplastic agents	1 (1.0)
Safety classification	
Boxed warning	17 (17.2)
Contraindication	17 (17.2)
Warnings	68 (68.7)
Precautions	58 (58.6)
Dosage administration	15 (15.2)
Drug interactions	6 (6.1)
Adverse reactions	11 (11.1)
Patient Package Insert/Medication Guide	23 (23.2)
Pregnancy	7 (7.1)
Other changes	20 (20.2)
Meta-analysis	9 (0.9)
Randomized controlled trials	76 (7.6)
Registry	43 (4.3)
Case Control/Cohort	74 (7.4)
Case Series	3 (0.3)
Case Report	791 (79.0)
Expert Opinion	5 (0.5)

^aPercentages could add up to greater than 100%

Table 2: Communication Characteristics vs. Level of Evidence (%)

Safety Characteristic	LOE A (n = 17)	LOE B (n = 68)	LOE C (n = 14)	Total	p
Year					
2010	2 (11.8)	13 (19.1)	5 (35.7)	20 (20.2)	
2011	6 (35.3)	23 (33.8)	4 (28.6)	33 (33.3)	
2012	4 (23.5)	12 (17.6)	3 (21.4)	19 (19.2)	
2013	4 (23.5)	14 (20.6)	1 (7.1)	19 (19.2)	
2014	1 (5.9)	6 (8.8)	1 (7.1)	8 (8.1)	
Single Agent	13 (76.5)	59 (86.5)	11 (78.6)	83 (83.8)	0.306
Drug class	4 (23.5)	9 (13.2)	3 (21.4)	16 (6.2)	0.306
Published	9 (52.9)	32 (47.1)	1 (7.1)	42 (42.4)	0.002
AHFS Classification					
Anorexigenic agent	0 (0.0)	1 (1.5)	0 (0.0)	1 (1)	
Bone resorption inhibitors	0 (0.0)	2 (2.0)	0 (0.0)	2 (2.0)	
Immunosuppressive Agents	1 (5.9)	2 (2.9)	5 (35.7)	8 (8.1)	
Local anesthetics	0 (0.0)	1(1.5)	0 (0.0)	1 (1.0)	
Other Misc. Therapeutic Agents	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.0)	
5-Alpha Reductase Inhibitors	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.0)	
Anti-Infective Agents	2 (11.8)	13 (19.1)	3 (21.4)	18 (18.2)	
Antidotes	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.0)	
Antineoplastic Agents	0 (0.0)	6 (8.8)	0 (0.0)	6 (6.1)	
Autonomic Drugs	4 (23.5)	1 (1.5)	0 (0.0)	5 (5.1)	
Blood Formation and Coagulation	1 (5.9)	2 (2.9)	3 (21.4)	6 (6.1)	
Cardiovascular Drugs	2 (11.8)	6 (8.8)	1 (7.1)	9 (9.1)	
Central Nervous System Drugs	3 (17.6)	18 (26.5)	0 (0.0)	21 (21.2)	
Electrolytic, caloric, and water balance	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.0)	
Expectorants and Cough Preparations	1 (5.9)	1 (1.5)	0 (0.0)	2 (2.0)	
Gastrointestinal Drugs	1 (5.9)	4 (5.9)	1 (7.1)	6 (6.1)	
Gold Compounds	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.0)	
Hormones	0 (0.0)	4 (5.9)	0 (0.0)	4 (4.0)	
Anti-infective agents, Cardiovascular drugs	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.0)	
Diagnostic agent, Cardiovascular drugs	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.0)	
Immunosuppressive agents, Antineoplastic agents	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.0)	
All AHFS Classifications	17 (17.2)	68 (68.7)	14 (14.1)	99	0.007
Reason					
Boxed Warning	5 (29.4)	11 (16.2)	1 (7.1)	17 (17.2)	0.243
Contraindication	4 (23.5)	12 (17.6)	1 (7.1)	17 (17.2)	0.476
Warnings	13 (76.5)	49 (72.1)	6 (42.9)	68 (68.7)	0.075
Precautions	12 (70.6)	39 (57.4)	7 (50.0)	58 (58.6)	0.478
Dosage administration	3 (17.6)	10 (14.7)	2 (14.3)	15 (15.2)	0.951
Drug interactions	1 (5.9)	4 (5.9)	1 (7.1)	6 (6.1)	0.983
Adverse reactions	5 (29.4)	5 (7.4)	1 (7.1)	10 (10.1)	0.055
Patient Package Insert/Medication Guide	3 (17.6)	18 (26.5)	2 (14.3)	23 (23.2)	0.515
Pregnancy	0 (0.0)	6 (8.8)	1 (7.1)	7 (7.1)	0.447
Other changes	3 (17.6)	15 (22.1)	2 (14.3)	20 (20.2)	0.772
Published reports available	11 (57.9)	36 (48.6)	1 (5.6)	48 (43.2)	0.002

Table 3: Type of Label Change vs. Publication Status (%)

Label Change	Not published	Published	Total	<i>p</i>
Boxed Warning	9 (15.8)	8 (19.0)	17 (17.2)	0.435
Contraindication	9 (15.8)	8 (19.0)	17 (17.2)	0.435
Warnings	36 (63.2)	32 (76.2)	68 (68.7)	0.122
Precautions	35 (61.4)	23 (54.8)	58 (58.6)	0.324
Dosage administration	10 (17.5)	5 (11.9)	15 (15.2)	0.316
Drug interactions	1 (1.8)	5 (11.9)	6 (6.1)	0.048
Adverse reactions	10	1	10 (11.1)	0.016
Patient Package Insert/Medication Guide	15 (26.3)	8 (19.0)	23 (23.2)	0.274
Pregnancy	2 (3.5)	5 (11.9)	7 (7.1)	0.113
Other changes	11 (19.3)	9 (21.4)	20 (20.2)	0.494
Total				0.002