

Supplementary Online Content

Moore TJ, Singh S, Furberg CD. The FDA and new safety warnings. *Arch Intern Med.* 2012;172(1):78-80.

eAppendix. Detailed Methods for FDA 2009 Safety Warnings Study

This supplementary material has been provided by the authors to give readers additional information about their work.

Detailed Methods for FDA 2009 Safety Warnings Study

The data for this study were extracted from these publicly available FDA sources: Drug Safety Labeling Changes for 2009 described in the MedWatch Safety Information and Adverse Event Reporting Program; ¹ the agency listing of 2009 Safety Alerts for Human Medical Products; ² the drugs@fda database of drug information, ³ and DailyMed database of prescribing information provided by the FDA and the US National Library of Medicine. ⁴

Safety Regulatory Actions

A major regulatory safety action was defined as a drug safety withdrawal, or a new or revised boxed warning, contraindication or warning in the prescribing information for an active drug moiety. (We did not study other sections of the prescribing information such as Precautions or changes to the Adverse Effects section.) Safety regulatory changes may be initiated by either the manufacturer or the agency, and the resulting changes (including safety withdrawal) typically represent an agreement between the two parties, although the FDA has the undiluted right of final approval.

Regulatory changes in the prescribing information were further classified as new, revision, or downgrade. For example, a *new* boxed warning refers to either a new topic added to an existing Boxed warning, or a new box altogether. A *revised* boxed warning, warning or contraindication is a wording change in a previously existing topic. A *downgrade* describes language removed from an existing section. A regulatory action was classified as new if it appeared in one of these sections for the first time, even if some language about the side effect had appeared elsewhere on the label.

Identification of Drugs

We defined a drug as the active moiety or ingredient in the regulatory action. When identical language was applied to an active moiety with more than one brand name, or to various combinations or formulations that included the same moiety, we counted this as a single safety regulatory action. Changes to labeling of over-the-counter drugs were excluded. It was possible for a regulatory action to be limited to a specific formulation or route of administration for a moiety (e.g. methylphenidate patch, fentanyl lozenge). If the same language was applied to different moieties, the actions were counted separately (see Class Warnings section below).

A brand name drug was defined as drug with no therapeutic equivalent listed in the FDA's database for approved drugs.³ A generic drug was defined as any approved drug with any form of therapeutic equivalent. The year of approval was calculated from the FDA regulatory database as the calendar year for approval of the reference drug.

Class Warnings

A class warning was defined as a regulatory action taken for two or more different moieties either at approximately the same time, or later extended to a new moiety. Class warnings are only initiated by the FDA, and are derived from custom and practice rather outlined in an explicit regulation or guidance.

Scientific Evidence

We evaluated the scientific evidence supporting regulatory actions in two different dimensions, evidence source and evidence inference. For evidence source we classified the regulatory actions into these categories: Clinical trials, meta-analysis of clinical trials, epidemiological studies, adverse event reports, and animal studies. If more than one source of evidence was cited, we selected the higher-ranked category in the order shown above. For evidence inference we classified the evidence as *direct*, meaning the evidence directly involved the drug, *structure/mechanism*, meaning the adverse effect had been observed in drugs with similar chemical

structure or mechanism of action, and *indication* meaning the adverse effect had been observed in drugs with similar indications, or patient populations. We defined a clinical study as any prospective, systematic study of a drug effect in human subjects, including randomized clinical trials, pharmacokinetic, pharmacodynamic, and interaction studies. If the adverse effect was observed in a clinical study, the evidence source was classified as a clinical study even if the event was rare or its incidence not statistically significant. The adverse event report classification included statements in the prescribing information that not only specifically cited “spontaneous reports” but also terminology such as “reported,” “associated with,” “rarely” or “may occur.” By definition, medication error warnings were classified as adverse events.

Data Extraction and Coding

The prescribing information, language changes and FDA statements were extracted verbatim from the data sources noted above and entered into a Microsoft Access database (Microsoft, 2010). Two of the coauthors (Mr. Moore and Dr. Singh) agreed on all coding classifications and the overall coding and schema was reviewed by the third coauthor (Dr. Furberg).

References

1. Drug Safety Labeling Changes. Food and Drug Administration Web site. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/default.htm>. Accessed July 24, 2011.
2. 2009 Safety Alerts for Human Medical Products. Food and Drug Administration Web site. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm091428.htm>. Accessed July 24, 2011.
3. Drugs@FDA: FDA Approved Drug Products. Food and Drug Administration Web site. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed July 24, 2011.
4. DailyMed: About DailyMed. Daily Med: Current Medication Information Web site. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Accessed July 27, 2011.