## OPTIONS FOR MANAGING RISK

The following six options are available to sponsors and FDA to manage risks associated with use of a drug. Some of the options are established by regulation giving FDA enforcement authority, others are voluntarily implemented. Most often, a combination of options is used to both manage risks and inform the public about these risks to promote safe use of a drug. Other options may also be possible.

### Labeling

Regulations require that, for prescription drugs, labeling on or within the package from which the drug is to be dispensed bears adequate information for its use. "Labeling" includes the immediate container labels, carton labels, and for prescription drugs, the package insert. Adequate directions for use includes any relevant hazards, contraindications, side effects, and precautions under which practitioners can use the drug safely for its labeled use. The indication section helps manage risk by identifying the patient population for which effectiveness was demonstrated. It often contains specific factors or disease manifestations that characterized the population studied where effectiveness was established. In addition, the indications section can give guidance on what types of patients, in what setting (under what conditions), and for what purpose the drug should be used. The medical community often has access to the package insert through reference books such as the *Physician's Desk Reference* or the internet.

In addition to the required sections of the package insert that address safety (CONTRAINDICATIONS, PRECAUTIONS, WARNINGS, ADVERSE REACTIONS), the following labeling options have been used by themselves and in combination with other options to manage drug risk:

- Boxed Warning: A labeling statement, required by regulation, of a serious problem, particularly one that could lead to death or injury, placed in a prominently displayed box. Boxed warnings have been used to convey information on monitoring to avoid potential serious adverse events, special instructions related to dosing and administration where incorrect use could lead to a serious consequence, and information on the indicated population where use in an inappropriate population could lead to a serious consequence.

- Patient Package Insert: An extension of the package insert intended to be distributed to patients with the drug that provides important information about the drug in lay language. The focus of a patient package insert could be to emphasize and instruct regarding side effects or precautions, to provide dosage and administration instructions, or to provide general information.

- Medication Guide: An information leaflet, required by regulation, to be distributed to patients with specified, predominantly self-administered prescription drugs, that provides important information about the drug in lay language to ensure its safe use. FDA can require a medication guide in a few drugs per year where the agency determines that patient education and knowledge will p0lay a major role in risk management. Unit-of-use packaging may be one way to enforce distribution of the Medication Guide with dispensed drug (See Packaging).

*Refer to Appendix 4a for the following supporting documents:*

- *Examples of boxed warnings, Patient Package Inserts, and Medication Guides*
- *Medication guides—preamble to the final rule and regulations*

**Communications to healthcare practitioners and consumers**

Publicizing new information about risks associated with use of a drug is used as an adjunct to labeling changes and other regulatory actions taken by FDA. Communication can be initiated by either the sponsor or the FDA, or jointly through a collaborative effort. For example, communication of a serious interaction that could result in long-term or permanent paralysis, was jointly undertaken by all the manufacturers of low molecular weight heparins or heparinoids and FDA through a coordinated release of a health advisory, talk paper, press release, and "Dear Healthcare Practitioner" letters.

The FDA uses multiple media options for publicizing important new information, including the internet and partnering with professional and consumer advocacy groups through MedWatch Partners.

The following formats for communications are available to the sponsor and/or FDA:

- Mailing of important information about drugs ("Dear Healthcare Provider" letters): The format for these mailings is determined by regulation for the FDA. Following the format described in the regulations is voluntary for sponsors. Mailings are targeted to practitioners most likely to prescribe or dispense the drug. Types include new drug warnings, new prescribing information, and corrections of drug information.

- Press Releases/Talk Papers: Communications to the consolidated press.

- Health Advisories: FDA uses this type of document to publicize particularly serious concerns or risks associated with use of a drug or class of drugs.

- Questions and Answers: "Q&As" are used to communicate information on frequently asked questions and are posted on the internet.

- Educational Programs: Sponsors have implemented prospectively designed educational programs as part of restricted marketing plans. These programs have been directed to healthcare practitioners to ensure prescribing to appropriate patients and implementation of necessary precautions when using a drug. Educational programs directed towards patients include a variety of mechanisms to provide drug information including toll free telephone numbers, internet sites, newsletters, and collaborative efforts with patient advocacy groups.

- Sales force outreach: Sponsors can tap into this resource to disseminate important new safety information to physicians.

- Publications: Articles about safety issues can be written for scientific, public policy, or the lay press.

*Refer to Appendix 4b for the following supporting documents.*

- *Examples of "dear health provider" letters, health advisories, talk papers, Q&A*
- *Regulations covering mailings of important information*
- *List of MedWatch Partners*

**Advertising**

Review of advertising for prescription drugs prior to dissemination is ordinarily not required except for drugs approved under the regulations for accelerated approval. In some instances, voluntary restriction of advertising to appropriate scientific journals has been agreed on in conjunction with restricted distribution to ensure that a drug is used in an appropriate setting (life-support facilities) and by trained clinicians (educational component of the marketing program).

All advertising for prescription drugs must present a fair balance of the benefit and risk information. The risk information must be presented with sufficient emphasis. Advertising must also present a true statement of information in brief summary relating to side effects, contraindications, and effectiveness. Reminder advertisements (ads that call attention to the name of the drug but do not include indications or other recommendations) are not permitted for a prescription drug whose labeling contains a boxed warning related to a serious hazard associated with use of the drug.

*Refer to Appendix 4c for the following supporting documents:*

- *Guidance for Industry: Consumer-Directed Broadcast Advertisements*
- *Guidance for Industry: Accelerated Approval Products—Submission of Promotional Materials*
- *Regulations pertaining to prescription drug advertising*

**Packaging**

Packaging configurations can be supportive of important labeling messages or distribution of information to the patient, promote safety in terms of inhibiting direct access to the drug by children, and warn against ingestion of adulterated products by providing evidence of tampering.

Unit-of-use packaging is a voluntary presentation configuration that can be used to ensure distribution of a drug in quantities or in a manner that promotes safe use of the drug. Unit-of-use packaging also limits the amount of drug prescribed which promotes regular interaction with a physician and/or pharmacist (refill prescriptions) and can assist with monitoring drug use.

Used in conjunction with a patient package insert or Medication Guide, unit-of-use packaging has been used to ensure distribution of patient information with the drug. For example, patient package inserts or Medication Guides are usually attached to the end of the professional labeling, or, multiple copies are provided to the pharmacist with each supply of drug. The pharmacist then gives this information sheet to the patient with the filled prescription. Although distribution of a Medication Guide is required by regulation, enforcement can be difficult. Attaching the patient Medication Guide to a unit-of-use package is one way to ensure that the patient receives important information with the prescription.

**Restricted Distribution**

Restricting a drug's distribution to ensure safe use can be done by regulation if the drug treats a serious or life-threatening illness and it provides meaningful therapeutic benefit to patients over existing treatments. FDA has had experience in restricted distribution with companies who have established registries to ensure patient compliance with blood testing to reduce the risk of agranulocytosis due to a drug ("No blood, No drug" program). Mandatory restriction to physicians and their patients who register with the company has also occurred to minimize birth defects associated with a drug.

Voluntary restriction of drug distribution to hospitals-only, to clinical settings where practitioners were certified as having undergone a training program put on by the company ("No training, No drug"), and to hospitals or physicians registered with the company have also occurred. Voluntary programs agreed to by the sponsor and FDA have attempted to decrease risk of hepatoxicity by limiting exposure to appropriate patients needing the specific benefits offered by the drug, and in another case to limit potential narcotic abuse.

Restricting distribution of the drug under regulation or voluntarily to physicians with specific medical skills in diagnosing a disease (such as a specialty group), monitoring adverse events (such as expertise with surveillance procedures) or managing adverse events is also possible.

Restricted distribution is generally implemented in conjunction with other risk management options (e.g. labeling).

*Refer to Appendix 4d for the following supporting documents:*

- *Restricted marketing under regulations for accelerated approval—preamble to the final rule and regulations*

**Cessation of marketing**

Cessation of marketing of a drug in the U.S. is ordinarily not considered until all other methods and options for risk management have been explored and found to be ineffective. A sponsor can, at any time, independently decide to cease marketing of a drug. However, when there is a safety issue this decision is usually reached after discussions with FDA.

Cessation of marketing may or may not involve withdrawal of approval of the drug. Withdrawal of approval by FDA involves published notification of the intent and an offer of an opportunity for a hearing for the sponsor. Voluntary withdrawal by the sponsor obviates need for the hearing procedure. Withdrawal for imminent hazard is a subset of withdrawal actions that FDA may pursue before offering a hearing.

Commercial distribution of a drug, by any sponsor, where a safety issue prompted cessation of marketing or withdrawal of approval is prohibited. Recall of drug already in the distribution system when manufacturing stops is an extreme option usually reserved for only the most serious of circumstances.

*Refer to Appendix 4e for the following supporting documents:*

- *Regulations for withdrawal of approval*

## RISK MANAGEMENT EVALUATION

The above options are interventions for managing risk. It is also important to design strategies to evaluate these interventions to assess their success. These evaluation studies can help tailor the risk management strategy to improve outcomes. FDA and pharmaceutical companies have evaluated compliance with labeling, boxed warnings, contraindications, precautions, and laboratory testing recommendations. Physician knowledge of risk messages and safe use of a drug has also been studied. If goals for compliance or knowledge of safety issues can be set prospectively, a plan can also be developed to address the continued problem if results fall short of goals. These plans could involve criteria to be used for escalating risk management.

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