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From the Department of Pharmacy

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# Drug Recalls

**By Meghan Lehmann, Pharm.D., BCPS**

**Background:** There has been an increasing trend in the number of prescription and over-the-counter drug recalls over the last 4 years.[1] In 2009, the Food and Drug Administration (FDA) reported 1,742 drug recalls representing a 309% increase over the 426 recalls reported in 2008. Of note, greater than 1,000 of the implicated medications were from the same drug repackaging firm. When this outlier was removed from consideration, drug recalls still increased 50% between 2008 and 2009.[1,2] Based on the number of recalls reported to the FDA during the first half of 2010, it appears this trend is likely to continue.[1]

**Reasons for Recalls:** There has been much speculation about factors contributing to the increasing number of drug recalls over recent years. Many are the result of problems occurring during the manufacturing or distribution process, including raw material contaminants or impurities, sub- or super-potent amounts of active ingredients in final products, stability or sterility issues, or labeling and packaging errors.[2] Some believe the push of generic companies to manufacture the first FDA-approved generic for brand name products coming off patent and outsourcing are resulting in significant quality assurance issues.[2,3] Another potential reason for the increased number of recalls is the elevated FDA scrutiny of manufacturers and facilities following high-profile recalls of agents such as heparin and Johnson and Johnson's over-the-counter products.[3] In addition, the publicity surrounding these recalls may have increased the vigilance of both healthcare providers and patients in reporting product problems and complaints to manufacturers and the FDA overall.

**Types of Recalls:** It is important to differentiate between drug recalls and market withdrawals. A recall is the removal or correction of a product due to problems that are in violation of law and therefore subject to legal action by the FDA. A market withdrawal also involves the removal or correction of a product; however, it is in response to a minor violation that would not typically be subject to legal action by the FDA.[4,5]

Recalls may be initiated by an individual manufacturer or distributor, by FDA request, or by FDA order under statutory authority.[4] The majority of drug recalls are voluntary, firm-initiated, without a request from the FDA. If the FDA recognizes there is a potential issue with a particular product it may formally request a firm recall a product. In most cases, the firm will voluntarily comply and issue a recall. Although the FDA has statutory authority to recall biologics, devices, and infant formulas, the Federal Food, Drug, and Cosmetic Act does not grant the FDA the authority to order or mandate a drug recall. Therefore, in those instances where a firm does not comply with a request, the FDA may pursue regulatory action to obtain an injunction or seizure of the product in question.[6]

When issuing voluntary recalls, a firm will assign each a depth. The depth of a recall refers to the level in the distribution chain to which a recall is extended based on the hazard associated with use of the affected product and the extent of its distribution.[4] The different levels are described in Table 1.[4] In addition to the depth or level assigned by a recalling firm, the FDA will categorize recalls as listed in Table 2.[5] Information about recalls, including class assignment and regulatory actions taken against individual firms are published weekly in the FDA Enforcement Report.[7]

**Table 1. Recall Depth/Level Descriptions[4]**

| Depth/Level | Definition |
|---|---|
| **Consumer or User Level** | Recall including individual patients, physicians, and hospitals |
| **Retail Level** | Recall to the level immediately preceding the consumer or user level. It includes retail and hospital pharmacies, dispensing physicians, and grocery stores |
| **Wholesale Level** | Recall involving all distribution levels between the manufacturer and retailer |

**Table 2. Recall Category Descriptions[5]**

| Category | Definition |
|---|---|
| **Class I Recall** | A situation in which there is a reasonable probability that the use of or exposure to a product will cause serious adverse health consequences or death |
| **Class II Recall** | A situation in which use of or exposure to a product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote |
| **Class III Recall** | A situation in which use of or exposure to a product is not likely to cause adverse health consequences. |

**The Drug Recall Process:** There are three general stages to all drug recalls: submission of the recall to the FDA, notifying the public, and evaluation of the recall process.[8] As soon as a manufacturer or distributor makes the decision to initiate a voluntary drug recall, it should notify the FDA of its intentions and begin developing a Recall Strategy. This strategy should include the depth of the recall, how the firm intends on notifying customers about the recall, instructions for customers on what to do with affected product (e.g., stop use immediately), and the process for returning affected product.[8] Since the FDA cannot mandate a recall, it provides guidance to recalling firms by reviewing and suggesting improvements to their outlined Recall Strategy.[9]

The FDA will classify the recall as described above by conducting health hazard evaluations to determine the potential risk imposed on the public by the recalled product.[6,9] In those situations where the recalled product is deemed to pose a significant health hazard and is likely in the possession of consumers (i.e., Class I or Consumer or User Level Recalls), the FDA will ask a recalling firm to issue a press release to alert the public. In some situations, the firm and FDA will issue a joint press release. If a firm has failed to issue a press release or the FDA believes the firm-issued press release is inadequate, the FDA may issue its own press release.[8] In addition to the press release, each firm must compose a Recall Notification Letter. These notifications should be sent to all customers that may have affected product in their possession and should include the product name, strength/concentration, NDC/UPC codes, lot numbers, and expiration dates, as well as the components listed in the Recall Strategy.[8] The FDA will post all recalls and pertinent updates on its website. It will also alert other state and federal government agencies as well as foreign governments of the recall if warranted.[9]

Once a firm has issued a recall it has the responsibility to assure its efforts were effective. Effectiveness checks should be conducted to verify customers received a Recall Notification Letter, the customer understood its instructions, and followed them. If it is determined initial efforts and strategy were ineffective, the recalling firm must attempt to make improvements by sending out a follow-up notification that better describes the recall and actions that should be taken by customers in response to the recall.[8] The FDA may also monitor and audit the effectiveness of a firm's recall efforts by contacting a percentage of customers affected by the recall to verify that the recall notification was understood.[8,9] A firm must also provide the FDA with Recall Status Reports at least monthly indicating the dates customers were notified, the number notified, the number responding, the quantity of recalled product returned or accounted for, and information about its recall effectiveness checks.[8] The recalling firm should investigate the root cause of the issue that resulted in product needing to be recalled and develop corrective actions to prevent the problem from occurring again.[8] The FDA will conduct follow-up inspections at the facilities involved with the recall to assure these steps are being taken. If the FDA feels a firm's recall actions are failing or it is not taking appropriate measures to make corrections it will take regulatory action.[9]

Once a firm has received responses from all customers and it is reasonable to assume all recalled product has been recovered, corrected, reconditioned, or destroyed it will send the FDA documentation. The FDA will review the documentation and if it agrees all recall actions are complete, it will provide written notification to the firm that the recall is officially terminated.[8,9]

**Sources for Recall Information:** Please refer to Table 3 for a list of websites that contain useful information about issued drug recalls.

**Table 3. Drug Recall Websites**

| Reference | Website Address |
|---|---|
| FDA Recalls, Market Withdrawals, and Safety Alerts | www.fda.gov/Safety/Recalls/default.htm |
| FDA Enforcement Reports | www.fda.gov/Safety/Recalls/EnforcementReports/default.htm |
| Recalls.gov | www.recalls.gov |
| American Society of Health-System Pharmacists | www.ashp.org |
| Individual Manufacturers' Websites | Various |

**Issues:** Although there is a process established for both recalling firms and the FDA, there are still deficiencies with drug recall management overall. There is concern surrounding how long it may take an individual firm to issue a recall once it becomes aware of a problem with a product. Since the FDA cannot mandate a drug recall, if a firm does not voluntarily initiate a recall on its own volition or after a request from the FDA, the FDA must take legal action which adds additional time to the process.[6] Providing timely information about a drug recall and how to respond to wholesalers, retail outlets, pharmacies, and in the case of Class I recalls, consumers, can also be a concern. Currently, there is no standardized format for Recall Notification Letters.[10] Some may not provide straightforward information about the depth of a recall, the reason for a recall, or how much of the product on the market is affected by the recall often necessitating clarification from the recalling firm. For large healthcare facilities that may have widespread use of a drug that is recalled, it may be challenging to make sure all affected product can be located and appropriately sequestered so that it is not administered to patients. Some drug recalls may result in nationwide drug shortages requiring healthcare providers to locate acceptable therapeutic alternatives for their patients.

In response to some of these issues, the American Society of Health-System Pharmacists is asking the FDA to standardize the recall notification process and format used by all manufacturers and distributors. It recommends drug manufacturers include lot numbers, expiration dates, and other pertinent product information on barcodes of all dosage forms to help prevent administration of recalled medications to patients at facilities using bedside barcoding technology. The group also asks that the FDA be granted authority to order mandatory drug recalls.[10] There are currently two federal bills that have been introduced advocating FDA authority over drug recalls.[11,12] One of these bills, the proposed *Drug Safety and Accountability Act of 2010*, would also enhance manufacturing standards by requiring companies to implement processes and plans to assure quality and safety of their drug components and document all facilities and entities involved in the manufacturing and distribution of their individual ingredients and final drug products. In addition, it would increase the oversight of over-the-counter medications.[12]

**Process for Managing Recalls at Cleveland Clinic:** Cleveland Clinic Department of Pharmacy has developed a Microsoft® SharePoint® site for managing drug recalls across the health system including Main Campus, Regional Hospitals, Retail Pharmacies, Family Health Centers, and Ambulatory Surgery Centers. As soon as pharmacy is alerted of a drug recall, information about the affected product(s) as well as the official Recall Notification Letter are uploaded onto the site. Purchase histories for each facility are obtained to help determine which sites may have affected product in stock. An email alerting each facility of the recall and its depth/classification is automatically generated. A Drug Recall Pharmacist will assess each recall and determine if additional unaffected product is available from the same manufacturer or a different manufacturer, or if a therapeutic alternative is warranted. Another email is automatically generated and sent to each facility providing information about alternative products, including how to obtain them. Each recall is housed on the searchable site which can be referred to in the future if a particular product is involved in more than one recall. If you should ever have a question about a drug recall, please contact the Drug Information Center at 216-444-6456, option #1.

**Conclusion:** Drug recalls have been on the rise over the last several years. With increased scrutiny over manufacturing quality issues, it is likely this trend will continue. Drug recall process standardization among manufacturers along with increased FDA involvement in mandating recalls will be crucial in effectively managing the increased number of recalls anticipated in the future.

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## *Formulary Update*

The CCHS Medical Staff P&T Committee met in July and the Local CC P&T Committee met in August and the following decisions were made:

***Formulary Additions/Changes:***

1. ***Generic meropenem*** will be the CCHS Formulary carbapenem product. The Cleveland Clinic Main Campus will be converting from imipenem to generic meropenem in the last quarter 2010.
2. ***Sipuleucel-T (Provenge®):*** It is FDA-approved for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. The patient's peripheral blood mononuclear cells are obtained via leukopheresis 3 days prior to the infusion date. These cells are activated during a defined culture period with PAP-GMCSF. The final product contains T-cells, B-cells, and natural killer cells. The patient receives three doses approximately 2 weeks apart and the dose is infused over 60 minutes. Provenge® will only be administered in the Taussig Cancer Center.
3. ***Abobotulinumtoxin Type A (Dysport®):*** It is FDA-approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously-toxin-treated patients. It is **restricted** to the Department of Neurology.
4. ***Recombinant Factor VIIa (NovoSeven®):*** There will be an additional restriction added for the use of NovoSeven®: It may be used in patients with warfarin-related life-threatening hemorrhage.
5. ***Denosumab (Prolia®):*** It is FDA-approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture. Denosumab works by a different mechanism of action than other medications currently approved for osteoporosis. It is a monoclonal antibody that neutralizes receptor activator for nuclear factor $_{K}$B ligand (RANKL). RANKL is a transmembrane-bound protein expressed on osteoblasts, T cells, and tumor cells and is responsible for osteoclast formation, function, and survival. RANK is a membrane-bound receptor located on osteoclasts and is responsible for their proliferation. The binding of RANKL to RANK activates osteoclasts and subsequently causes bone resorption (breakdown). Osteoprotegerin, a cytokine of the tumor necrosis family, competitively inhibits binding of RANKL to RANK, thus stopping bone resorption. Denosumab acts in a similar manner to osteoprotegerin. It competes with RANKL for RANK binding sites and prevents osteoclast-mediated bone resorption. Denosumab 60 mg is administered once every 6 months as a subcutaneous injection. It is **restricted** to outpatient use only for the treatment of osteoporosis.

***Formulary Denials:***

1. ***Asenapine (Saphris®):*** It is an oral atypical antipsychotic. Asenapine is non-formulary for initiation of therapy for inpatients; however, if patients are admitted to the hospital, they can be prescribed asenapine as continuation of therapy from home.
2. ***Milnacipran (Savella®):*** It is FDA-approved for the management of fibromyalgia. Milnacipran is non-formulary for initiation of therapy for inpatients; however, if patients are admitted to the hospital, they can be prescribed milnacipran as continuation of therapy from home.
3. ***Olanzapine long-acting injection (Zyprexa Relprevv®):*** It is a long-acting atypical antipsychotic. There are other long-acting atypical antipsychotics on the Formulary.
4. ***Ferumoxytol (Feraheme®):*** It is intravenous (IV) iron product. There was not overwhelming data that ferumoxytol is any better than the IV iron products on the Formulary. In addition, the effects on MR imaging were concerning to the CCHS Medical Staff P&T Committee. Furthermore, it is more expensive than other IV iron products.
5. ***Mesalamine enteric-coated tablets (Lialda™):*** It is a once-a-day mesalamine product. An automatic therapeutic interchange from Lialda™ to another mesalamine product already on the Formulary will be developed.