

10 Turning Points in Pharmaceutical Packaging

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Life is full of turning points. Sometimes we immediately recognize their significance; other times it's only as we look back that we recognize a change in the course of events.

In pharmaceutical packaging, several industry-altering episodes have occurred during the years, including passage of the Poison Prevention Packaging Act; the Tylenol tampering incident; the addition of senior-friendly requirements to child-resistant (CR) packaging requirements; the mandate for simpler over-the-counter (OTC) product labels; CGMP changes to minimize the chance of mislabeling; the phase-out of chlorofluorocarbon (CFC) propellants in inhalers; and the development of blister packaging, transdermal delivery systems, blow-fill-seal systems, and barrier isolators.

Poison Prevention Packaging Act

The passage of the Poison Prevention Packaging Act in 1970 is responsible for two milestones in pharmaceutical packaging. The first is the requirement that certain products be housed in special packaging. CR packaging of aspirin and prescription drugs, one of packaging's major success stories, is credited with saving an estimated 900 lives during the past 30 years. Much to its credit, this significant accomplishment has been imitated elsewhere in the world.

Senior friendly

Unfortunately, CR packaging is often difficult to open by anyone, especially elderly and disabled patients with diminished manual strength or dexterity. When the Consumer Product Safety Commission realized that a rising number of poisonings were occurring at grandma's house because she was transferring her medication to non-CR containers or not reclosing her

pill bottles properly, the agency mandated a change in testing protocols to ensure packaging would be both CR and senior friendly as specified in the original law.

The revised protocol, which took effect in January 1998, tests children between ages 42 and 51 months in groups of 50 for 10 min and adults between ages 50 and 70 years in groups of 100. Packaging passes if 85% of the children cannot gain access to medication in the allotted time and 90% of the adults can open the package in 5 min and reclose it in 1 min. However, despite the development of packaging designs that pass the protocol test, only a modest improvement in senior friendliness has been made. When it takes 5 min and/or use of a tool to open a package, we still have a long way to go. We owe it to our most vulnerable populations (and the able-bodied, who also will benefit) to deliver opening/reclosing mechanisms that are easier to manipulate, perforations that tear neatly, and backing that peels smoothly.

Tamper-evident packaging

In 1982 the horror of seven deaths as a result of the ingestion of poisoned Tylenol capsules led to regulations requiring tamper-evident (TE) packaging for most OTC products.

The regulation specifies that a TE package has one or more barriers to entry, which, if breached or missing, will provide visible evidence to consumers that the package has been violated. The package can be distinctive in design, like an aerosol, or have barriers to entry that employ an identifying design that cannot be reproduced by commonly available materials or processes. The TE feature(s) may be located on the primary or secondary container or any

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combination of the two and must be accompanied by a printed statement that draws attention to the nature of the device (1).

In 1986, following three deaths from the ingestion of poisoned Excedrin capsules, rules regarding capsules were strengthened. Two TE features are required for this dosage form, one of which can be sealing of the capsule itself.

In both cases the industry and regulators reacted quickly, and packaging was revamped with unprecedented speed. When several years passed without a high-profile incident, everyone hoped the problem had been solved. Unfortunately, some consumers relaxed a bit too much. In 1991 two people in Washington state died when they swallowed contaminated Sudafed capsules. In this case the tampering job

was crudely done and should have been readily obvious to the victims.

Although TE packaging is effective, the industry cannot become complacent. It must continuously remind consumers that they are the final barrier to tampering and must take responsibility for their own safety by paying attention to the presence and condition of the TE devices that have been provided for their protection. The industry also must be willing to invest in new technologies that could provide a hard-to-breach barrier.

Preventing mislabeling

During the 1980s, when it became apparent that a high percentage of Class 1 recalls (product poses the threat of death or serious injury) were caused by mislabeling, FDA identified the circumstances under which mistakes were most likely to happen and drafted regulations to prevent such occurrences. The regulations, which took effect in 1994, prohibit gang-printed cut labeling to be used for different drug products, the same product at different strengths, or net contents unless the labeling so printed is adequately differentiated by size, shape, or color (2).

Under the regulations, cut labels may be applied using automated equipment only if the filling or packaging line is dedicated to a product and product strength or if 100% inspection is conducted by appropriate electronic or electromechanical equipment. If 100% electronic inspection is used, FDA exempts the manufacturer from label-reconciliation requirements. This has prompted the development of ever faster and more powerful machine vision systems or bar code scanners to confirm label accuracy. Although mislabeling still triggers recalls, the number of incidents has fallen dramatically.

Simpler OTC labeling

After seeing how nutritional labeling requirements provided consumers with the information needed to make healthier eating choices, FDA decided OTC medications could benefit from a similar initiative. A final rule published in March 1999 standardizes the presentation of information about OTC labels and improves readability. The regulations, which will take effect April 2002, are spawning increased use of extended-content labels and creative

carton designs to provide space for the mandated information. The transition also is influencing the design of more colorful, easier to read inserts. Because packaging must be changed to meet the new requirements, this is a good opportunity for pharmaceutical manufacturers to update and upgrade primary label panel graphics or make the transition to a different packaging format. With less than a year re-

maining before the deadline, manufacturers must put the redesign process in motion quickly if it hasn't already been started. FDA has indicated it is disinclined to grant exemptions to the regulation and is expecting a good-faith effort before it will give a deferral.

Montreal Protocol

CFC propellants were banned in 1978 by

FDA and the Environmental Protection Agency for all but a few exempted drug inhalers. After the US Congress ratified the Montreal Protocol on Substances that Deplete the Ozone Layer in 1987, it banned the production and importation of CFCs as of January 1996 under Title VI of the Clean Air Act. Medical products remain exempt from the ban if no acceptable alternatives are available. Specific exemptions must be approved annually by the international parties to the Montreal Protocol.

After more than a decade of development related to more ozone-friendly propellants, progress has been slow because alternatives to CFCs require substantial changes in active and inactive ingredients as well as components in the metered-dose inhaler (MDI) itself. In addition, dose uniformity often suffers. To date, FDA has approved only one non-CFC MDI, Proventil HFA (albuterol sulfate) from Schering-Plough Corp. (Madison, NJ) and continues to request exemptions for CFC-MDIs currently on the market. The agency has pledged that CFC-MDIs will not be removed until sufficient alternative medicines exist to serve the needs of patients (3).

Although it's essential that these medications remain available, resistance to continued exemptions is sure to build as environmental consciousness increases. If non-CFC propellants are not meeting objectives, it's time to shift resources to fast-tracking the development of other alternatives like propellantless inhalers, dry-powder inhalers, and liquid atomization.

Blister packaging

Long popular in Europe for both unit- and multidose formats, blister packs, which protect single doses in sealed cells or pockets, are growing in popularity in the United States. Because one machine forms, fills, and seals the packaging, blister packaging lines require fewer pieces of equipment than bottle-filling lines. Unit-dose blisters frequently are found in institutional settings in which the format protects product potency and helps prevent medication errors because identifying information is carried with the dose to the point of administration.

Multicell formats can be designed to enhance compliance for complex dosage regimens. One of the earliest examples of this type of package is the dial pack for

oral contraceptives. This circular blister card, which holds a month's worth of pills inside a reusable, compact-like dispenser, replaced an awkward-to-manipulate strip pack. This format now is standard for this type of medication, and similar compliance packs have been adopted for other classes of drugs.

Wider use of this format, which helps patients take the right dose at the right time, could help reduce the expensive, health-threatening compliance problem we have in the United States. However, many existing blister designs, especially if they are CR, can be difficult to open and require some creative thinking to develop more user-friendly and compliance-enhancing structures.

Transdermal packaging

Transdermal packaging also is underused. For more than 25 years it has combined drug and delivery method in a primary package — a multilayer, pressure-sensitive patch that is applied to the skin. Initial products were used to treat angina and motion sickness. Manufacturers are showing renewed interest in this packaging format, and several new transdermal products recently have appeared on the market. Because absorption through the skin provides a more consistent dose delivery than does oral ingestion and one patch often can be worn for several days, transdermal products make it possible to maintain more uniform drug levels in the bloodstream. They also reduce compliance problems because once they are applied, dosing is automatic and patches generally don't have to be changed as often as an oral dose typically would have to be taken. Transdermal delivery doesn't require the drug's active ingredient to pass through the digestive tract, so it may be possible to produce therapeutic results at lower dosage strengths than would be required for an oral dosage form. More consistent bloodstream levels and lower dosage strengths can translate into fewer, less-severe side effects.

Blow-fill-seal containers

Another packaging format that has not yet realized its full potential in the United States is the blow-fill-seal container. Domestic pharmaceutical manufacturers have not been as enthusiastic about this format as have manufacturers in Japan

and Europe, despite the format's numerous benefits. Because containers are formed, filled, and sealed by the same machine, the expenses related to shipping, cleaning, storing, and sterilizing preformed containers are eliminated. Combining and automating these operations also remove several production steps and reduce labor requirements. Less human intervention means improved quality and consistency, lower costs, and simpler validation. In addition, because closures are formed as the container is molded, specialized dispensing features can be built in, and so can embossed product information and lot numbers. Because filling occurs just after molding when the container is still at a temperature of about 37 °C, the system can perform aseptic fills.

Barrier isolators

For more than a decade, equipment builders and pharmaceutical manufacturers have worked on developing filling and closing machines equipped with barrier isolator enclosures to provide an aseptic filling environment without the need to use a cleanroom. Advantages include reduced construction expenses and operator gowning requirements, removal of operators from the immediate filling area, and a smaller area requiring a controlled environment. Now with a handful of isolator-equipped lines approved by FDA for filling sterile products and a third generation of equipment being built, current technology holds considerable promise for more cost-effective packaging of sterile or highly toxic compounds and likely will change the way many sterile products are filled.

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