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Inactive Ingredients, Active Risks

The inactive ingredients in medicines can pose risks. Who is watching over this corner of the pharmaceutical world?

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By Michael Eisenstein on September 19, 2018

A medicine's so-called 'inactive ingredients' can have dire consequences without the appropriate framework for oversight and control. Credit: Daniel Wilson/Alamy

You've got a headache, so you take some acetaminophen. But, you're not only swallowing the active ingredient—it's just a small component of each tablet. For most medicines, up to 90% of each dose is made up of excipients: substances added to improve formulation, performance, taste, appearance, color, or even consumer appeal.

Excipients are officially designated, and therefore often dismissed, as 'inactive' ingredients. "The first time I mentioned them to my internist a few years ago, he looked confused," says Robert Osterberg, a pharmaceutical industry consultant, and a member of a committee working on excipient issues at USP, also known as the US Pharmacopeia. But, like active ingredients, excipients are selected because of their distinct chemical or physical properties, and the consequences of defective ones can be dire. In 2006, Panamanian drug-makers unwittingly manufactured hundreds of thousands of bottles of cold syrup in which the safe glycerin was substituted with toxic diethylene glycol. Authorities later found that a manufacturer had intentionally mislabeled the ingredient as pharmaceutical-grade glycerin for economic gain—and no one receiving the mislabeled product tested it before using it. By the time it was intercepted, the tainted medicine had claimed hundreds of lives. "Many people died from kidney failure," Osterberg says.

A framework exists to prevent these kinds of incidents. The FDA regulates excipients for use in drug products for the US market and, collaboratively, the USP sets quality standards for excipient manufacturers and pharmaceutical companies. Until recently, this has been a relatively neglected corner of the regulatory world. With the development of new classes of therapeutics and increasingly globalized supply chains, oversight and interest in excipients has steadily grown. But quality oversight systems must adapt to a rapidly evolving pharmaceutical marketplace to ensure that these inactive ingredients get the attention they deserve.

QUALITY CHALLENGES

Poor excipient oversight and control was a critical element in the birth of the modern regulatory system. In 1937, the drug company Massengill released a formulation of the potent antibacterial drug sulfanilamide dissolved in a solution of diethylene glycol— the same compound that wreaked fatal havoc in Panama in 2007. In the 1930s, Massengill scientists were unaware of diethylene glycol's toxicity, and they were under no obligation to test it. "It was a beautiful shade of blue, it was sweet, and it was an elegant-looking prescription," says Osterberg. Within months, more than 105 people were dead. The resulting public outcry led to the empowerment of the FDA as a national arbiter of food and drug safety in 1938, with a mandate that each excipient undergo toxicological testing essentially equivalent to that performed on active pharmaceutical ingredients.

Today's medicines typically contain anywhere from two to six different excipient compounds, Osterberg estimates, and some pediatric over-the-counter medicines can contain up to 17. Some perform pedestrian but important tasks, such as making foul-tasting medicines palatable to kids, while others are crucial in controlling when and to where in the body a drug gets delivered. And while many of those excipients are familiar household names—starch, gelatin and talc—quality control becomes more difficult and important when setting standards for medicine. "There is general indication that starch is OK to eat," says Osterberg. "But when it comes to making a pharmaceutical that contains starch, like a tablet, the purity standards are much more rigorous."

USP works with regulators and manufacturers to define analytical procedures that can discriminate a product suitable for pharmaceutical use, as opposed to use in manufacturing or food preparation. But, those procedures need regular review and updating, since even familiar products, like talc, can present risks if not sourced and quality-checked carefully. "It's a mined material that may contain asbestos,"

says Jaap Venema, chief science officer at USP, "and you really want to make sure that the tests that you use can detect the types of asbestos that are harmful."

Globalization also presents new challenges. With ingredients arriving from around the world, often brokered by distributors, companies must be more diligent to ensure quality. "It's up to the drug manufacturer — not the offshore excipient manufacturer — to make sure that it conforms to all the things the FDA requires," Osterberg says.

STAYING AHEAD OF THE CURVE

New excipients pose even greater challenges. "Most countries do not have a regulatory mechanism by which you can register a new excipient for approval," Venema says. "It has to be part of a drug application," so most manufacturers shy away from the risk of introducing a novel excipient in a drug application.

When they do use a new excipient, it's usually only by necessity. For example, from 1987, manufacturers of asthma inhalers had to replace chlorofluorocarbon (CFC) propellants. Today, inhalers use more environmentally-friendly hydrofluoroalkane (HFA) propellants, but this required considerable re-invention. "Most people in the reformulation business thought it was going to be easy —but it ended up taking 15 years for the first product," says Anthony Hickey, a pharmacologist at the Research Triangle Institute and member of a USP subcommittee focusing on aerosols.

But as new therapies continue their march to market, the need for new excipients is becoming inevitable. For example, drugs for neurological disease, which must efficiently cross the blood-brain barrier, will require new excipients. So too, will cell and gene therapies and implanted products. Each brings unique challenges for its route of application, and existing excipients may not be deemed safe for use in these products.

"20 years ago there wasn't much discussion around excipients," Osterberg says. "Now I'm seeing a lot of activity from the International Pharmaceutical Excipients Council (IPEC) Federation, and they work very closely with the USP and the FDA to make these components a central part of the conversation."

Global harmonization of standards is also a primary goal of this collaboration, gathering manufacturers from all nations in the hope of preventing substandard and adulterated excipients from reaching the marketplace. That work is slow and building consensus is difficult, but essential to avoid repeating disasters like the mass diethylene glycol poisonings in Panama. Says Osterberg, "I hope we never see these cases again."

To learn more about the need for quality standards in medicines, visit The Science of Quality.