

Dose Response

Fall 2002

Your source for business news and information on today's
oral dosage delivery systems

The Debate Over Tablet Splitting Heats Up



With the U.S. media's increased focus on prescription drug spending, and no drug benefit for U.S. seniors yet in sight, tablet splitting - the

practice of asking patients to cut tablets in half - has been identified in news reports as a way for patients to reduce medication costs. However, those reports often omit how the practice may negatively affect patient safety by increasing dosing errors.

Tablet-Splitting Advocates

Despite those warnings, Illinois' Department of Public Aid recently proposed a change to the Medicaid preferred drug list. They want to require patients, who take 50 mg of the selective serotonin reuptake inhibitor (SSRI) Zoloft, to receive 100 mg tablets instead, and then split it into two doses. Since there is very little or no price differential between the strengths of Zoloft, Illinois is hoping to halve that medication cost.

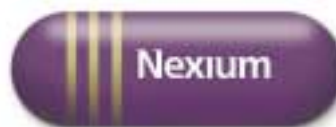
Similarly in 2000, United Healthcare mandated tablet splitting for some of its health plan beneficiaries' prescriptions. Lee Newcomer, MD, United Healthcare's senior vice-president for health policy, went on Good Morning America to explain the appropriateness of the practice. His cost-containment argument conflicted with Susan Winckler's, group director of policy and advocacy for

continued on p. 2

The Importance of Color Selection & Imprints, and How They Effect Compliance

The New York Times called patients' failure to take medications as prescribed the world's "other drug problem." The U.S. Chamber of Commerce found that only 50 percent of all medications filled are taken correctly. Other statistics associate 125,000 annual deaths and 10 to 25 percent of hospital and nursing home admissions with patients' noncompliance.

But the use of pharmaceutical branding may help patients take their medications properly and decrease those numbers.



A Case Study

Edward Weirauch, program manager of GI public affairs for AstraZeneca, discussed how heartburn medication Nexium's marketing, which is closely identified with its trade dress,

encourages proper dosing. Advertisements are predominantly purple, the product's website is hosted at www.purplepill.com, and the brand name is written plainly on the capsule.

"We've continued to use purple, a very distinctive and specific color first developed for Prilosec, because it enables patients to easily differentiate Nexium from other pills

they may be taking. A byproduct of the advertising - whether people are watching TV or looking through a newspaper or magazine - is compliance and they're reminded to take their medication."

Branding Helps

A study published in *Pharmacy World & continued on p.3*

Product Life Cycle Management – Maximize Revenue Through Reformulation in Other Dosage Forms

The threat of generic competition is forcing companies to place an unprecedented emphasis on life cycle management. The industry stands to lose more than \$165 billion in revenue as a result of 31 megabrand patent expirations set to occur between 2000 and 2005, according to Datamonitor. Seeking to stop the pinch from the loss of its blockbusters, 60 percent of those companies are opting to reformulate their products, hoping to keep consumers from switching to cheaper drugs by offering them improved administration, efficacy, and tolerability - the tools needed to increase compliance. Reformulations also offer pharma a chance to recoup the discovery and development dollars invested in the original molecule, since reformulations cost only ten percent of, and take a fraction of the time to commercialize as, the initial product.

"There are fewer new products coming through companies' pipelines. In both Europe and the United States, the number of drug approvals in 2002 will probably be way down from the previous year," says Peter Norman, MBA, PhD and author of Decision Resource's *How Delivery*

continued on p.4

the pharmacist trade organization American Pharmaceutical Association. She demonstrated that tablets often break or crumble unevenly when split in half - potentially creating situations where patients either don't receive a therapeutically beneficial amount of medicine or experience an overdose. In addition, variation in drug particle size, particle shape, or bulk density can cause variations in a product, suggesting that half a tablet doesn't necessarily provide half the medicine.

Winckler notes that there are circumstances where tablet splitting is appropriate, particularly when there is no commercially viable form of the dose needed. "But tablet splitting keeps resurfacing as a way for health plans to save money. It's just not as simple as looking at the price of two different strengths of medication."

Are seniors at greater risk?

A recent research paper published in the *Journal of the American Medical Association* found that when a sample of elderly patients hand-split tablets, the dose deviated between 9 and 37 percent from that intended. The study's authors write, "While an approximate deviation of 10 percent may not be clinically significant, the larger deviations in this study could be hazardous in the case of medications with a narrow therapeutic index."

A recent research paper published in JAMA found that when elderly patients hand-split tablets, the dose deviated between 9% and 37% from that intended.

The authors suggest that the use of, and instruction in, tablet splitters may improve accuracy. However, Tom Clark, director of professional affairs for the American Society of Consultant Pharmacists, a professional association for senior-care pharmacists, says that because Medicaid and third party plans don't cover tablet-splitters, or compensate pharmacists for spending extra time educating patients, those practices are less likely to happen. And even when tablets are split appropriately, proper dosing - a critical factor in successful pharmaceutical treatment - cannot be ensured since the unused portion can continue to crumble when returned to the prescription bottle.

A study conducted by Stanford University Medical Center researchers noted that some physicians are reluctant to suggest pill-splitting because of those concerns. However, Stanford's press release - which triggered headlines on CNN as well as National Public Radio - advocated the cost-reduction strategy for only 11 medications, out of the possible 265 commonly used medications analyzed. Researchers balanced the listing of those drugs, which includes Celexa and Paxil, with a discussion of the types of medications that should never be split, including those that have extended-release mechanisms or enteric coatings.

Compounding the problem is that elderly patients, who are more likely to split pills because they have a disproportionately lower income, are also the most likely to do so incorrectly because of their increased risk for cognitive or visual impairment, arthritis, Parkinson's disease, or decreased manual dexterity.

How can tablet splitting be prevented?

"It doesn't take many patients winding up in the hospital to more than wipe out any savings from the drug cost that can accrue from this practice," says Clark. "Companies are going to adopt policies or make changes

to discourage tablet splitting. There are a number of ways to do that. They may decide it's beneficial to use capsules instead of tablets, put tablets in individual blister packages instead of a bottle, or formulate tablets that make them very difficult to split."

Marketing managers should examine and understand how patients are taking their medications. If patients are splitting pills, brand teams may think about reformulating the product in order to encourage safe patient dosing.

According to a Stanford study, only 11 out of 265 commonly used medications analyzed would realize savings from tablet splitting.

Upcoming Events

January 22 - 24, 2003: Molecular Biopharmaceutics, Sheraton Waikiki Resort, Hawaii, USA, tel. 734.663.4233, email sjohnson@ddfint.org, www.ddfint.org

January 28 - 30, 2003: 7th Annual Drug Delivery Partnerships Conference, The Hotel Del Coronado, Coronado, CA, USA, tel. 800.345.8016, ext. 3057, email cbuhler@iirusa.com, www.drugdeliverypartnerships.com

February 17 - 19, 2003: World Drug Discovery and Development Summit, Radisson SAS Scandinavia, Copenhagen, Denmark, www.wdd.worldtradeco.com

March 31 - April 2, 2003: International Pharmaceutical Industry Congress 2003, Jacob K. Javits Convention Center, New York City, USA, tel. 203.840.5924, email rpalermo@reedexpo.com, www.pharmacongress.net

April 7 - 8, 2003: 6th Annual Drug Delivery Systems, Philadelphia, PA, USA, tel. 800.817.8601, email cbireg@cbinet.com, www.cbinet.com

May 13 - 15, 2003: Applied Clinical Trials European Summit, Management Centre Europe, Brussels, Belgium, tel. +44.1244.393.159 for Siân Winston, email swinston@advanstar.com, www.appliedclinicaltrials.co.uk

continued from p. 1

Science, the official journal of three European pharmacy organizations, concluded that the visual appearance of pills does affect patients' preference for and compliance with prescriptions.

Diane Cousins, R.Ph, vice-president of the U.S. Pharmacopeia's practitioner and product experience division, notes that including color can help eliminate dosing errors. "People, especially the elderly, can get confused when they take various medications and more than one is a small white tablet."

Indeed, researchers found in this study that patients favor white medicine over any other color. But that preference changed when the study compared those who swallowed more than ten pills daily with those who swallowed less. Patients taking more drugs preferred bright pill colors. That is especially interesting news for companies developing products to treat age-related diseases since the typical Medicare beneficiary uses an average of 18 to 24 prescriptions a year, according to the Senate's Aging and Youth Committee. Marketers interested in reducing medical errors might consider including color and color combinations as one of their strategies.

Other Factors

But in a crisis situation - such as reporting an overdose - color, and even size and shape, are subject to interpretation. Therefore, imprints, required by the FDA, are the only nonbiased way of identifying pills. Companies may want to develop imprints that are meaningful, and therefore allow easy identification by consumers, physicians, emergency room workers, or poison control centers. A remarkable imprint can also help patients take medication correctly, further differentiating it from other pills prescribed.

In addition to those elements of branding, perceptions of swallowability may also affect

compliance. Of the 331 Pharmacy World & Science study participants, 66 percent preferred capsules, citing them as easier to swallow; 18 percent preferred coated tablets; and only four percent preferred uncoated tablets.

"Swallowability is really important," says Lucien Wilkins, MD, a North Carolina-based internist and cofounder of the American Physician Partners Association,

an organization that filters product information from the pharma industry to physicians. "Medications like Fosamax for osteoporosis, which can get stuck in the esophagus, can be really detrimental to patients' health. It would be very beneficial to have a formulation that allows it to go through the esophagus more easily."

Instead of struggling for small improvements in market share, formulators can focus on making their medications more patient-friendly and increasing compliance. By creating an identifiable brand that incorporates the use of color and logos, and by improving swallowability, companies have an opportunity to help their patients, and their bottom line.



Several studies have focused on the relationship of color to perceived potency. Researchers found that patients respond best when the pill color corresponds with an expected therapeutic benefit. For example, the color blue is generally



categorized as depressing or tranquilizing whereas yellow and red are correlated with stimulating. Patients perceive red and black capsules to be more powerful than blue, green, orange, and yellow ones, and white capsules were thought to be less powerful.

Did You Know?

Up to 70 percent of new chemical entities do not generate enough revenue to recoup their R&D costs.

Source: Boston Consulting Group

Articles of Interest

The Effects of Print Format in Direct-To-Consumer Prescription Drug Advertisements on Risk Knowledge and Preference
Source: Drug Information Journal, Vol. 36, pp. 693-705, 2002

Broadening Utility of Tablet and Capsule Imprints
Source: Journal of Pharmacy Practice, Vol. XIII, No. 2, April 2000

Patients' Evaluation of Shape, Size and Colour of Solid Dosage Forms
Source: Pharmacy World & Science, Volume 23, No. 5, 2001

Europe seeks to calm nerves over US-style drug advertising/MEPs face a cultural divide on giving patients information
Source: Financial Times, Thursday, October 24, 2002

EU industry/MEPs kick out "drug advert" proposals
Source: EIU ViewsWire European Union, Tuesday, October 29, 2002

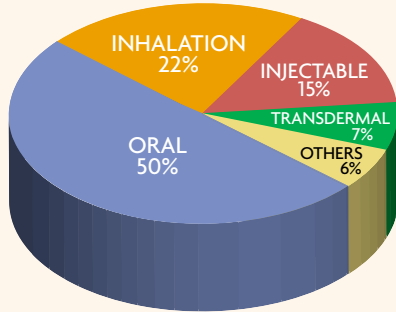


Figure 1: Drug Delivery Breakdown

Technologies Extend Drug Life Cycles. “The less products that come through, the more companies need to try and sustain the life cycle of existing products, or at minimum, the more lucrative ones.”

Indeed, analysts report that, in the future, therapeutic class leaders will be differentiated by their drug delivery technology. A Datamonitor report estimates that the drug delivery market will grow from \$28 billion in 1998 to \$78 billion by 2005. Oral delivery technologies represent half that market. The other half of the market is split between inhalation, injectable, transdermal, and other technologies (See Figure 1).

A Successful Example

Executives can look to Marion Laboratories’ (now Aventis) reformulation strategy for its

calcium channel blocker Diltiazem as a case study for effective life cycle management. In a series of collaborations, Marion developed the original medication, a three times-daily orally administered product, and produced a sustained-release twice-daily formulation, Cardizem SR; a once-daily formulation, Cardizem CD; an extra-strength formulation of Cardizem CD; and a new encapsulated extra-strength formulation. Twelve years after the original product was marketed, line extensions of that same molecule bring in about \$800 million yearly, despite generic alternatives.

Tick Tock

A rule of thumb is that first-to-market products generally maintain a competitive advantage. Often, a few months difference in drug development time can impact market share. Therefore, companies need to ensure that both marketing managers’ and R&D formulators’ product strategies are focused on reducing total development time.

To that end, osteoarthritis treatment Celebrex gained a significant advantage over competitor Vioxx by **getting to the market first**. Company executives and scientists knew that by developing Celebrex in a capsule, they could eliminate three to six months of development time. That

is because capsules use a lower number of excipients than other oral dosage delivery forms. With fewer ingredients required, not only is less time required for raw materials evaluation and validation, but also formulators have more flexibility when developing the dose. Also, like most other Rx products where early phase formulations are in capsules, there was no need for additional bioequivalence testing, which would be required to support a conversion to a tablet.

Looking Ahead

Pharma companies are now making much more of an effort to develop the most therapeutically advantageous formulations early on, according to Peter Norman. As such, there may be a trend away from reformulation strategies in general. But many opportunities remain today.

By 2005, the global pharma market will derive 20 percent of its revenue from reformulated products. As such, pharma companies should re-examine if its product life cycle management is viable, and look for areas where they can save time and money. Those incremental adjustments may just be pharma’s best solution for generic competition and risk-filled pipelines.

About Dose Response

Dose Response is published three times per year, with a focus on helping pharmaceutical companies gain competitive advantage via dosage form design. It is published by Capsugel (a division of Pfizer), a recognized leader in technical support for oral dosage forms. For further information, visit www.capsugel.com, and click on the Dose Response Newsletter icon.

Capsugel
P.O. Box 7266
East Brunswick, NJ 08816
USA

Pre-Sorted
First Class
U.S. Postage
Paid
Summit, NJ
07901
Permit #550

CAPSUGEL®
Quality
People and Products Working Together™