Could Clinical Trial Packaging Influence the Drug Itself?

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Could patient noncompliance during a clinical trial lead to later use of a higher drug dose than necessary? Ward Smith believes so, adding that such higher-than-needed doses could amplify side effects and even threaten trial success. He suggests that use of compliance-style blister packaging can help study patients take drugs as directed and ensure that specified dosing is actually being put to the test.

To be clear, Smith is the director of marketing for **Keystone Folding Box Co.**, whose blister design is featured on page 42. He has also served as a compliance packaging specialist and clinical trial specialist at MeadWestvaco Corp. But he also was executive director at the Atlanta Institute of Medicine & Research, which runs clinical studies.
"In a clinical trial such as one involving a dose-ranging study, poor dosing compliance could direct the developer to a higher than needed dose to show drug response," says Smith. "At the extreme, it could lead to study failure of an otherwise effective compound. But if compliance packaging is used to guide subjects toward compliance, it's a big win for the drug developer in both phase II/III studies."

Smith points out that a number of already approved drugs have had their doses reduced. "One study reports that since 1980, one out of every 4.5 drugs approved has seen a postmarketing dose reduction by up to 50%," Smith says. (He points to two papers published in Pharmacoepidemiology and Drug Safety in 2002.)

There could be safety (and possibly liability) issues when using a higher dose than needed for therapeutic benefit, notes Smith. "In addition, manufacturer revenue could change when a product once sold at $25 per 100 mg drops to a recommended dose of 50 mg, for example," he adds. "It is better to lead with the right dose."

Companies therefore need "to be accurate when determining dose levels in smaller studies such as phase II studies," Smith explains. "You want to identify the optimal effective dose, rather than the highest tolerated. Doing so could limit unwanted long-term drug side effects." Using compliance packaging could help achieve such accuracy, Smith says. "Study subjects in clinical trials are subject to the same type of dosing errors that occur with real-world patients. You can't lose sight of the fact that study subjects are people recruited from the real world."

In addition, "since we often pay study subjects and provide access to healthcare at no-cost, patients are incentivized to withhold details about being noncompliant. Well-designed unit-dose packaging will help patients take drugs as directed, and smart packaging could be used to identify noncompliant subjects who miss doses and dump study drug—those who maintain the appearance of being compliant," he says.

There could be financial incentives to encouraging compliance: "Consider the average cost-per-patient in phase II—$20,000—and phase III—$30,000," says Smith. "The incremental cost of a compliance package over a bottle, while measurable, is a drop in the bucket. While managing costs is important, don't be penny-wise and pound-foolish about packaging."

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