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PHARMACEUTICAL & MEDICAL Packaging NEWS®

THE PACKAGING MAGAZINE FOR THE HEALTHCARE INDUSTRY

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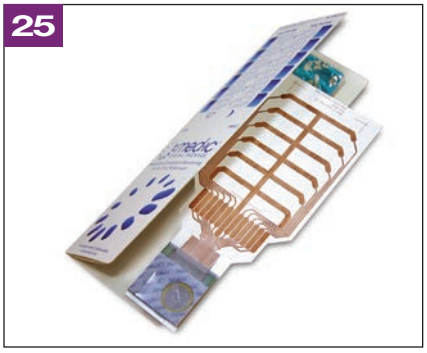

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Building Trial Adherence With Packaging

By David Vaczek, Senior Editor

Persistently high non-adherence and drop-out rates in clinical trials are driving interest in compliance-prompting formats.

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Driving Patient Safety

By Daphne Allen, Editor

Parenteral packaging needs to address patient safety, attendees at Pharmapack Europe are advised.

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By Daphne Allen, Editor

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PACKAGING RESOURCE CENTER

Cover: Image of the Med-ic Smart Label, courtesy of Information Mediary Corp.

Building Trial Adherence With Packaging

As the cost of running clinical trials climbs, compliance formats have gained favor for addressing persistently high non-adherence rates.

By David Vaczek
Senior Editor

Patient non-adherence is a prevalent concern in clinical trials and one reason why clinical trial costs are on the rise. When medication adherence rates are low, trials often have to be expanded with more participants to achieve meaningful results, adding to trial costs.

If patients leave off taking the drug, yet maintain the appearance of being compliant, non-adherence may go unrecognized.

Trial investigators will then be led to underestimate the therapy's effectiveness, and the drug may be launched at a higher dose than is therapeutically necessary. If the dose is subsequently reduced post-market, the company has to back-peddle on its revenue forcast.

Drug companies running trials are turning to compliance formats, as studies demonstrate the value of patient-friendly designs in keeping patients on track with study protocols.

Studies showing adherence improvement when compliance formats are used with commercially available drugs provide insights for clinical trial packaging, Dr. Kathy Zonca, patient adherence consultant, C3i Inc. (www.c3i-inc.com), said in a presentation at the Healthcare Compliance Packaging Council's RxAdherence conference.

Zonca recommended that companies take these documented results with approved drugs and extend the lessons learned to the clinical trial setting.

"Packaging can be both a behavioral and educational support for patients in clinical trials, acting as reminders as to whether the medications have or have not been taken, and offering clear directions, instructions in how to accurately take the medication in order to follow the trial protocol," Zonca said.

Trials are growing increasingly complex, with increasingly complex patient instructions. A factor in non-adherence rates, trial complexity is also driving a slide in patient trial retention rates, Zonca said.

Trial procedures—questionnaires and assessments, routine exams, lab procedures—add complexity for patients and investigators. Median total procedures per protocol were 166 procedures in 2008–2011, a 57% increase from 2000–2003.

Among patients receiving treatment for chronic conditions in clinical trials, average adherence rates are 42% to 78%, Zonca said.

The patient retention rate has dropped precipitously. Less than 25% of patients screened were retained until trial completion in 2010, compared with nearly 50% of patients screened completing the trial in 2001.

PROACTIVE MEASURES

When adherence is low in a clinical trial, researchers have to increase the sample size to maintain study power. A 20% decrease in medication adherence may result in the need for a greater than 50% increase in sample size to maintain equivalent power. A trial with 50% mean compliance could require about 4 times as many participants as a trial with 100% compliance, Zonca said.

The trial's goal is for patient adherence to the trial protocol. For a marketed drug, the objective is to maintain therapy towards having a healthier patient.

Yet the proactive measures for improving adherence work in both settings. They include: increased contact, reinforcement of the value of participation, and reminders—which include patient friendly packaging with clear, concise labeling, Zonca said.

"Early intervention is critical. Effective interventions combine education, motivation, support, reminders, and rewards," Zonca said.

Fisher Clinical Services is using more blister packaging in trials, as a preferred alternative to bottles. "Most importantly, the packaging features enhanced graphics and 'pictures', and more emphasis on patient directions," says Mike McNear, vice president and global head of clinical supply optimization services, Fisher Clinical Services (www.fisherclinicalservices.com).

"Fundamentally, a well-planned program thinks about how the patient will take their medicine and be more likely to adhere to their dosing regimen. Patient-friendly packaging is all about ensuring that a patient clearly understands how the medicine is to be administered. In a trial where a patient may take multiple medications, a blister package helps lay out the protocol," McNear adds.

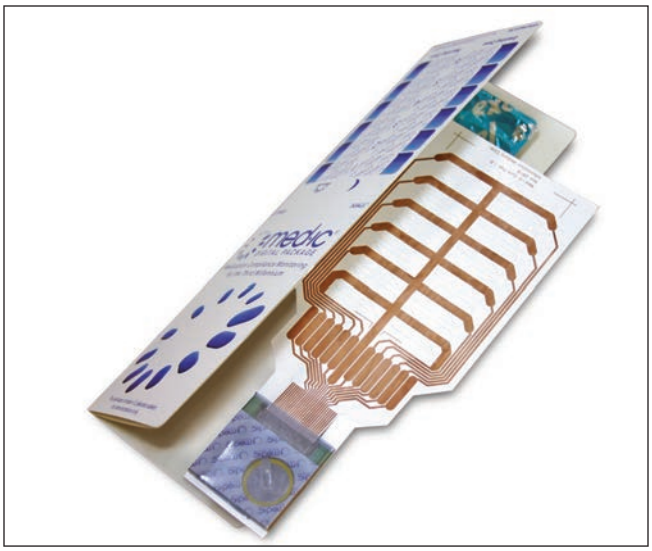
Clinical trials often have complex dosing regimens. Many protocols require patients to take multiple pills from various columns presented in a blister card, at different intervals each day.

Study sponsors will look for enhanced graphical elements to help patients understand the correct way to take each scheduled dose, says Ward Smith, director of marketing, Keystone Folding Box Co.

"Companies are now recognizing that the complexity of a dosing regimen contributes to non-adherence. They look to reduce dosing errors via package design. [For example] they will ask us to use color blocking to visually group pills to be taken at a specific time. Icons of the sun and moon are commonly printed to designate the time of day each dose is to be taken," Smith says.

Most recently, clinical trials have begun to favor Keystone's Ecoslide-RX package, adopted by Walmart last year for packaging generics in the chain's $4 prescription drug program. As the Ecoslide-RX's calendarized design supports adherence, the package offers improvement in fulfillment by eliminating the need for heat sealing.

In the assembly of the patented Ecoslide-RX, a small nylon rivet is snapped to the back of the blister. When the blister is loaded into the sleeve, the rivet engages with the carton to function as a child-resistant lock-and-release button.



The Med-ic Smart Label from Information Mediary Corp. is custom designed to fit medication blister packages for recording the time each dose is removed. The removable, reusable electronic content monitor tag that records the activity is hidden inside the card.

"We have seen wide spread interest in the last few months from clinical trial material packagers. Customers are seeing Ecoslide-RX as a solution that reduces both material and labor costs. You can achieve dramatically faster throughput as smaller packaging crews can run a higher number of pieces per hour. You effectively reduce your total-delivered-package-cost," Smith says.

Companies are realizing that the benefits of using adherence packaging in clinical trials outweigh the minimal additional costs, says John Musaus, global director, electronic adherence solutions, MWV Healthcare.

"Cost and speed have been the two historical issues, [with] clinical trial budgets oftentimes fixed to a certain style of package. Clinical trial teams need packaging that is child-resistant and easily manufactured," Musaus says.

"But more and more, people are realizing that the package can also play an integral role in assuring that patients stay on their assigned treatment protocol. Study data is clearly showing that adherence packaging used instead of bottles helps people stay on protocol.

"The whole value chain is seeing that it pays to spend a little more time to get the package right. It has a small effect on overall trial costs, and they can get a more accurate trial result," Musaus says.

CAPTURING DOSING HISTORY

With so much at stake in a clinical trial, it is little wonder that smart packaging—packaging that incorporates electronic circuits for tracking patients' use of a package—is receiving greater interest.

Smart packages provide a means of capturing unbiased information on patient's dosing history. The data can be analized to help clinical trial teams better understand patient adherence and exposure to the drug. This dosing information can also be used in counseling patients to stay compliant with the protocol.

In its draft guidance, "Enrichment Strategies For Clinical Trials" (Docket #: FDA-2012-D-1145-0037) issued in December 2012, FDA cites "smart bottles" as a tactic for encouraging patient compliance. MWV Healthcare has submitted comments calling on the agency to use the term "smart packaging," noting that electronic medication event monitoring is also a feature in unit-dose blisters, pumps, syringes, and tubes.

"And we believe the use of smart packaging should be more strongly encouraged [as it] offers the ability to capture robust and highly reliable dosing history data in an unobtrusive and non-invasive manner, and it has been used successfully in hundreds of clinical trials involving hundreds of thousands of subjects," MWV Healthcare wrote.

"Smart packages tie right in with the rise of telemonitoring and telehealth that we are seeing start to come into more common use," Zonca said.

"I believe that as reimbursement for these services starts to come into play and as doctors, clinics, and ACO's are measured on outcomes that smart packages will be one of the tools they will be looking for to support patients in achieving the best possible outcomes for them," Zonca said.

Though trial clinicians generally recognize the benefit of the data obtained from smart packaging, packaging departments also have to buy into it.

"There is lots of data to support that patients monitored and counseled are much more compliant overall. With smart cards, you can measure exactly when patients extract their medication during the trial to help sites understand the patients and counsel them appropriately," McNear says.

"We have seen several trials utilize the Med-ic smart card product (from Information Mediary Corp.) over the last two years. Two critical factors are enabling this: the price point has to be more realistic, and [you need] the ability to use it with standard blister card formats currently deployed in the industry," says McNear.

"The key for any technology advancement is volume. As volume used goes up, the price point goes lower. In my opinion, smart packaging technology will increase significantly over the next several years in clinical research as well as perhaps specialty commercial markets," McNear adds.

MWV's smart package portfolio includes Aardex Solutions' MEMSCap, the child-resistant Cerepack, and the Helping Hand package, which measures the instances when the blister card is slid in and out of the package.

"Interest and adoption of smart packaging has increased dramatically as researchers and statisticians begin to fully appreciate the utility of the patient usage data collected by the package. Adherence data collected through smart packaging is now being used as an additional vital sign," Musaus says..

UNBIASED DATA SETS

The data collected via smart packaging is unbiased, unlike data obtained from pill counts and patient diaries that depend on patient recall and are subject to patient manipulation.

Studies by MWV and others have related patients' dosing patterns measured with smart packages with their pharmacokinetic (PK) profiles, demonstrating significant correlation. Patient drug dosing history captured by the package is measured and compared with the PK values obtained from monthly blood work visits.

"We have published study data from trials showing that accessing the medicine through the pack is equivalent—with high statistical reliability—to blood level serum concentrations. So we can show how the dosing profile correlates with how the blood level rose and fell during the course of the trial,"says Musaus.

"The utility of smart packaging for illuminating patient behavior is hard to overstate. If you are not measuring the

adherence, you have no concept of what is happening with dosing behavior in between visits," he adds.

In a recent soon-to-be-published study funded in Europe, the authors reviewed and analyzed the literature on 79 clinical trials published from 1995 to 2011, where medication adherence was assessed through electronically compiled drug dosing histories.

One study analysis showed an 8.8% increase in adherence when the intervention included feedback to the patient of their recent dosing history. A second analysis on a subset of studies showed double the adherence improvement in patients receiving this feedback.

"The study shows that having a healthcare professional counsel a patient based on the individual's drug dosing history collected via electronic packaging is the most successful technique for increasing adherence rates in trials, as compared with methods such as texting and reminders.

"The clinician at the trial site is taking the patient's own data and pointing out how they can change their behavior," Musaus says.

NEW MODELS

Though larger clinical trials have been a trend of recent years, newer models have emerged as drug companies focus on making trials both more efficient and informative.

"The mega trial seems to be dropping back [in favor of] more studies, more study starts, and fewer patients in many cases. Sponsors are getting more sophisticated with forecasting and developing techniques to predict enrolment," McNear says.

"We're seeing this with adaptive design clinical trials [where the trial study design changes as data accumulates], but also where companies are looking to get a 'go, no-go' decision in the quickest possible manner," he says.

Direct-to-patient or "virtual" clinical trials have far reaching potential to improve trial costs by avoiding the need for patients to visit clinics and doctors' offices. In this home-based model, patients are screened for enrollment on line and participants receive their medications in the mail. Patients report from their homes using smart phones and computers as they are remotely assessed by investigators.

The model has been held up as promising speedier study recruitment and enrollment. Increased patient compliance and retention rates are seen as another potential benefit, as patients follow their regimens in the comfort of home.

Pfizer notably tested the direct-to-patient concept with the overactive bladder drug Detrol in 2011 in the first-ever FDA-approved virtual clinical trial.

"The direct-to-patient model—if it comes to fruition—will put ever more onus on packaging design to be self-explanatory and to ensure compliance and appropriate use of the medication. Packaging that features enhanced instruction and more use of graphics would be a stand-in for visits by trained medical personnel,"McNear says. ■