

Testing Effectiveness of Patient Package Inserts and Guides: Mitigate Medical Product Risk and Improve Safe Use

Abstract

The adequacy of labeling for instructions, cautions, and contraindications becomes pivotal in the benefit/risk assessment of medical products. Our research using observational study designs in mock product use trials has predicted medication use error rates in the range of 40-70% for drug device combination products. Early testing of proposed labeling can identify problem areas in label comprehension that leads to a potential medication or administration error or user frustration resulting in medication non-compliance. A well designed labeling comprehension study is not an expensive proposition; most studies can be performed with a small sample size ($n \leq 100$) for baseline observations and testing of label revision(s). In our experience, such studies support labeling changes that can significantly reduce potential product misuse and medication error to acceptable rates.

I. Introduction

Initiatives to reduce health care spending have ultimately resulted in many medical procedures increasingly being moved to the outpatient environment and/or home care setting. As such, patients, family members and/or other non-medically trained personnel are performing therapeutic and diagnostic procedures such as drug administration using alternative drug delivery devices, inhaled therapies, glucose tests, etc. Adequacy of the labeling instructions, cautions, and contraindications and the use of supplemental instructional labeling have become pivotal in the benefit-to-risk assessment of these treatments or tests. This paper describes a research methodology offered by BioTrak Market Intelligence, Inc. (BioTrak) for evaluating the effectiveness of combination drug/device product labeling prior to product registration as an aid in the development of appropriate labeling and during the post-approval period to assess comprehension and compliance among patients, dispensing pharmacists and patient care providers.

The medication errors staff in the FDA Office of Post-Marketing Drug Risk Assessment (OPDRA) search the FDA Adverse Event Reporting System (AERS) database for all cases of medication error. In a report published in 2001 (Drug Topics October 2001, p 23-24), labeling was identified as one of the leading causes (20%) of medication error along with misinterpretation of the order (10%) and written communication (8%). Additionally, human factors are the leading cause (42%) of comprehension and performance deficit. These data illustrate the importance and need for clear use labeling.

II. Regulatory Context

The FDA has promulgated detailed regulations specifying the form, content and wording of labeling for items such as the identity, dosing, supporting studies, warnings, adverse reactions, contraindications with respect to established drugs and biologics dispensed by a pharmacy or sold over-the-counter (OTC). (Title 21 Subchapter C-Drugs: General Part 201 Labeling). Likewise the labeling requirements for medical devices are specified in Part 801 Labeling. The FDA has required sponsors to thoroughly investigate the adequacy of labeling for OTC switches of prescribed medications. For example, FDA and consumer groups required sponsors to conduct five labeling comprehension studies and five actual use studies before the approval of Prilosec® for OTC marketing. FDA plans to conduct labeling comprehension studies of their own prior to issuing new regulations for covering the wording of statements that request patients to report adverse events. Among the reasons cited for testing these statements were: (1) to determine the best and most precise wording for the statements, (2) to evaluate consumer comprehension of the proposed statements, and (3) to address concerns that consumers who read the statement will mistakenly call FDA in search of medical advice (Federal Register / Vol. 72, No. 22 / Friday, February 2, 2007 / Notices).

For combination products sponsors are expected to submit adequately well controlled scientific evidence for the safety and effectiveness of their labeling. However, to date the FDA has not issued guidance for combination product labeling comprehension studies.

III. Strategies for Labeling Studies

In today's climate of increasing regulatory control, authorities are demanding more controlled studies to evaluate and verify product safety and the accuracy of product use instructions by all product stakeholders involved in the prescribing, dispensing and administration of the product. Common methods used to evaluate labeling comprehension (prescribing, dispensing and use instructions) typically include one or a combination of the following:

Product Use Simulation Studies – Proposed labeling is drafted and applied to test articles for hands-on evaluation by target stakeholders required to take specific action(s) demonstrating proper administration of the proposed product (drug, device or drug/device combination product).

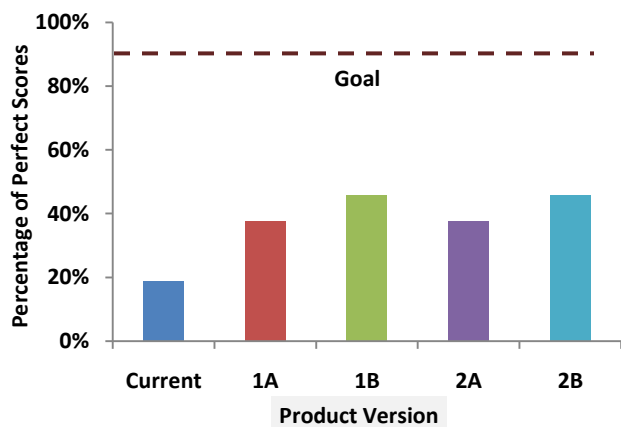
Ailment Panel Survey Research – Patients (or patient caregivers) who are potential users of the proposed drug, device or drug/device combination product are surveyed (online, paper-based MD office exit interviews, etc) regarding their interpretation of specific use instructions using both objective and subjective queries.

Patient Registries and Post-Market Surveillance Studies – Once the approved drug, device or drug/device combination product is commercialized, sponsors are frequently required to monitor compliance for a period of time (1 to 3 years is common) to generate patient experiential data. Depending on the risk level of a labeling compliance error, post-market surveillance studies can either be mandatory for all product dispensed (high risk for severe AE), or, in the case of a relatively low risk potential, the post-marketing surveillance can be self-reported by the patient or caregiver on a voluntary participation basis.

IV. Case Studies of Labeling Comprehension Trials

Studies of labeling comprehension, compliance and product usability have revealed surprisingly poor product safety and performance results by patients, caregivers, and pharmacists. Figure 1 below is an example of a caregiver study involving manipulations with a novel drug delivery device. One device represented the currently marketed product; the other four devices tested were replacement prototypes. The study revealed labeling as a major source of end user confusion.

Figure 1. A Study of Caregivers Ability Properly Perform a Drug-Device Delivery without Error (n=48)



Several case study examples follow which we have found indicative of user performance with initial labeling and new product designs. Each example involves a drug with novel delivery device for administration by a patient or caregiver.

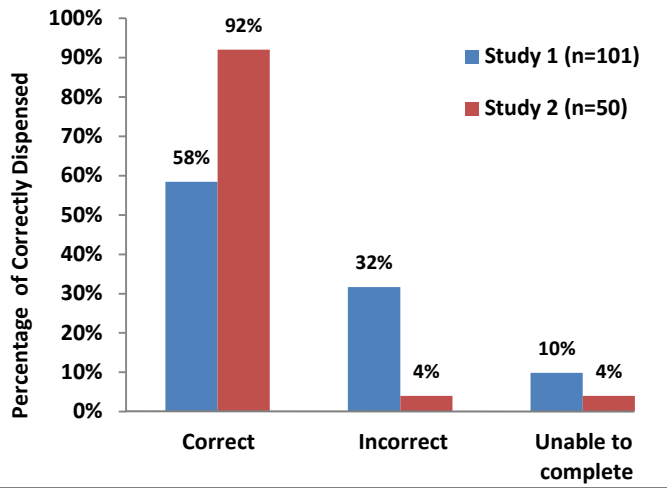
Case 1: Pharmacist Study of Dispensing Error with an Adjustable Drug Delivery Device

A pharmaceutical company had developed an adjustable dosage delivery device for an approved medication to treat an acute disorder. The adjustable device was developed to reduce the range of inventory SKUs while offering more available dosing increments. Prior to use, the device required pharmacy setting and locking of the patient specific dose. The device was made available as a pack of two set at an arbitrary default dosage; pharmacists were to set the device at each prescribed dose and lock it. Labeling consisted of an outer box label and insert providing a diagram accompanied by a step by step written procedure. The principle failure modes were identified as 1) failure to set the correct dose resulting in incorrect dosing and 2) failure to lock the device thereby disabling its use.

Two studies were conducted to simulate as close as possible real practice dynamics to evaluate the labeling effectiveness. In each study, a mock prescription order and final packaged product was handed to a pharmacist in their own setting and they were given a reasonable period of time to “fill the prescription”. The study monitor collected the filled prescription, scored the results as correct or incorrect, and took observations of pharmacist behavior while setting and locking the device. An initial study of one hundred and one retail pharmacists was performed to test labeling comprehension.

As shown in Figure 2, the initial study (Study 1) demonstrated a 42% rate of dispensing error, signaling a need for labeling revisions to the outer box and instructional labeling. Following label revisions and beta testing of the revised articles as part of the design control process, a second study (Study 2) was performed with fifty retail pharmacists to measure effect of the labeling changes with dispensing pharmacists. The comparative results for study 1 and 2 are shown in Figure 2. The error rate from study 1 to study 2 declined from 42% to 8% based on the effect of labeling changes.

Figure 2. Labeling Comprehension Study with Pharmacists: Results Before and After Label Revisions

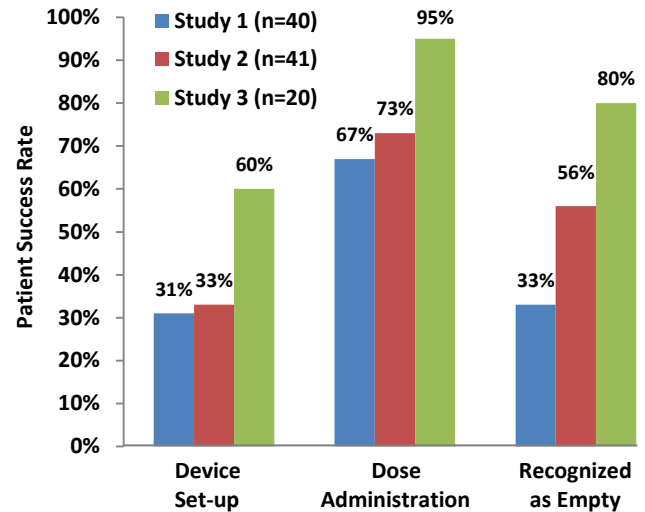


Case 2: Patient Self Administration with a Novel Drug Delivery Device

A pharmaceutical company had developed an adjustable dosage delivery device for an approved medication to treat a common disease. The device was developed to offer patients more convenience and portability of dose administration and potentially more accurate dosing. Prior to use, the device required priming and setting of the patient specific dose by the patient or caregiver. The device was initially set at an arbitrary default dosage.

Three product use trials were conducted with pre-registration materials. An initial study with forty patients was performed to test labeling comprehension and product usability with the target patient population. This study (blue bars in Figure 3) identified several issues with label comprehension with just 31% performing device setup correctly and only 67% correctly administering doses from the device. As a result, labeling revisions were made to the device and instructional insert, and a second study was conducted with forty-one patients to retest label comprehension and product usability. This study (red bars in Figure 3) demonstrated improvement, however the results remained unsatisfactory. More significant labeling and instructional insert changes were made by the pharma company, and a third study with 20 subjects was conducted to confirm the improved efficacy of the labeling revisions. The comparative results for studies 1, 2 and 3 are given in Figure 3. A dramatic improvement was observed from study 1 to study 3 with overall error reduced in half or more for each key measure, including a 95% success rate with dose administration in the last study.

Figure 3. Labeling Comprehension Study with Patients: Results Before and After Two Label Revisions



V. Discussion

BioTrak has conducted other studies similar to those reported here with initial study observational product use error rates typically in the in the range of 40-70% for respondents naive to a novel drug delivery device. Sponsors are often shocked at these findings which suggest far greater label comprehension issues than what can be estimated from calls and complaints to medical affairs departments. A well designed labeling comprehension study is not an expensive proposition, most study designs can evaluate labeling materials with 40-100 subjects before and 40-100 subjects after label revision. These studies demonstrate the benefit of conducting label comprehension studies as a means for improving product safety, efficacy, and usability.

VI. Conclusions

A well designed mock trial where product use is simulated has in our experience correlated well with actual field results. Such studies can provide a significant reduction in product use errors with the potential outcome of improved safety, efficacy, and competitiveness. Early testing of proposed labeling can identify problem areas in label comprehension that lead to a potential medication or administration error and/or frustration with product use. Such studies validate design control, quality of labeling and can facilitate the product registration process.

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