Reducing the Potential for Mistakes With Investigational Drugs
Matthew Grissinger, RPh, FASCP

Routine practices that are used to name, label, package, and store investigational drugs have raised serious concerns about patient safety.

**Problem:** A pharmacist notified the Institute for Safe Medication Practices (ISMP) of an example illustrating how the labeling of investigational drugs could result in errors. In a Bristol-Myers Squibb investigational study comparing apixaban (BMS-562247) and enoxaparin (Lovenox, Sanofi-Aventis), the packaging of the enoxaparin and placebo syringes is problematic. The labels on the plain-looking syringes include identification numbers but do not include lot numbers or expiration dates. The most prominent feature on the syringes is the company name. The syringes are provided in a labeled carton, but when they are removed from the box, the carton label, which contains important information, is lost.

Based on this scenario, we see how easy it would be for patients receiving the study drug or placebo to be given a medication from the wrong syringe when the products were sent to a patient-care unit (Figure 1). Similarly, apixaban tablets are provided in bulk supplies, not in unit-dose packages, adding to the potential for inaccurate doses.

According to a number of pharmacists who have contacted us at the ISMP, many other safety concerns exist with respect to investigational agents. Some of these problems are discussed next.

**Drug names.** Investigational drugs are usually identified by a number that is preceded by an abbreviation of the sponsoring company’s name, much like a vehicle’s license plate (e.g., BMS-562247, for an agent sponsored by Bristol-Myers Squibb). Many organizations that participate in trials of investigational drugs are involved in multiple studies sponsored by the same company; thus, the sponsor’s abbreviation preceding the identification number adds to the confusion resulting from numerous drugs with similar identification numbers and letters.

Some letter and number designations are as long as 25 characters, or they may be described with multiple words, forcing pharmacy computer systems to truncate the code name because of field size limitations. Because many blinded studies employ placebo drugs, the product number should be clearly visible and easily confirmed to ensure that the patient receives the correct medication and dose.

Identifying products is often a challenge because of the sponsor’s naming method. During the life of a study, a product with a license plate–type code name may be given a generic or common name. In many cases, the code name remains on the product label, but the research team often refers to the drug by its new generic name. It is even possible for the code name to change, particularly if the sponsor is part of a merger or if the company or product is sold.

**Drug labels.** The labels of many investigational drugs are printed in very small type, and a magnifying glass is usually needed to read the label. The same small font size is often used throughout the label, with little use of bold type, color, tall-man letters, or other styles to help differentiate products. Thus, drug packages look remarkably similar, which can lead to confirmation bias when products are selected from the shelf. The labels might not include the drug strength or concentration even if there are multiple drug strengths or concentrations in use.

If the drug is being tested in an international study, the directions are sometimes printed in two or more languages on the same label. Labels have also included ambiguous abbreviations or unclear dose designations, such as 5IU (which looks like 51 Units), or trailing zeros (such as 1.0 mg).

**Drug packaging.** Many oral investigational agents are not supplied in unit-dose packages. In addition, vial sizes of parenteral drugs are sometimes inappropriate for the dose being studied in a trial, so that dozens of vials might be required to prepare a single dose. This practice sensitizes practitioners to ex-

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**Figure 1** A and B. Scarce label information on syringes in the trays makes identification difficult.
pect to use many vials when they are preparing a dose of the medication. In such cases, it is more difficult to recognize a possible overdose during the preparation of an investigational agent than during the preparation of other drugs; in the latter situation, the use of dozens of vials for a single dose would clearly signal an error.

**Tablet markings.** Tablets available in multiple strengths often appear identical in color and size and have no markings to help differentiate the strengths. Although this practice might be essential for blinded studies (in which the strength is not known to the patient, the provider, or the research team at times), the same batches of look-alike tablets may be used for open-label studies as well (in which the tablet strength is known to all parties).

**Expiration dates.** Because “beyond use” dates of investigational drugs may be updated during a trial based on ongoing testing, some sponsors do not list an expiration date on the product package or even on a packing slip or receipt. Instead, the sponsors require participating organizations to call an interactive voice response system to check expiration dates—a time-consuming process. Lag time with the voice response system has led to cases in which expired drugs have not been replaced in time or have resulted in the need for direct intervention with the sponsor in order to avoid dispensing a drug that would reach its expiration date during outpatient use.

**Space limitations.** Separate, dedicated storage space is required for investigational drugs. However, as new protocols are added to a research organization’s products, the storage space allotted for these agents can quickly become exhausted. Also, pharmacy space is often used to store investigational drugs that are awaiting pickup and disposal by the sponsor. Some smaller facilities have stored these products in the office of a research pharmacist or nurse. Space limitations lead to crowded shelves and other unsafe storage conditions, increasing the risk of choosing the wrong look-alike medication.

**Reporting errors.** Similar to the reporting of an adverse reaction, when an error occurs with an investigational drug, the adverse event must be reported to the drug sponsor and the organization’s institutional review board (IRB). The error is also conveyed through an organization’s internal reporting system and is investigated in the same manner as other serious errors.

The principal investigator (from within the organization) and a study monitor (who is responsible for following the investigational drug protocol at multiple sites) usually determine whether the error should be classified as a deviation or a violation of the study’s protocol; the information is then reported to the sponsor. Patients who are affected by the error are often withdrawn from the study, and the site where the error occurred may also be excluded from the study. Yet the causes of these system-based errors, under the direct control of the sponsor (i.e., naming, labeling, or packaging of the drug), are rarely addressed or remedied. After an error has been reported to the drug’s sponsor, it is unclear whether the error was reported or must be reported to the FDA. Our sources suggest that adverse reactions, rather than actual errors, are more likely to be reported to the FDA.

**Risk of errors overlooked.** Although the many conditions leading to errors might be readily apparent to practicing health care professionals, scientists involved in new drug development, product manufacturing, and protocols for clinical trials are rarely well versed in basic medication safety principles. In many cases, they have little or no recent practical experience prescribing, dispensing, or administering medications. The sponsoring company’s attention tends to be on the safety profile of the drug and its clinical effects on patients; adherence to safe labeling and packaging practices is a low priority. This also seems to be the case when outside companies run clinical trials for the sponsors. Further, there appears to be little regulatory oversight governing the labeling, packaging, or nomenclature used to identify investigational drugs.

**SAFE PRACTICE RECOMMENDATIONS:**

The risks related to medication errors with investigational drugs are not easily remedied because many problems stem from the way in which the sponsor names, labels, and packages the agent. To that end, the ISMP held a summit in 2008 with industry leaders to explore problems and propose solutions. Following are some steps that organizations can take to reduce the risk of mishaps.

**Providing safe storage areas.** Adequate space should be allowed to stock investigational drugs away from other medications. Organizations that participate in many studies often have a separate pharmacy for these medications. In the pharmacy, these drugs are often placed in separate bins and labeled with their associated IRB number. Staff members should consider drug storage needs when they review new protocols submitted for IRB approval and should address any concerns before participating in the study. Sponsors should be notified that unneeded study medications and supplies will be discarded by a specific date if they are not picked up before then. If possible, unneeded supplies can be moved to a secure, locked space outside the pharmacy until retrieval.

**Highlighting label information.** An auxiliary label prepared by the pharmacy can be affixed to individual drugs or a bag that holds a supply of vials or containers of the same strength or concentration. These labels should supply information that is missing on the product label (e.g., the strength, concentration, or lot number) or information that is poorly visible on the label. A colored highlighter pen or a black Sharpie pen can be used to bring attention to key information on the label, to mark the identification code on top of each kit or bottle top, or to rewrite the strength in milligrams on an empty portion of the label. Auxiliary labels and highlighting should be applied before the drugs are added to stock or dispensed to patient-care areas.

In some cases, it might be appropriate to repack the drug in unit doses before dispensing the drug to patient-care areas unless the characteristics or stability of the drug make this impossible or unless the research protocol disallows it.

**Enhancing prescription labeling.** Sponsors do not usually allow investigational drugs to be transferred out of the original container. Thus, when dispensing an investigational drug to a patient, the pharmacy should provide a supplemental label that meets all standards for dispensing prescriptions that are applicable in the state. Flagging or folding the continued on page 138
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label might be necessary to avoid covering information on the original container.

Educating sponsors. A risk assessment of new investigational drugs should be performed, and any safety problems involving a medication error should be communicated to the sponsor during the study initiation meeting. Employees should realize that they might be providing information about the risk of medication errors to a sponsor’s representative who has never considered these issues. Although it is unlikely that immediate changes will be made based on safety concerns expressed by the staff, consistent feedback to sponsors about medication concerns may result in safer product naming, packaging, and labeling in future studies.

Assessing the potential for errors during the IRB review. Pharmacists should be included in an organization’s IRB membership. Before approval is granted, the IRB should assess protocols for investigational agents and should consider other matters relating to their safety (e.g., proper labeling). If data regarding drug labeling and packaging have not been provided with the protocol, this information should be requested from the sponsor to help facilitate the evaluation.

Reporting errors. Errors should continue to be reported to the IRB and the study sponsor. The ISMP also urges organizations to report errors concerning investigational drugs to the ISMP’s Medication Errors Reporting Program. These reports are then shared with the FDA. The reporter’s identity can be omitted if requested.

By learning more about these errors, patient safety advocates can work with sponsors in the pharmaceutical industry to spur necessary changes. Appropriate agencies within the National Institutes of Health, such as the National Cancer Institute, should also be notified of errors so that appropriate agencies can monitor clinical trials more effectively.

The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the ISMP Web site (www.ismp.org) or communicated directly to ISMP by calling 1-800-FAILSAFE or via e-mail at ismpinfo@ismp.org.