U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Geri Niebauer
Compliance Officer
Recalls and Compliance Division
Office of Compliance

Tel: (301) 504-0608 x1160
Fax: (301) 504-0359
Email: gniebauer@cpsc.gov

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Telecopy (310) 445-4269 / Electronic mail (daphne.allen@cancom.com)

Ms. Daphne Allen
Editor
Pharmaceutical & Medical Packaging News
Canon Communications LLC
11444 W. Olympic Blvd.
Los Angeles, CA 90064

Re: Drugs dispensed for household use in clinical trials

Dear Ms. Allen:

As you know, the U.S. Consumer Product Safety Commission (CPSC) administers the Poison Prevention Packaging Act (PPPA) and its regulations. Congress enacted this law in 1970 to address the rising numbers of deaths and serious injuries to young children from the handling or ingestion of hazardous household substances and drugs. In 1974, twenty five years ago, a child-resistant packaging regulation for certain prescription drugs went into effect. That regulation requires all prescription drugs for human use intended for oral administration to comply with the child resistant (CR) packaging requirements unless specifically exempted. 16 C.F.R. § 1700.14(a)(10). The regulation applies to drugs dispensed for household use, but does not cover those drugs dispensed for use in hospitals or similar institutions. Clinical trial drugs for human use in a dosage form intended for oral administration are subject to these requirements when they are dispensed on an out-patient basis for use in the household. Additionally, over-the-counter drugs used in clinical trials that are dispensed for out-patient use must comply with the CR packaging requirements if they are subject to one or more of the other regulations issued under the PPPA. [1]

Over the past few years, the practice of conducting clinical trials on an out-patient basis has increased. We recently became aware that child resistant packaging has not always been used for oral prescription drugs dispensed in clinical trials for household use. We have had several meetings with industry representatives to discuss this issue. We understand that their primary concern with complying with the CR requirements relates to clinical trials that require the use of unit dose packaging because of the complexity of the studies and the importance of the

[1] 16 C.F.R. 1700.14(a)(1) [aspirin], (3) [methyl salicylate], (4) [controlled drugs], (12) [iron], (16) [acetaminophen], (17) [diphenhydramine], (20) [ibuprofen], (21) [loperamide], (23) [lidocaine], (24) [dibucaine], (25) [naproxen], (26) [ketoprofen], (27) [fluoride], and (28) [minoxidil].

patient compliance aspects of the trials. The packaging for each of these trials is specially designed to meet the needs of the protocol and may not necessarily be used when the product is ultimately marketed. The industry representatives expressed concern that the development of a unit dose package for use in each clinical trial that is both child-resistant and effective in accomplishing the objectives of the protocol could be difficult. They also noted the varying amounts and types of drugs used during cross-over and titration studies could have significant effects on the costs of such packaging and the time necessary to acquire it. The industry requested that the Commission consider a two year phase-in period during which firms would develop and implement an immediate package for use with clinical trial drugs that is child-resistant.

The CPSC staff appreciates the need to ensure patient compliance during clinical trials. By the same token, however, we are concerned that allowing clinical trial drugs to enter households in packages that are not child-resistant could expose young children to serious injury if the children ingest those products. On May 23, 2000, we issued a statement that strikes a balance between these competing concerns. The statement, an exercise of our enforcement discretion, permits manufacturers of drugs dispensed for household use in clinical trials to use the following alternatives to strict compliance with the requirements of the Poison Prevention Packaging Act that the immediate package of such a drug meet the requirements for child-resistant packaging.

- Non-CR packaging may be used if the amount of drug that is dispensed into the household will not cause serious injury or illness to a young child. Firms packaging clinical trial drugs who wish to take advantage of this option must maintain data that demonstrate that that amount, if ingested, would not be expected to cause serious injury to children. This data must be made available to CPSC staff upon request.
- Clinical trial drugs with sufficient toxicity to cause serious injury or illness to a young child ("toxic") must be packaged with a child-resistant feature. This can be achieved in one of two ways. The units can be made with any of the features described in ASTM D-3475, provided that the packaging has at least one recognized child-resistant feature. To further clarify this option, its purpose is to alleviate the need to conduct tests on the packaging of each different drug that is to be used in clinical trials. Thus, we would generally expect manufacturers who avail themselves of the option to procure packaging from firms who can demonstrate that the package designs to be used with clinical trial drugs have been tested and meet the requirements for child-resistance. The clinical trial package itself, however, would not require testing.
- Alternatively, subject to the time limitations discussed below, non-CR unit dose packages can be placed in an outer container that meets the standards for child resistance (16 C.F.R. § 1700.15). This will allow firms to comply by using CR outer containers which protect children from accidentally ingesting toxic substances dispensed during clinical trials until the manufacturers are able to use CR unit packaging.

The options listed above may be used in Phase IV clinical trials only when it is not possible to use a commercially available child-resistant package or when the use of such a commercial package configuration would be detrimental to the study. If neither of the preceding conditions exists, commercially available CR packaging must be used during Phase IV trials.

Child-resistant outer packages are currently available, and can be used without the need to change the immediate package of a clinical trial drug. Accordingly, all drugs used in Phase II, III, or IV clinical trials initiated[2] after six (6) months from our May 23, 2000 statement must be packaged in accordance with the guidance above. Of course, we encourage all firms currently conducting clinical trials and firms who initiate clinical trials within six (6) months of the date of this letter to utilize CR packaging whenever it is available, technically feasible, practicable and appropriate for the clinical application.

Finally, the immediate packages of all toxic oral drugs intended for human use that are dispensed for household use in Phase II, III, or IV clinical trials initiated after twenty-four (24) months from our May 23, 2000 statement, must be child-resistant. This means that, after this date (May 23, 2002), firms conducting new clinical trials can no longer use a CR outer container to satisfy the CR requirements. Based on our familiarity with the packaging industry, we believe that this is a reasonable time frame. As stated previously, non-CR packaging may be used if the amount of drug that is dispensed into the household will not cause serious injury or illness to a young child. Firms packaging such clinical trial drugs must maintain data that demonstrate that that amount, if ingested, would not be expected to cause serious injury to children. This data must be made available to CPSC staff upon request.

In summary, the CPSC staff is exercising its enforcement discretion to permit manufacturers to use non-CR packaging for clinical trial drugs dispensed for household use which:

- are currently being used during clinical trial studies (Phase II, Phase III, or Phase IV), or
- will be used during clinical trial studies (Phase II, Phase III, or Phase IV) that are initiated before November 23, 2000 (six months from our May 23, 2000 statement).

The following examples should provide further clarification:

Example 1

If a Phase II trial is initiated in June 2000 (less than 6 months after May 23, 2000), the packages do not have to be CR, and no overpackage is required. If the Phase III trial of this study is initiated January 2001 (more than 6 months after May 23, 2000), then the drugs used in this phase must, at a minimum, be in a CR overpackage. If the Phase IV trial of this study is initiated June 2003 (after 2 years from May 23, 2000), these drugs must be dispensed in CR immediate packaging.

Example 2

If a Phase II trial is initiated in January 2001 (after 6 months from May 23, 2000), then the drugs in this phase must, at a minimum, be in a CR overpackage. If the Phase III trial of this study is initiated in March 2002 (after 6 months from May 23, 2000 but still before 2 years from May 23, 2000), then the drugs in this phase must, at a minimum, be in a CR overpackage.

[2] "Initiated" is defined as the date a firm submits its protocol to conduct a clinical trial to the U.S. Food and Drug Administration (FDA).

However, if the Phase III trial of this study were initiated June 2002 (after 2 years from May 23, 2000), these drugs must be dispensed in CR immediate packaging.

Example 3

If a Phase II trial is initiated after 2 years from May 23, 2000, then all drugs used in Phase II, III, and IV trials of this study must be dispensed in CR immediate packaging.

We note that these options are not normally available under the PPPA. However, because of the issues discussed above, we are exercising our enforcement discretion with regard to Phase II, Phase III, and Phase IV clinical trials as described above.

These determinations are based solely on the information currently available to the staff and the enforcement posture the CPSC currently has in effect. It could be changed if the facts change, and could be changed or superseded by the Commission.

Please contact me by email at gniebauer@cpsc.gov, by phone at 301-504-0608 x1160, or by fax at 301-504-0359, with any questions you have about this letter.

Sincerely,

Geri Niebauer