Inspections, Compliance, Enforcement, and Criminal Investigations

CPG Sec. 446.100 Regulatory Action Regarding Approved New Drug and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations (CPG 7132c.06)

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BACKGROUND:

FDA is issuing this policy guide to describe the circumstances in which the agency may initiate regulatory action regarding the marketing of approved new drugs and antibiotics that have been subjected to further processing or other manipulation, such as repacking, that is not covered by an approval under sections 505 or 507. (See U.S. v. Baxter Healthcare Corp., et al., CCH 38,166 Docket Nos. 89-2087/8 (7th Cir. May, 1990)).

Section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) requires FDA approval of any new drug prior to marketing. Under the terms of that section, approval must be based on, among other things, the processes, facilities and controls used in the manufacture of the product. This is because various aspects of the manufacturing process, such as sterilization, mixing, filling, and packaging, can have a significant effect on safety and efficacy of a drug product.

Under section 507 of the Act, FDA requires an approved application, similar to an NDA under section 505, for any antibiotic to be exempted from the statutory requirement of batch certification. Thus, the agency conducts the same review, including an inspection of the manufacturer's facility, for approval of an antibiotic under section 507 as for approval of a new drug under section 505.

Under these provisions, each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product. Pharmacists are not exempt from these statutory requirements; however, the agency regards mixing, packaging, and other manipulations of approved drug by licensed pharmacists, consistent with the approved labeling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients. Processing and repacking (including repackaging) of

approved drugs by pharmacists for resale to hospitals, other pharmacies, etc., are beyond the practice of pharmacy and are thus subject to the requirements of premarket approval.

The only repacking outside the practice of pharmacy that has been sanctioned in the absence of FDA approval is that of solid oral dosage forms of products already approved under section 505. See U.S. v. Kaybel, Inc., et al., 430 F.2d 1346 (3d Cir. 1970) (repacking of approved Enovid (estrogen) tablets from large bottles into small bottles allowed without an additional approval under section 505).

The repacking of approved new drugs and antibiotics by entities outside the terms of the respective approvals has become much more common due to the increased demand for varied product package sizes, including products for "unit-dose" dispensing by doctors, pharmacists, and institutions. Agency policy concerning unit-dose labeling for oral and liquid oral dosage forms is stated in CPG 7132b.10 (See Sec. 430.100). The expiration dating and stability requirements for unit-dose repacked drugs are covered in CPG 7132b.11 (See Sec. 480.200). Custom repackers have responded to this increased demand by performing manipulations that are well beyond the intended uses approved in the labeling for pharmacists and physicians. Such manipulations result in new products whose safety and effectiveness have not been established. During the drug approval process, specifications are set for active ingredients, identity and limits for degradation products, sterility assurance, and closure integrity. Repacking by a new manufacturer may result in an unanticipated interaction between the pharmaceutical entity and the new packaging, such as absorption and degradation, which may affect the quality and purity of the product.

STERILE DRUG PRODUCTS:

The FDA has an even greater concern about the manipulation of approved sterile drug products, especially when the sterile container is opened or otherwise entered to conduct manipulations such as dissolving, diluting or aliquoting, refilling, resterilizing, or repackaging in new containers. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard(s) are compromised and are no longer valid. These quality standards that include product stability and sterility must be restored.

Non-invasive manipulations may also raise questions of sterility, as when intact containers are repacked into a tray with other drugs, needles, gauze, etc., and the resulting package is sterilized and marketed as a unit for clinical use. Sterilization is an operation that must be documented and rigorously reviewed, and the FDA has consistently maintained that sterility is an absolute concept that must be ensured not only by sterility testing of the finished product, but also by validation of the sterilization process. Requirements for sterilization are covered in CPG 7132a.06 (See Sec. 410.100).

POLICY:

To protect the public health and to carry out its responsibility under sections 505 and 507, FDA will seek to ensure that all significant phases of the manufacture and processing of new drugs and antibiotics are approved. The agency may initiate regulatory action regarding the marketing of any new drug or antibiotic that has been subjected, for example, to any of the following manipulations, unless the manipulation is covered by an approval under sections 505 or 507: (1) mixing, (2) granulating, (3) milling, (4) molding, (5) lyophilizing, (6) tableting, (7) encapsulating, (8) coating, (9) sterilization, (10) repacking (including repackaging). The details of each manipulation, including the site(s) at which they will occur, must be the subject of an approved application or supplement filed pursuant to sections 505 or 507.
EXCEPTIONS:

Consistent with its enforcement policy subsequent to the Kaybel decision, the agency does not intend to initiate regulatory action with regard to the repacking of already-approved, solid oral dosage form drug products if (1) the repacking operation does not include any of the steps identified above, (2) the drug to be repacked is approved under sections 505 and 507, and (3) the labeling used for the repacked product is identical to that of the approved drug except for labeling changes necessary for compliance with section 502(b) of the Act.

In addition, the agency continues to regard manipulations that are performed within the practice of pharmacy, consistent with the approved labeling of the product, as approved uses of the product.

REGULATORY ACTION GUIDANCE:

Recommendation for regulatory action should be discussed with the Office of Compliance (HFD-310) prior to referral of the case.

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