

(3) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004.

(d) If the maximum level of aluminum is 25 µg/L or less, instead of stating the exact amount of aluminum as required in paragraph (c) of this section, the immediate container label may state: "Contains no more than 25 µg/L of aluminum." If the SVP or PBP is a lyophilized powder, the immediate container label may state: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L".

(e) The package insert for all LVP's, all SVP's, and PBP's used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

(f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under §314.60 or §314.96 of this chapter.

[65 FR 4110, Jan. 26, 2000, as amended at 67 FR 70691, Nov. 26, 2002; 68 FR 32981, June 3, 2003]

§ 201.325 Over-the-counter drugs for vaginal contraceptive and spermicide use containing nonoxynol 9 as the active ingredient; required warnings and labeling information.

(a) Studies indicate that use of vaginal contraceptive drug products containing nonoxynol 9 does not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against the transmission of other sexually transmitted diseases (STDs). Studies also indicate that use of vaginal contraceptive drug products containing nonoxynol 9 can increase vaginal irritation, such as the disruption of the vaginal epithelium, and also can cause epithelial disruption when used in the rectum. These effects may increase the risk of transmission of the AIDS virus (HIV) from an infected partner. Therefore, consumers should be warned that these products do not protect against the transmission of the AIDS virus (HIV) or other STDs, that use of these products can increase vaginal and rectal irritation, which may increase the risk of getting the AIDS virus (HIV) from an HIV infected partner, and that the products are not for rectal use. Consumers should also be warned that these products should not be used by persons who have HIV/AIDS or are at high risk for HIV/AIDS.

(b) The labeling of OTC vaginal contraceptive and spermicide drug products containing nonoxynol 9 as the active ingredient, whether subject to the ongoing OTC drug review or an approved drug application, must contain the following warnings under the heading "Warnings," in accordance with 21 CFR 201.66.

(1) "[bullet] For vaginal use only [bullet] Not for rectal (anal) use" [both warnings in bold type].

(2) "Sexually transmitted diseases (STDs) alert [in bold type]: This product does not [word "not" in bold type] protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner".

(3) "Do not use" [in bold type] if you or your sex partner has HIV/AIDS. If you do not know if you or your sex

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partner is infected, choose another form of birth control”.

(4) “When using this product [in bold type] [optional, bullet] you may get vaginal irritation (burning, itching, or a rash)”.

(5) “Stop use and ask a doctor if [in bold type] [optional, bullet] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis”.

(c) The labeling of this product states under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), “[bullet] when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS.

(d) The labeling of this product includes the following statements either on the outside container or wrapper of the retail package, under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert:

(1) “[bullet] studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase the risk of getting HIV/AIDS from an infected partner”.

(2) “[bullet] you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors”.

(3) “[bullet] use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors”.

(4) “[bullet] ask a health professional if you have questions about your best birth control and STD prevention methods”.

(e) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after June 19, 2008, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352), is a new drug under section 505 of the act (21

U.S.C. 355), and is subject to regulatory action.

[72 FR 71785, Dec. 19, 2007]

§ 201.326 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.

(a) *Labeling.* The labeling for all over-the-counter (OTC) drug products containing any internal analgesic/antipyretic active ingredients (including, but not limited to, acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate) alone or in combination must bear the following labeling in accordance with §§ 201.60, 201.61, and 201.66.

(1) *Acetaminophen*—(i) *Statement of identity.* The statement of identity appears in accord with §§ 201.61 and 299.4 of this chapter. The ingredient name “acetaminophen” must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(A) At least one-quarter as large as the size of the most prominent printed matter on the principal display panel (PDP), or

(B) At least as large as the size of the “Drug Facts” title, as required in § 201.66(d)(2). The presence of acetaminophen must appear as part of the established name of the drug, as defined in § 299.4 of this chapter. Combination products containing acetaminophen and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name “acetaminophen” and the name(s) of the other active ingredient(s) in the product on the PDP in accord with this paragraph. Only the name “acetaminophen” must appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(ii) *Active Ingredient and Purpose Headings.* The information required under § 201.66(c)(2) and (c)(3) of this chapter must be included under these headings. The information under these headings, but not the headings, may appear highlighted.