

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

DDM  
Display Date 10-23-08  
Publication Date 10-24-08  
Certifier N. Hawkins

[Docket No. FDA-2008-N-0549]

**Opportunity for Hearing on a Proposal to Withdraw Approval of Prescription Polyethylene Glycol 3350 Abbreviated New Drug Applications**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is proposing to withdraw approval of the following abbreviated new drug applications (ANDAs) for drug products containing polyethylene glycol 3350 (PEG 3350) labeled for prescription only use: ANDA 76-652 held by Schwarz Pharma, Inc.; ANDA 77-736 held by Kali Laboratories, Inc.; ANDA 77-706 held by Nexgen Pharma Inc. (formerly known as Anabolic Laboratories, Inc.); ANDA 77-893 held by Coastal Pharmaceuticals, Inc.; and ANDA 77-445 held by Teva Pharmaceutical Industries, Ltd. (collectively, the PEG 3350 ANDAs). The proposal is based on the switch of MiraLax from prescription only (“Rx only”) to over-the-counter (OTC) use. This switch was pursuant to the submission of a new drug application (NDA) for MiraLax (NDA 22-015), which was approved by the agency on October 6, 2006, establishing that PEG 3350 may be used safely and effectively without the supervision of a licensed healthcare professional. The Federal Food, Drug, and Cosmetic Act (the act) does not permit both Rx and OTC versions of the same drug product to be marketed at the same time. Under the act, a drug to which the prescription provisions of the act do not apply (i.e., an OTC drug) shall be deemed to be misbranded if at any time prior to

dispensing the label of the product bears the “Rx only” symbol. Because the PEG 3350 generic drug products are labeled as Rx only, they are misbranded and may not be legally marketed. Thus, FDA is proposing to withdraw their approval.

**DATES:** Submit written or electronic requests for a hearing by [*insert date 30 days after date of publication in the **Federal Register***]; submit data and information in support of the hearing request by [*insert date 60 days after date of publication in the **Federal Register***]. Submit written or electronic comments by [*insert date 60 days after date of publication in the **Federal Register***].

**ADDRESSES:** Submit written requests for a hearing, any data and information justifying a hearing, and any other comments identified with Docket No. FDA–2008–N–0549 to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic requests for a hearing, any data and information justifying a hearing, and any other comments identified with Docket No. FDA–2008–N–0549 to <http://www.regulations.gov>.

**FOR FURTHER INFORMATION CONTACT:** Elizabeth Sadove, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 10903 New Hampshire Ave., Bldg.51, rm. 6368, Silver Spring, MD 20993–0002, 301–796–3601.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

*A. Original Approval of MiraLax NDA and Subsequent ANDA Products*

MiraLax is an osmotic laxative containing the active ingredient polyethylene glycol 3350. MiraLax was approved as a prescription drug on February 18, 1999, under Braintree Laboratories, Inc. (Braintree), NDA 20–698,

for up to 14 days of use for the treatment of occasional constipation in adults. In patients with a history of constipation, MiraLax therapy increases the volume and frequency of bowel movements. The approved prescription dosing and administration regimen stated:

- “The usual dose is 17 grams (about 1 heaping tablespoon) of powder per day (or as directed by physician) in 8 ounces of water. Each bottle of MiraLax is supplied with a measuring cap marked to contain 17 grams of laxative powder when filled to the indicated line.
- Two to 4 days (48 to 96 hours) may be required to produce a bowel movement.”

Five ANDAs for PEG 3350 powder for oral solution, 17 gram (g)/single-dose were subsequently submitted and approved based on this reference-listed drug MiraLax Powder for Oral Solution for Rx only use. These ANDAs were approved under the requirements of section 505(j) of the act (21 U.S.C. 355(j)) and §§ 314.92 and 314.94 (21 CFR 314.92 and 314.94). The approved labeling of these PEG 3350 ANDA products is the same as that of the reference-listed drug, NDA 20–698.

#### *B. Switch of Innovator Product*

On October 6, 2006, FDA approved a new NDA for MiraLax (NDA 22–015) submitted by Braintree, switching its use from Rx only to OTC. By approving this NDA, FDA determined that PEG 3350 may be used safely and effectively OTC for the treatment of occasional constipation and that the Rx only limitation on PEG 3350 for occasional constipation was no longer necessary or appropriate. The sponsor was granted 3 years of exclusivity based on the studies necessary to establish that PEG 3350 would be safe and effective when used OTC for the treatment of occasional constipation. According to

FDA's Approved Drug Products With Therapeutic Equivalence Evaluations, NDA 22-015 is the subject of marketing exclusivity for the OTC use of MiraLax until October 6, 2009. Schering-Plough Corp. now holds NDA 22-015 and markets its PEG 3350 product for OTC use under the brand name MiraLax®.

### *C. The Durham-Humphrey Amendments*

The distinction between prescription and OTC drugs was codified by the Durham-Humphrey Amendments, which were enacted in order to address the marketplace confusion that arose from the simultaneous marketing of identical or nearly identical drugs on a prescription and OTC basis for identical or equivalent uses (Public Law 82-215, 65 Stat. 648 (1951). See, e.g., H.R. Rep. No. 82-700, at 5 (1951); see also 70 FR 52050 at 52051, September 1, 2005). Prescription drugs are defined as those which because of their toxicity or other potentiality for harmful effect, or the method of use, or the collateral measures necessary to their use, are not safe for use except under the supervision of a practitioner licensed to administer such drugs, or those drugs which are limited by an approved application under section 505 of the act to use under the professional supervision of a practitioner licensed to administer such drugs (see section 503(b)(1) of the act). A drug that does not meet this definition is an OTC drug.

The Durham-Humphrey Amendments prohibit marketing both Rx and OTC versions of the same drug product at the same time (21 U.S.C. 353(b)). Under section 503(b)(4)(B) of the act, a drug to which the prescription provisions of the act do not apply (i.e., an OTC drug) shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the "Rx only" symbol. Once FDA determines that the prescription provisions of the act in section 503(b)(1) (21 U.S.C. 353(b)(1)) do not apply a manufacturer

is expressly prohibited from labeling the drug product as prescription only for the OTC uses under section 503(b)(4)(B) of the act. Specifically, such labeling would cause the drug to be misbranded under section 503(b)(4)(B) of the act. Under section 301(a) of the act (21 U.S.C. 331(a)), it is a prohibited act to introduce a misbranded drug product into interstate commerce.

These provisions of the Durham-Humphrey Amendments apply to the PEG 3350 drug products. PEG 3350 was initially approved as a prescription product under the requirements of section 503(b)(1) in NDA 20–698 submitted by Braintree. The PEG 3350 ANDAs were approved based on reference to NDA 20–698 and FDA’s determination that the products covered by the ANDAs contained the same active ingredient; were in the same dosage form, strength, and route of administration; and had the same labeling as the Braintree product. In approving NDA 22–015, FDA determined that MiraLax is safe and effective for OTC use and that the prescription provisions of section 503(b)(1) of the act no longer apply. Thus, no manufacturer of a PEG 3350 product that is the same as the OTC drug product can market its product for Rx only use under section 503(b)(4)(B) of the act. The manufacturers of PEG 3350 products approved in ANDAs that referenced NDA 20–698 are prohibited by sections 301(a) and 503(b)(4)(B) of the act from labeling their PEG 3350 products as Rx only for marketing in interstate commerce.

#### *D. FDA’s Notice to the PEG 3350 ANDA Holders*

On April 20, 2007, FDA sent to the five sponsors of the approved PEG 3350 ANDAs letters that articulated the agency’s position regarding the legality of marketing of PEG 3350 for Rx use. FDA’s letters explained that section 503(b) of the act does not permit both Rx and OTC versions of the same drug product to be marketed at the same time. FDA’s letters informed the ANDA

holders that their Rx products, which bear the “Rx only” symbol, are misbranded and may not be legally marketed. FDA’s letters further explained that if an ANDA holder wished to continue marketing its product, the company must submit a new ANDA using the appropriate reference listed drug, NDA 22–015, and that such ANDA, among other things, must include the same OTC labeling as the reference listed drug.

The letters noted that the sponsors could not simply supplement their existing ANDAs because section 505(j)(2)(D)(i) of the act does not allow an applicant to amend or supplement an application by referring to a different listed drug.

#### *E. Grounds for Withdrawal Under the Standard of Section 505(e) of the Act*

##### 1. Statutory Authority

Section 505(e) of the act states that the Secretary of Health and Human Services (the Secretary) may, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application if the Secretary finds that “on the basis of new information \* \* \* the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of.” As stated previously, FDA sent letters on April 20, 2007, to the five sponsors of the approved PEG 3350 ANDAs informing them that their Rx products, which bear the “Rx only” symbol of the reference listed drug product in NDA 20–698, are misbranded under section 503(b)(4)(B) of the act and may not be legally marketed because the same PEG 3350 drug as the reference listed drug was approved as safe and effective for OTC use in NDA 22–015. Thus, in accordance with section 505(e) of the act, the ANDA holders have been given written notice that the

Rx only labeling for their drugs is false and misleading, because FDA has determined that the drug product may be used safely and effectively OTC. The sponsors have failed to submit new ANDAs using the appropriate reference listed drug, NDA 22–015, including, among other things, the same OTC labeling as the reference listed drug. In addition, the applicants have not voluntarily sought withdrawal of the approval of their respective ANDAs.

Therefore, FDA is proceeding with this notice of opportunity for a hearing on the agency’s proposal to withdraw approval of these ANDAs for the Rx only PEG 3350 products. As explained previously, FDA is basing this proposal to withdraw approval under section 505(e) of the act on the “false and misleading” labeling of the Rx only products, which are misbranded under section 503(b)(4)(B) of the act because they bear the “Rx only” symbol and the same PEG 3350 product was approved for OTC use.

## 2. The Rx and OTC Products Are the Same Drug Under Section 503(b) of the Act

In determining whether an Rx drug product and an OTC drug product are the same, FDA considers whether there are any meaningful differences between the OTC and Rx products that would justify the different marketing status of the products. When considering whether a drug switched from prescription to nonprescription status differs from the prescription drug in some meaningful way, the agency considers such factors as the indication, strength, route of administration, dosage form, or patient population (see 70 FR 52050 at 52051, September 1, 2005). If there are no meaningful differences between the Rx version of the drug and the OTC version of the drug that would support the continued marketing of the Rx version of the drug, the drug with the Rx labeling is misbranded under section 503(b)(4)(B) of the act.

The agency has determined that there is no meaningful difference between the Rx and OTC PEG 3350 drug products. There is no meaningful difference between the PEG 3350 prescription drug product that was approved under NDA 20–698 and the PEG 3350 switched to OTC status under NDA 22–015, nor is there a meaningful difference between the ANDAs referencing the PEG 3350 prescription drug product under NDA 20–698 and the OTC PEG 3350 product under NDA 22–015. There are no meaningful differences between the Rx and OTC products in any of the factors considered when evaluating meaningful differences, including the active ingredient, dosage form, strength, route of administration, indications, or patient population. The active ingredient in both drug products is polyethylene glycol 3350. Each is a powder for solution which is to be taken orally once daily by dissolving a 17-g dose in 4 to 8 ounces of liquid. Both drugs are indicated for use in patients with constipation. Finally, both drugs are for patients 17 years of age or older. Thus, these products are the same. The continued marketing of the same PEG 3350 drug product on both a prescription and nonprescription basis could result in the consumer confusion that Congress intended section 503(b)(4)(B) of the act to prevent.

### 3. Nonmeaningful Label Differences

As explained previously, NDA 20–068 and NDA 22–015 are the same drug for purposes of determining Rx/OTC status under section 503(b)(4)(B) of the act. There are, however, minor differences in the labeling between the Rx and OTC drugs that are based on the agency’s practice under the OTC drug monograph system of having consistent labeling for lawfully marketed OTC laxative drugs. These differences are not meaningful for purposes of

determining the appropriateness of continued Rx marketing under section 503(b)(4)(B) of the act.

Specifically, there are minor, nonmeaningful differences in duration of use and in the wording of the indication between the Rx and OTC products.<sup>1</sup> The labeling of NDA 20–068 states: “For the treatment of occasional constipation. This product should be used for 2 weeks or less as directed by a physician.” The NDA 22–015 (MiraLax OTC) label states: “Relieves occasional constipation (irregularity). Generally produces a bowel movement in 1–3 days.” Also, the MiraLax OTC label states: “Use no more than 7 days.”

These minor variations in labeling statements are not based on any differences in use necessitated by science or safety concerns, but rather are based on differences inherent in all OTC laxative drugs. The 7-day duration of use for OTC laxatives is derived from advice from the advisory panel convened over 3 decades ago, when they considered appropriate labeling for laxatives to be regulated under the OTC Monograph for Laxative Drug Products for OTC Human Use (40 FR 12902 at 12906, March 21, 1975). The panel noted a concern about the safety of labeling nonprescription laxatives for longer than 1 week, noting that a consistent message regarding duration of use of OTC laxatives (for a maximum of 7 days) helps to promote safety in case the

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<sup>1</sup> There have been numerous instances in which a drug has been switched from Rx to OTC status and there has been a change in its duration of use (e.g., ranitidine). In these cases, the drug remained prescription for one duration of use while becoming OTC for the other duration of use only when there was an additional and more fundamental difference between the products, such as a different indication, dose, duration of therapy, and/or target population. Often these drugs are initially approved as Rx and then subsequently switched to OTC for certain indications with corresponding different durations of use. The Rx version of the drug continues to be marketed with indications for which consumers cannot self-diagnose and treat the disease or condition, requiring physician supervision. The manner in which a particular drug is dosed or administered (e.g., dose titration, duration of use) may also require clinical judgment and physician supervision, and thus Rx status, while a corresponding OTC version of the drug can be available at a different dosing regimen or duration of use that does not require physician involvement. Therefore, for the Rx and OTC versions of other drugs (e.g., omeprazole, ibuprofen), there are meaningful differences that are distinguishable from the nonmeaningful differences between the Rx version (NDA 22–068) and the OTC version (NDA 22–015) of MiraLax.

consumer is constipated from a serious condition for which he or she should seek care from a physician. Also, the consistency of OTC laxative labeling for the maximum 7-day duration of use helps to avoid consumer confusion regarding how long to use different laxative products.

In addition, the Tentative Final Monograph for Laxative Drug Products for OTC Human Use (50 FR 2124, January 15, 1985) uses the phrase “For the relief of occasional constipation” in the labeled indication statement. Thus, FDA approved the OTC MiraLax drug with a similar indication statement (relieves occasional constipation) for consistency with other OTC marketed laxative products. As noted previously, the consistency of OTC laxative labeling helps to avoid any consumer confusion that might arise from differences in wording of the indication statement between OTC laxative products. The limited duration of use and use of the word “relieves” instead of “treatment” are factors inherent to all OTC laxative products and do not demonstrate a meaningful difference between a specific OTC drug and an Rx drug.

The Rx-to-OTC switch of MiraLax was a full switch of the same drug for the same indication. The differences in labeling for the duration of use and the words “relieves” and “treatment” exist because of the need for OTC labeling statements across OTC laxative products to be consistent. These minor changes to the MiraLax labeling for OTC use do not constitute a meaningful difference for purposes of section 503(b)(4)(B) of the act. If such differences in labeling were considered meaningful, no Rx and OTC laxative drug would be considered the same, and the prohibition of section 503(b)(4)(B) of the act would never apply to these products, and thus would be meaningless. Thus, there are no meaningful differences between the PEG 3350 Rx and OTC drugs or their indications.

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#### 4. Same Safety and Efficacy Profiles

Moreover, the data in the MiraLax OTC NDA did not demonstrate there is a difference between the safety and efficacy profiles of the Rx and OTC drugs. To support its original NDA 20–698 for the Rx marketing of MiraLax, the sponsor submitted study data that demonstrated that the drug was safe and effective for Rx use. In patients with a history of constipation, FDA determined that MiraLax therapy increases the volume and frequency of bowel movements. To support its NDA 22–015 for an Rx-to-OTC switch of the MiraLax drug, the sponsor submitted three studies evaluating the safety and efficacy of the drug in adults (including a subset of elderly subjects) for a period longer than the previously-approved period of up to 14 days of use. Although OTC MiraLax is indicated for a period of up to 1 week, the submitted long-term safety studies allowed for a better assessment of whether the drug would be safe in the OTC environment, where repeated purchase and use is likely. The primary endpoints for these three studies were all longer term assessments of safety and efficacy and not the day to first bowel movement.

The following summaries describe the studies that formed the basis for approval for NDA 20–698, MiraLax (PEG 3350).

- Study 851–3 was a single center, double-blind, triple-crossover, study which randomized 50 constipated patients to a first period (10 days) of either 17 or 34 g of PEG 3350 therapy. Subsequently, without a washout interval, subjects were randomized to second or third periods (also 10 days) of placebo or the alternate PEG 3350 dose. The primary endpoints of efficacy were stool frequency and stool weight. All 50 patients completed this trial. This study helped to define a dose-response for PEG 3350.

- Study 851–6 was a double-blind, parallel trial which enrolled 151 subjects who were randomized to placebo or PEG 3350 17 g. The treatment period lasted 14 days. The primary efficacy endpoint was bowel movement frequency with success defined as >3 bowel movements per 7-day period, and failure defined as <3 bowel movements per 7-day period, use of a laxative or enema or withdrawal from the study. One hundred thirty three subjects completed this study.

The studies submitted with NDA 22–015 to support the Rx to OTC switch are briefly described as follows:

- Study 851–CR1 was a randomized, double-blind, placebo-controlled, multicenter study of 304 subjects comparing 6 months of treatment with PEG 3350 17 g/day to daily treatment with a matched placebo.

- Study 851–CR3 was an open-label, long term, multicenter study of 311 subjects using PEG 3350 17 g/day for 12 months.

- Study 851–ZCC was an open-label, randomized, parallel arm, multicenter study of constipated adult patients randomized to treatment with either 17 g/day PEG 3350 or Zelnorm (tegaserod maleate) for 28 days.

Eligible subjects were constipated, but otherwise healthy, adults with no documented organic cause for constipation who met protocol-specified modified Rome Criteria for constipation. (Rome criteria are consensus criteria developed by the Rome Coordinating Committee (RCC) on various medical topics.) In study 851–CR3, all subjects were treated with MiraLax. In study 851–CR1, subjects who met study criteria were randomized 2:1 to PEG or placebo treatment. In study 851–ZCC, subjects were randomized 1:1 to PEG or Zelnorm. The primary endpoint(s) for these three studies were all longer

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term assessments of efficacy and safety and not the day to first bowel movement.

There was no suggestion in any of the reviews that the drug MiraLax would act any differently in the OTC consumer than in a patient who would have previously taken the drug by a physician's prescription. There was no data in the three studies submitted in the OTC switch application that showed a different efficacy or safety profile in the treated populations. The three studies provided evidence that MiraLax would be safe if repeatedly used over time in an OTC setting. When considering the data from study 851-ZCC in conjunction with other efficacy data, one could reasonably conclude that MiraLax, whether a prescription or OTC drug, is efficacious for the vast majority of users with constipation within 7 days and generally produces a bowel movement by day 3. This information enabled FDA to inform consumers about the expectation of benefit on the OTC label.

Based on its review of the study data for the Rx-to-OTC switch of MiraLax, FDA concluded that there was no indication that the MiraLax drug would act differently in the OTC consumer than in a patient who took the drug by a physician's prescription. In particular, there was no data in the three studies submitted in the OTC switch application that showed a different efficacy or safety profile between the populations taking the OTC drug and those taking an Rx drug. The three studies provided sufficient evidence that MiraLax would be safe if repeatedly used over time in an OTC setting. FDA concluded that OTC MiraLax is efficacious for the vast majority of users with constipation within 7 days and generally produces a bowel movement by day 3.

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## 5. NDA 20–698, NDA 22–015, and the PEG 3350 ANDAs Are the Same Drug

The fact that FDA approved the MiraLax OTC drug under a different NDA (22–015) than the MiraLax Rx NDA (20–698) does not demonstrate that there is a meaningful difference between the MiraLax Rx and OTC drugs. The data in the MiraLax OTC NDA did not demonstrate any differences between the safety and efficacy profiles of the Rx and OTC drugs. Whether the sponsor sought an Rx-to-OTC switch of the drug through a supplement to the original NDA, or by submission of a separate NDA, is a reflection of the sponsor's choice and administrative processes within the agency, and is irrelevant in determining whether the Rx and OTC products are the same for the purpose of section 503(b)(4)(B) of the act. The content of the applications to support such a switch would be the same, regardless of the form of the applications. All of the approved indications in NDA 20–698 were switched to OTC uses in 22–015.

As explained previously, there are no meaningful differences between the drug approved in NDA 20–698 and NDA 22–015. With the exception of slight differences in labeling necessitated by the OTC switch, they are the same drug for purposes of section 503(b) of the act. Under section 503(b)(4)(B), the innovator (Schering-Plough Corp.) cannot legally market the misbranded Rx drug product that had been approved in NDA 20–698. Therefore, the manufacturers of the PEG 3350 Rx drugs approved in ANDAs, which are the same as the reference listed Rx drug approved in NDA 20–698, are also prohibited from marketing their misbranded Rx drugs.

## **II. Notice of Opportunity for a Hearing**

The Director has evaluated the information discussed previously and, on the grounds stated, is proposing to withdraw approval of ANDA 76–652,

ANDA 77-736, ANDA 77-706, ANDA 77-893, ANDA 77-445 and all amendments and supplements thereto, on the ground that the drugs covered by the applications are misbranded and the labeling for such drugs is false and misleading.

In accordance with section 505 of the act and part 314 (21 CFR part 314), notice is given to the sponsors of the PEG 3350 ANDAs, and to all other interested persons, that FDA is hereby providing the applicants an opportunity to request a hearing to show why the applications listed should not be withdrawn.

Any applicant who decides to seek a hearing shall file: (1) On or before [*insert date 30 days after date of publication in the **Federal Register***], a written notice of appearance and request for a hearing and (2) on or before [*insert date 60 days after date of publication in the **Federal Register***], the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of material fact that requires a hearing to resolve, as specified in § 314.200.

Any other interested person may also submit comments on this notice on or before [*insert date 60 days after date of publication in the **Federal Register***]. The procedures and requirements governing this notice of opportunity for a hearing, notice of participation and request for a hearing, information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 and in 21 CFR part 12.

The failure of an applicant to file a timely written notice of participation and request for a hearing, as required by § 314.200, constitutes an election by that applicant not to avail itself of the opportunity to request a hearing concerning the action proposed and constitutes a waiver of any contentions

concerning the legal status of that applicant's drug products. In such instance FDA intends to withdraw approval of the applications and to take other appropriate action. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of material fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request that there is no genuine and substantial issue of material fact, or if a request for a hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a hearing must be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: 10/16/08

October 16, 2008.



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Jeffery Shuren  
Associate Commissioner for Policy and Planning.

[FR Doc. 08-????? Filed ??-??-08; 8:45 am]

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