TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR section	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
1210.15	2	1	2	.05 (3 minutes)	.10 (6 minutes)

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Upon review of the information collection, we have retained the currently approved estimated burden. The estimated number of respondents and hours per response are based on our experience with the import milk permit program and the average number of import milk permit holders over the past 3 years. Assuming two respondents will submit approximately 200 Form FDA 1996 reports annually for a total of 600 responses, and that each response requires 1.5 hours, we estimate the total burden is 600 hours.

The Secretary of Health and Human Services has the discretion to allow Form FDA 1815, a duly certified statement signed by an accredited official of a foreign government, to be submitted in lieu of Forms FDA 1994 and 1995. To date, Form FDA 1815 has been submitted in lieu of these forms. Because we have not received any Forms FDA 1994 or 1995 in the last 3 years, we assume no more than one will be submitted annually. We also assume each submission requires 0.5 hour for a total of 0.5 burden hour annually.

We estimate that two respondents will submit one Form FDA 1997 report annually, for a total of two responses. We estimate the reporting burden to be 2.0 hours per response, for a total burden of 4 hours. We estimate that two respondents will submit one Form FDA 1993 report annually, for a total of two responses. We estimate the reporting burden to be 0.5 hour per response, for a total burden of 1 hour. We estimate that two respondents will submit one Form FDA 1815 report annually, for a total of two responses. We estimate the reporting burden to be 0.5 hour per response, for a total burden of 1 hour.

With regard to records maintenance, we estimate that approximately two recordkeepers will spend 0.05 hour annually maintaining the additional pasteurization records required by § 1210.15, for a total of 0.10 hour annually.

No burden has been estimated for the tagging requirement in § 1210.22 because the information on the tag is either supplied by us (permit number) or is disclosed to third parties as a usual and customary part of the shipper's normal business activities (type of product, shipper's name and address). Under 5 CFR 1320.3(c)(2), the public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public is not subject to review by the Office of Management and Budget under the Paperwork Reduction Act. Under 5 CFR 1320.3(b)(2)), the time, effort, and financial resources necessary to comply with a collection of information are excluded from the burden estimate if the reporting, recordkeeping, or disclosure activities needed to comply are usual and customary because they would occur in the normal course of business activities.

Dated: March 27, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–06595 Filed 3–30–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0549]

Prescription Polyethylene Glycol 3350; Denial of a Hearing and Order Withdrawing Approval of Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs (the Commissioner) is denying requests for a hearing and issuing an order withdrawing approval of abbreviated new drug applications (ANDAs) for certain prescription laxatives with the active ingredient polyethylene glycol 3350 (PEG 3350), listed in this document, because the drug products are misbranded under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

DATES: This order is applicable May 2, 2018.

ADDRESSES: For access to the docket, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 between 9 a.m. and 4 p.m., Monday through Friday. Publicly available submissions may be seen in the docket.

FOR FURTHER INFORMATION CONTACT: Julie Finegan, Office of Scientific Integrity, Office of the Chief Scientist, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4218, Silver Spring, MD 20993–0002, 301–796–8618.

SUPPLEMENTARY INFORMATION:

I. Background

A. Procedural Background

On February 18, 1999, the U.S. Food and Drug Administration (FDA or the Agency) approved a new drug application (NDA) submitted by Braintree Laboratories, Inc., (Braintree) for prescription (or ''Rx'') PEG 3350 (MiraLAX) (NDA 20–698). Subsequently, FDA approved five ANDAs for prescription PEG 3350.[1] On October 6, 2006, FDA approved a new NDA (NDA 22–015) submitted by Braintree, removing their PEG 3350 laxative drug product from prescription dispensing requirements of section 503(b) of the FD&C Act (21 U.S.C. 353(b)).[2]

Section 503(b)(1) of the FD&C Act requires that a drug which: (1) Because

[1] The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (the Hatch-Waxman Amendments) created new section 505(j) of the FD&C Act, which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the drug product described in an ANDA has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the reference listed drug (section 505(j)(2)(A)(i)–(v) and (j)(4) of the FD&C Act). In addition, the ANDA applicant must submit evidence that its proposed drug product is bioequivalent to the reference listed drug (section 505(j)(2)(A)(iv) of the FD&C Act).

[2] On October 10, 2008, Braintree requested that FDA withdraw approval of the NDA for prescription MiraLAX (NDA 20–698) under 21 CFR 314.150(c) because it had stopped marketing the product. On February 11, 2009, FDA withdrew approval of the NDA for prescription MiraLAX in a **Federal Register** notice (effective March 13, 2009)(74 FR 6896 at 6899 (February 11, 2009)).

of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug or (2) is limited by an approved application under section 505 of the FD&C Act (21 U.S.C. 355) to use under the professional supervision of a practitioner licensed by law to administer such drug, be dispensed only upon prescription of a practitioner licensed to administer such drug. Under section 503(b)(4)(B) of the FD&C Act, a drug, to which the prescription dispensing provisions of section 503(b)(1) do not apply, shall be deemed to be misbranded if at any time prior to dispensing, the label of the drug bears the ''Rx only'' symbol.

Likewise, at section 503(b)(4)(A), drugs that are subject to the prescription dispensing provisions of section 503(b)(1) must bear the ''Rx only'' symbol; if not, they would be misbranded. These provisions mean that nonprescription (over-the-counter (OTC)) drugs must not bear the ''Rx only'' symbol and prescription drugs must bear the ''Rx only'' symbol; otherwise, they each would be misbranded. FDA has long interpreted these provisions to mean that section 503(b) of the FD&C Act does not permit the same active ingredient to be simultaneously marketed in both a prescription drug product and a nonprescription drug product, unless a meaningful difference exists between the two that makes the prescription product safe only under the supervision of a licensed practitioner.[3]

FDA's regulation at § 310.200 (21 CFR 310.200) sets forth the procedure for exempting a drug approved for prescription use from the prescription dispensing requirements of section 503(b)(1)(B) of the FD&C Act. A drug limited to prescription use under section 503(b)(1)(B) shall be exempt from the prescription dispensing requirements if FDA determines that the prescription dispensing requirements are ''not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and [FDA] finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.'' (See § 310.200(b).) In this instance, based on studies submitted by the sponsor, FDA determined that the original prescription MiraLAX product no longer met the criteria in section 503(b)(1) of the FD&C Act for prescription use. Therefore, FDA changed MiraLAX's status from prescription to nonprescription (commonly referred to as an ''Rx to OTC switch''). When FDA concludes, as it did with MiraLAX, that no prescription indications remain, FDA describes the Rx to OTC switch as a ''full'' or ''complete'' switch. The Braintree product continued to use the trade name MiraLAX when it switched from prescription to nonprescription.

Due to this change in MiraLAX's status from prescription to nonprescription, in an April 20, 2007, letter to the ANDA holders, FDA noted that the approved ANDAs were based on a reference listed drug (RLD) with labeling for prescription only use (NDA 20–698) and that MiraLAX had recently switched from ''Rx-only'' to OTC marketing. FDA explained that the FD&C Act does not permit both prescription and nonprescription versions of the same drug product to be marketed at the same time. The Agency notified the PEG 3350 ANDA holders that their prescription products, which bear the ''Rx only'' symbol, are misbranded and may not be lawfully marketed. FDA explained that if the ANDA holders wished to continue marketing PEG 3350, they may not do so pursuant to the ANDAs referencing prescription MiraLAX. FDA informed the ANDA holders that they must file new ANDAs referencing NDA 22–015 and the new ANDAs must include the same OTC labeling as the RLD. FDA also explained that under section 505(j)(2)(D)(i) of the FD&C Act, the ANDA holders were not permitted to supplement their ANDAs to reference NDA 22–015, which was not the RLD identified in their ANDAs. The ANDA holders did not seek voluntary withdrawal of their applications.

In the **Federal Register** of October 24, 2008 (73 FR 63491), the Center for Drug Evaluation and Research (CDER) published a notice of opportunity for a hearing (NOOH) proposing to withdraw approval of the ANDAs for drug products containing the active ingredient, PEG 3350, approved for prescription use. Schwarz Pharma Inc. (Schwarz), ANDA 76–652; Paddock Laboratories, Inc. (Paddock), ANDA 77–893; Gavis Pharmaceuticals, LLC (Gavis), ANDA 77–736; and Nexgen Pharma Inc. (Nexgen), ANDA 77–706 (collectively, the ''ANDA holders''), each submitted timely requests for a hearing and each submitted evidence in support of their requests. Teva Pharmaceutical Industries, Ltd., now Teva Pharmaceuticals USA, (Teva), ANDA 77–445, did not submit a request for a hearing. Teva's Rx PEG 3350 product has been discontinued. On May 22, 2014, consistent with § 314.200(g)(3) (21 CFR 314.200(g)(3)), CDER served upon the ANDA holders a proposed order denying their requests for hearing and withdrawing approvals of their ANDAs and providing the ANDA holders 60 days to respond with sufficient data, information, and analysis to demonstrate that there is a genuine and substantial issue of fact that justifies a hearing. CDER subsequently extended this 60-day deadline. Breckenridge Pharmaceutical Inc. (Breckenridge) (ANDA 77–736); Kremer's Urban Pharmaceuticals, Inc. (Kremer's) (ANDA 76–652); Nexgen; and Paddock submitted objections to the proposed order. The Commissioner has reviewed the ANDA holders' objections and is denying their requests for hearing and withdrawing approval of their ANDAs.

B. The October 24, 2008, NOOH

The NOOH proposed the withdrawal of the PEG 3350 ANDAs on the basis of the switch of MiraLAX from Rx to OTC. The NOOH noted that the FD&C Act does not permit both Rx and OTC versions of the same drug product to be marketed at the same time. Under the FD&C Act, a drug to which the prescription dispensing requirements do not apply (*i.e.,* an OTC drug) shall be deemed misbranded if at any time prior to its dispensing, the label of the product bears the ''Rx only'' symbol. The NOOH explained that the ANDA products' labels, which bear the ''Rx only'' symbol, are false or misleading because the same PEG 3350 product was approved for OTC use. The NOOH proposed the withdrawal of the ANDAs under section 505(e) of the FD&C Act.

The Background section of the NOOH described the original approval of prescription MiraLAX and the subsequent approval of the OTC product. The NOOH summarized the two studies that formed the basis for approval of NDA 20–698, the prescription MiraLAX product for the treatment of occasional constipation, as follows:

- Study 851–6 was a double-blind, parallel trial that enrolled 151 subjects who were randomized to placebo or MiraLAX 17 grams (g). The treatment lasted 14 days. The primary efficacy endpoint was bowel movement frequency with success defined as more

[3] In an advanced notice of proposed rulemaking (ANPRM), FDA previously solicited public comment on the factors that it generally would consider in determining whether there is a meaningful difference between prescription and OTC drug products. See ''Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-the-Counter Product'' (70 FR 52050, September 1, 2005).

than 3 bowel movements per 7-day period, and failure defined as fewer than 3 bowel movements per 7-day period, use of a laxative or enema, or withdrawal from the trial. A total of 133 subjects completed this study.

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

TABLE 1—DAYS TO FIRST BOWEL MOVEMENT MIRALAX RX PIVOTAL STUDIES

Study	Measure	Day 1	Day 2	Day 3	Day 4
851–3	Pt w/BM*	23	35	42	45
(n=48)	%	47.9	72.9	87.5	93.8
851–6	Pt w/BM	28	48	59	63
(n=76)	%	36.8	63.2	78.9	84.2

*Pt w/BM = The cumulative number of patients who had at least one bowel movement up to the fourth day of therapy with 17 g MiraLAX daily. For both studies, the majority of patients (72.9% and 63.2%, respectively) had at least one bowel movement by the second day of therapy.

Table 1 illustrates that in both studies submitted to support the prescription MiraLAX NDA at least one-third of subjects taking 17 g of MiraLAX had a bowel movement by Day 1 and at least three-fourths had a bowel movement by Day 3. Based on the results of these studies, a length of treatment of 2 weeks or less was recommended.

To support approval of the nonprescription application for MiraLAX for occasional constipation, Braintree submitted three studies (described in bullets below) evaluating safety and efficacy 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 nonprescription MiraLAX is indicated for a period of up to 1 week, the submitted long-term studies supported a determination that the product would be safe for use in the OTC setting, where repeated purchase and use may be likely. Subjects who participated in these long-term studies were constipated, but otherwise healthy, adults with no documented organic cause for constipation who met protocol-specified modified Rome Criteria [4] for constipation. The primary endpoint(s) for these three studies were all longer term assessments of safety and effectiveness, not the number of days to first bowel movement.

• 851–CR1: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study of 304 subjects comparing 6 months of treatment with MiraLAX 17 g per day to daily treatment with a matched placebo. Of the patients enrolled in this study 75 (25 percent) were 65 years of age or older. This was an efficacy study in which efficacy was measured by outcomes of more than 3 satisfactory stools per week and the occurrence of one or fewer of the following symptoms: Straining in more than 25 percent of defecations; lumpy or hard stools in more than 25 percent of defecations; or sensation of incomplete evacuation in more than 25 percent of defecations. More than 80 percent of patients in this study experienced a bowel movement within 1 to 3 days of starting therapy.

• 851–ZCC: An open-label, randomized, parallel-arm, multicenter study of constipated adult patients randomized to treatment with either 17 g per day MiraLAX or Zelnorm (tegaserod maleate, indicated for the short-term treatment of women with irritable bowel syndrome whose primary bowel symptom is constipation) for 28 days. This study excluded elderly and male patients because of Zelnorm labeling restrictions. This study demonstrated that MiraLAX is more effective than Zelnorm at treating constipation over a 4-week period. Overall, patients who were having fewer than three bowel movements per week began having approximately one bowel movement per day by weeks 1 and 2.

• 851–CR3: An open-label, extended use, multicenter, single-treatment study of 311 subjects using MiraLAX 17 g per day for 12 months. Of the patients enrolled in this study 117 (38 percent) were 65 years of age or older. This was a 1-year safety study of MiraLAX use, and no placebo arm was included. Patients treated with MiraLAX for up to 12 months achieved similar benefits to those previously reported in shorter studies. According to the self-assessment measure used, 80 to 88 percent of patients (and 84 to 94 percent of elderly patients) rated themselves successfully treated during the course of the study.

According to CDER, after reviewing the results of these studies, FDA determined that the three studies provided evidence that nonprescription MiraLAX could be used by consumers effectively in the OTC setting, concluding 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, and would also be safe if repeatedly used over time. FDA determined that the criteria in section 503(b)(1) of the FD&C Act were no longer met and that the criteria for switching prescription MiraLAX to nonprescription status under § 310.200 were met. Thus, the Agency approved MiraLAX as a nonprescription product for occasional constipation.

As CDER stated in the NOOH, for the prescription and nonprescription versions of PEG 3350 to be lawfully marketed simultaneously, there must be some meaningful difference between the two products (*e.g.,* indication, strength, route of administration, dosage form, patient population) that makes the prescription product safe only under the supervision of a practitioner licensed by law. The NOOH then described the evidence CDER considered in determining that there is no meaningful difference between the prescription and nonprescription versions of the PEG 3350 laxative products.

CDER explained that it determined that there is no meaningful difference between the prescription PEG 3350 ANDA holders' laxative products and the nonprescription MiraLAX product based upon an evaluation of the active ingredient, dosage form, strength, route of administration, indications, and patient population for both versions. As stated in the NOOH, CDER found that

[4] The Rome Criteria is a system developed to classify the functional gastrointestinal disorders (disorders of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormality), based on clinical symptoms. Some examples of these types of disorders include irritable bowel syndrome, functional dyspepsia, functional constipation, and functional heartburn. See *https://therome foundation.org/.*

the nonprescription and prescription PEG 3350 products are the same. They have: (1) The same active ingredient, PEG 3350; (2) the same dosage form, a powder for solution; (3) the same strength, a 17g dose in 4 to 8 ounces of liquid; (4) the same route of administration, oral; (5) the same indication, *i.e.* for patients with occasional constipation; and (6) the same patient population, patients that are 17 years of age or older. With regard to any differences in the labeling between the prescription and nonprescription products, CDER concluded that any differences are non-meaningful and are based upon the Agency's practice under the OTC drug monograph system of having consistent labeling for OTC laxative groups. For example, CDER found that the differences in duration of use between the prescription and nonprescription products were not meaningful and were related only to advice from the OTC laxative monograph panel that labeling for a 7-day duration of use helps to promote safety in case the consumer is constipated from a serious condition for which he or she should seek care from a physician. The NOOH noted that the OTC MiraLAX labeling included the phrase ''relieves occasional constipation'' for consistency with other OTC products and to avoid consumer confusion that may result from differences in the indication statement among OTC laxative products. A comparison of the two products' labels is set forth in table 2.

TABLE 2—COMPARISON OF THE PRESCRIPTION AND NONPRESCRIPTION LABELS

	Prescription MiraLAX/PEG 3350	Nonprescription MiraLAX
Indication	For the treatment of occasional constipation	Relieves occasional constipation (irregularity).
Strength	17g	17g.
Route of Administration	For oral administration after dissolution in water. The cap on each bottle is marked with a measuring line and may be used to measure a single MiraLAX dose of 17 g (about one heaping tablespoon).	The bottle top is a measuring cap marked to contain 17g of powder when filled to the indicated line. Stir and dissolve in any 4 to 8 ounces of beverage (cold, hot, or room temperature) then drink.
Dosage Form	Powdered form	Powdered form.
Duration of Use	This product should be used for 2 weeks or less or as directed by a physician.	Use no more than 7 days. Ask a doctor if you need to use a laxative for longer than 1 week.
Effectiveness	Treatment for 2 to 4 days may be required to produce a bowel movement.	Generally produces a bowel movement in 1 to 3 days.
Population	Adults	For adults and children 17 years of age and over.

CDER concluded that, where there is no meaningful difference between nonprescription MiraLAX and the prescription PEG 3350 products, the continued marketing of the same PEG 3350 product could result in the consumer confusion that Congress intended to prevent through section 503(b)(4)(B) of the FD&C Act. CDER reasoned that the display of the Rx-only symbol on the ANDA holders' PEG 3350 products rendered the labeling of those products false or misleading where the same PEG 3350 product was approved for OTC use. Accordingly, CDER concluded that the labeling of the prescription PEG 3350 products is false and misleading, and the products are thus misbranded under section 502 of the FD&C Act (21 U.S.C. 352) because they continue to bear the ''Rx only'' symbol.[5] CDER thus proposed withdrawal of the ANDAs pursuant to section 505(e) of the FD&C Act. Under section 505(e), FDA may, after due notice and an opportunity for a hearing, withdraw the approval of an application submitted under section 505(j) of the FD&C Act if the Secretary finds that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, 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.

The NOOH informed the PEG 3350 ANDA holders that if they requested a hearing they would have to present data and information showing that there is a genuine and substantial issue of fact requiring a hearing. The NOOH also stated that if it conclusively appeared from the face of the data, information, and factual analyses submitted in support of a hearing request that there was no genuine and substantial issue of fact precluding the withdrawal of the PEG 3350 ANDAs, or if the requests for a hearing were not made in the required format or with the required analyses, the Commissioner would enter summary judgment against the holders of the PEG 3350 ANDAs, making findings and conclusions, and denying a hearing (73 FR 63491).

II. Statutory and Regulatory Framework Regarding 21 CFR Part 12 Hearings

The specific criteria considered when determining whether a hearing is justified are set out in § 12.24(b) (21 CFR 12.24(b)). Under that regulation, a hearing will be granted if the material submitted by the requester shows, among other things, the following: (1) There is a genuine and substantial factual issue for resolution at a hearing; a hearing will not be granted on issues of policy or law; (2) the factual issue can be resolved by available and specifically identified reliable evidence; a hearing will not be granted on the basis of mere allegations or denials or general descriptions of positions and contentions; (3) the data and information submitted, if established at a hearing, would be adequate to justify resolution of the factual issue in the way sought by the requestor; a hearing will be denied if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate; (4) resolution of the factual issue in the way sought by the person is adequate to justify the action requested; a hearing will not be granted on factual issues that are not determinative with respect to the action requested (*e.g.,* if the Commissioner concludes that the action would be the same even if the factual issue were resolved in the way sought); (5) the action requested is not inconsistent with any provision in the FD&C Act or any FDA regulation; and (6) the requirements in other applicable regulations, *e.g.,* 21 CFR 10.20, 12.21, 12.22, and 314.200, and in the notice issuing the final regulation or the NOOH are met.

[5] See section 502(a) of the FD&C Act (deeming a drug to be misbranded if its labeling is false or misleading in any particular); see also section 503(b)(4) and § 310.200(d).

A party seeking a hearing is required to meet a ''threshold burden of tendering evidence suggesting the need for a hearing.'' (*Costle* v. *Pacific Legal Found.,* 445 U.S. 198, 214 (1980), *reh'g denied*, 446 U.S. 947 (1980) (citing *Weinberger* v. *Hynson, Westcott & Dunning, Inc., 412* U.S. 609, 620–21 (1973).) A party's argument that a hearing is necessary to ''sharpen the issues'' or to ''fully develop the facts'' does not meet this test. (*Georgia Pacific Corp.* v. *U.S. EPA,* 671 F.2d 1235, 1241 (9th Cir. 1982)). If a hearing request fails to identify any factual evidence that would be the subject of a hearing, FDA will not provide one (*Hynson,* 412 U.S. at 620). FDA may deny a hearing and enter an order withdrawing approval of an application when it appears from the request for hearing that there is no genuine and substantial issue of fact. (See § 314.200(g); *Hynson,* 412 U.S. at 620; *John D. Copanos & Sons, Inc. and Kanasco, Ltd.* v. *FDA,* 854 F.2d 510, 522 (D.C. Cir. 1988).)

A hearing request must not only contain evidence, but that evidence should raise a material issue of fact concerning which a meaningful hearing might be held (*Pineapple Growers Ass'n* v. *FDA,* 673 F.2d 1083, 1085–86 (9th Cir. 1982).) When the issues raised in the objection are, even if true, insufficient to alter the decision, the Agency need not grant a hearing. (See *Dyestuffs & Chemicals, Inc.* v. *Flemming,* 271 F.2d 281, 286 (8th Cir. 1959), cert. denied, 362 U.S. 911 (1960).) A hearing need not be held to resolve questions of law. (See *Citizens for Allegan County, Inc.* v. *FPC,* 414 F.2d 1125, 1128 (D.C. Cir. 1969); *Sun Oil Co.* v. *FPC,* 256 F.2d 233, 240 (5th Cir. 1958), cert. denied, 358 U.S. 872 (1958).) Mere allegations or conclusory statements are not sufficient to justify a hearing (§ 12.24(b)(2); 39 FR 9750 at 9755, March 13, 1974). In determining whether a hearing is justified, FDA will analyze the data and information underlying a conclusion by the person requesting a hearing that a hearing is necessary (39 FR 9750 at 9755; see also *Evers* v. *General Motors Corp.,* 770 F.2d 984, 986 (11th Cir. 1985) (It is settled that ''a party may not avoid summary judgment solely on the basis of an expert's opinion that fails to provide specific facts from the record to support its conclusory allegations.''); accord *United States* v. *Various Slot Machines On Guam,* 658 F.2d 697, 700 (9th Cir. 1981) (''in the context of a motion for summary judgment, an expert must back up his opinion with specific facts''); *Merit Motors, Inc.* v. *Chrysler Corp.,* 569 F.2d 666, 673 (D.C. Cir. 1977)).

In summary, a hearing request must present sufficient credible evidence to raise a genuine and substantial issue of fact and the evidence presented by the requestor, if established at a hearing, must be adequate to resolve the issue as requested and to justify the action requested.

III. Analysis

The Commissioner has reviewed the evidence submitted by the holders of the PEG 3350 ANDAs and finds that they have not raised a genuine and substantial issue of fact requiring a hearing under §§ 12.24(b) and 314.200(g), that the legal objections offered are without merit and cannot justify a hearing, and that summary judgment should be granted against them. The Commissioner also orders that, under section 505(e) of the FD&C Act, approval of the PEG 3350 ANDAs, including all related amendments and supplements, are hereby withdrawn, effective May 2, 2018.

The reasons for the Commissioner's decision are described more fully below.

A. Hearing Request

As noted, each of the PEG 3350 ANDA holders, except Teva, requested a hearing and submitted evidence, including information and factual analyses, as to why FDA should grant a hearing regarding their requests. As § 12.24(b) makes clear, FDA requires ''specifically identified reliable evidence'' to grant a hearing. FDA will not grant a hearing based solely upon ''mere allegations or denials or general descriptions of positions and contentions.'' Furthermore, courts have held that ''general and unsupported statements . . . of experts . . . [that] fail to address the specific problems identified by the FDA . . . do not create a genuine issue of fact.'' (*Copanos*, 854 F.2d at 526.) Similarly, the Supreme Court noted that it was appropriate to withdraw a drug from the market if the only evidence presented in opposition to its withdrawal is ''clinical impressions of practicing physicians,'' as that does not constitute the type of evidence upon which FDA bases its regulatory decisions. (*Hynson,* 412 U.S. at 630.)

None of the PEG 3350 ANDA holders submitted data or other information in support of their requests for a hearing that presents a genuine and substantial issue of fact that would be determinative with respect to whether there is some meaningful difference between the prescription and nonprescription products approved by FDA that makes the prescription product safe only under the supervision of a licensed practitioner. Instead, they made numerous assertions and included anecdotal evidence in the form of declarations from practicing physicians, published medical literature, and trade publications on issues that are not material to this proceeding. Much of the information submitted by the PEG 3350 ANDA holders overlapped, and some ANDA holders chose to reference other submissions. Nexgen submitted five declarations from practicing physicians, one news release, and one document outlining objections to the medical review of NDA 22–015 (nonprescription MiraLAX). Nexgen also submitted a bibliography of journal articles cited by its medical experts in their declarations. Paddock submitted a wide variety of documents, including labeling for different products, published medical literature, letters sent to the company by FDA, a copy of the NOOH, a copy of the tentative final monograph (TFM) for OTC laxatives, and various web publications on constipation and its comorbidities. Paddock also referenced a number of online resources in its footnotes and cross-referenced three of the declarations submitted by Nexgen—those of Thomas Quincy Garvey III, M.D., Paul Erick Hyman, M.D., and Irvin Wechsler, B.Sc Pharm. Schwarz did not submit any original evidence, but rather chose to incorporate all of Nexgen's arguments and evidence by reference. Gavis submitted no evidence in support of its assertions.

The ANDA holders object to the proposed order's treatment of their evidentiary submissions. They maintain that the proposed order misapplied the summary judgment standard and misinterpreted FDA regulations and precedent relevant to summary judgment. Nexgen and Breckenridge submitted a joint objection to the proposed order in which they maintain that FDA cannot impose summary judgment where it has not issued a regulation setting forth the standard on which summary judgment will be based (Nexgen/Breckenridge Joint Objection (hereafter Nexgen Objection) at 13–17). Nexgen and Paddock contend that summary judgment is inappropriate where the term meaningful difference has not been defined and the determination of meaningful difference is inherently factual (Paddock Comments at 19; Nexgen Objection at 21–22). Nexgen complains that FDA applied the concept of material fact so narrowly that no issue is likely to satisfy those criteria (Nexgen Objection at 19). Kremers maintains that the proposed order's application of the summary judgment standard violates due process

because it holds that FDA will not allow its scientific judgment to be challenged in an administrative hearing (Kremers Objection at 13–14). Likewise, Paddock complains that the proposed order impermissibly assessed the persuasiveness of the evidence, which is more appropriately done at a hearing (Paddock Objection at 11–12, 15–17). The ANDA holders argue that FDA erred in rejecting the expert affidavits because language in the preamble to part 12 (21 CFR part 12) suggests that expert disagreement is sufficient to create a factual dispute for which a hearing is needed (Kremer's Objection at 8–10). They contend that the expert affidavits contain facts and analysis that, if proven at a hearing, demonstrate meaningful differences between Rx and OTC PEG 3350 products. They maintain that basing the hearing denial on the lack of clinical data was improper in this particular proceeding, where the efficacy of PEG 3350 is not at issue (Nexgen Objection at 18–19; Kremers Objection at 8–9; Paddock at 13–14).

The Commissioner has reviewed the evidence presented and finds that it either fails to address the specific problems identified by FDA and/or that it does not constitute specifically identified reliable evidence. In the ANPRM and the NOOH, FDA stated that in determining whether the same active ingredient can be simultaneously marketed in prescription and OTC products, FDA would consider whether there is a meaningful difference between two drug products, such as active ingredient, dosage form, strength, route of administration, indications, or patient population that makes the prescription product safe only under the supervision of a licensed practitioner. Much of the evidence submitted by the ANDA holders does not warrant granting a hearing because the evidence is not relevant to the above factors. A significant portion of the evidence submitted by the ANDA holders in support of the hearing includes published medical literature and affidavits summarizing the impressions of practicing physicians regarding unapproved uses of PEG 3350, such as chronic constipation, opioid-induced constipation, and use in pediatric patients (see, *e.g.,* Waymack Declaration ¶¶ 17–25, 28; Waymack Bibliography 1–2, 5–6, 8–9); Hyman Declaration ¶¶ 8–23; Hyman Bibliography 1–2, 4, 6–14; Weschler Declaration ¶¶ 9–14). The indication for both OTC MiraLAX and the generic prescription PEG 3350 products is occasional constipation. Neither the prescription products nor OTC MiraLAX are indicated for treatment of chronic constipation or opioid-induced constipation or for treatment of pediatric patients. Evidence regarding these unapproved uses of PEG 3350 is not relevant and does not raise a material issue of fact regarding the factors FDA set forth in the ANPRM or the NOOH.

The expert statements regarding duration of use likewise fail to meet the criteria at § 12.24 for granting a hearing. The NOOH explained that, in previous switches, a drug remained prescription for one duration of use while becoming OTC for the other duration 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 (73 FR 63491 at 63493 n.1), none of which are present here. The NOOH further explained that the 7-day duration of use for OTC MiraLAX was based upon the labeling intended for the OTC audience and to ensure consistent labeling among OTC laxative products. The ANDA holders did not dispute this. Nevertheless, they made arguments and submitted affidavits of impressions of practitioners citing review documents and approved labeling related to duration of use. The ANDA holders focus on PEG 3350's alleged increased efficacy after 2 to 4 weeks and maintained efficacy from 4 weeks to up to 6 months of use, based upon the ''or as directed by a physician'' language in the prescription labeling. Also relying upon the ''or as directed by a physician'' phrase in the prescription labeling, the ANDA holders contend that such language indicates that prescription MiraLAX has an unlimited duration of use. They further maintain that OTC MiraLAX has a maximum duration of use of 7 days.

Prescription PEG 3350 is approved for a duration of use of ''2 weeks *or less* or as directed by a physician.'' Nonprescription MiraLAX's labeled duration of use states: ''use *no more* than 7 days''; ''Stop use and ask a doctor if . . . you need to use a laxative for longer than 1 week''; and ''do not take more than directed *unless* advised by your doctor.'' The labeling of both products states that the patient may use the product for less than the 7-day or 14-day duration the ANDA holders cite. In addition, the labeling for both products explicitly states that the products can be expected to be effective in producing a bowel movement in less than 7 days,[6] which is consistent with the fact that both products are indicated for occasional constipation and not chronic constipation. Both products' labeling also acknowledges the discretion of a treating physician to recommend a duration of use beyond the labeled duration.[7] For this reason, the ANDA holders' attempts to show that there is increasing efficacy over an extended period of time is not determinative of whether there is a meaningful difference between the prescription and OTC products as approved by FDA. Moreover, although the PEG ANDA holders complain that the proposed order improperly relied upon a lack of data, the ANDA holders raised the issue of comparative efficacy over time based upon a misplaced reliance on the data from the MiraLAX application and without submitting supporting data.

Duration of use alone was not set forth in the ANPRM or the NOOH as a factor the Agency considers in determining whether there is a meaningful difference between a prescription product and an OTC product. Moreover, the NOOH made clear that the duration of use on the OTC label resulted from the intended audience (consumers) and the need to maintain consistency with the labeling of other OTC laxative products, and not from any difference necessitated by science. The plain language of the labeling provides discretion to patients and physicians with regard to duration of use. Considering all these factors, the Commissioner in this proceeding declines to conclude that duration of use alone, without an additional more fundamental difference between the products, is sufficient to establish a meaningful difference. As such, the evidence and affidavits regarding duration of use do not raise material issues of fact that would be determinative with respect to this action, and thus do not justify a hearing. Additional discussion of the meaningful difference standard and duration of use is found in section III.D.

Other evidence submitted by the ANDA holders consists of expert statements or impressions of practitioners that challenge FDA's 2006 decision to approve MiraLAX—or, in some instances, any laxative product—as an OTC product (see, *e.g.,* Garvey Declaration ¶¶ 10–17, 21–25; Waymack Declaration ¶¶ 9–10, 26–27, 29; Beier Declaration ¶¶ 8, 10–17; Weschler Declaration ¶¶ 15–17); see also Nexgen

[6] The prescription labeling states, ''Treatment for 2 to 4 days may be required to produce a bowel movement.'' The nonprescription labeling states, ''Generally, produces a bowel movement in 1 to 3 days.''

[7] FDA does not seek to interfere with the exercise of the professional judgment of health care providers in prescribing or administering, for unapproved uses for individual patients, most legally marketed medical products.

Comments at 46–48 (contrasting FDA's approval of OTC MiraLAX with a prior decision to approve OTC Plan B only for individuals 16 years of age and older); Nexgen Objection at 37–40, 47 (raising arguments related to a lack of labeling comprehension, self-selection, and actual use studies and an advisory committee meeting prior to MiraLAX's OTC approval). Other statements focus on issues such as whether the clinical trials were adequate to support the efficacy of MiraLAX within 7 days, whether constipation is a self-limiting condition suitable for treatment with an OTC drug, and whether FDA correctly concluded that MiraLAX may be used safely for up to 7 days (with certain exceptions set forth in the OTC label) without the supervision of a licensed practitioner.

This evidence challenges FDA's decision to approve MiraLAX as an OTC product. As explained in the Background section, the PEG 3350 ANDAs were approved based upon FDA's finding that the generic PEG 3350 products have the same active ingredient, indication for use, route of administration, dosage form, strength, and labeling as, and that they were bioequivalent, to prescription MiraLAX. The PEG ANDA holders were not required to submit evidence to establish the safety and efficacy of their products. Rather, the ANDAs relied upon FDA's prior finding of MiraLAX's safety and efficacy for approval, which was supported by the evidence submitted in the previously approved NDA for prescription MiraLAX (NDA 20–698). Subsequently, FDA approved NDA 22–015 for OTC MiraLAX, which has the same active ingredient, indication for use, route of administration, dosage form, and strength as prescription MiraLAX. The ANDA holders now challenge the decisions made in the course of the approval of NDA 22–015 and seek a hearing on these issues. Neither the FD&C Act nor its implementing regulations require that the ANDA holders be afforded a hearing on FDA's decision to approve the NDA for OTC MiraLAX, and that issue is not determinative in this proceeding, which is only to decide whether OTC MiraLAX as already approved by FDA is meaningfully different from the approved prescription products. Accordingly, the Commissioner finds that a hearing on this evidence submitted with regard to these issues is not warranted. (See § 12.24(b); *Hynson,* 412 U.S. at 620; *Capanos,* 854 F.2d at 522, 526).

The Commissioner further concludes that a hearing may be denied in this proceeding, even in the absence of a regulation setting forth the standard for determining whether there is a meaningful difference between prescription and nonprescription products containing the same active ingredient. This is so because the meaningful difference standard was set forth in the ANPRM and the NOOH, and the NOOH discussed in detail the facts and evidence that formed the basis for CDER's proposed withdrawal of the ANDAs. Where the NOOH provides such information, precise regulations specifying the type of evidence necessary to justify a hearing are not required (*Capanos,* 854 F.2d at 520; cf. *American Cyanamid Co.* v. *FDA,* 606 F.2d 1307, 1312–13 (D.D.C. 1979); *Hess & Clark, Inc.* v. *FDA*, 495 F.2d 975, 984 (D.C. Cir. 1974)). Furthermore, the factors set forth in the ANPRM and the NOOH, which FDA will consider in determining whether there is a meaningful difference between prescription and nonprescription drug products containing the same active ingredient (indication, strength, route of administration, dosage form, patient population), are clearly set forth in the products' labeling.

As to the complaint that the proposed order ''applied the concept of 'material fact' '' so narrowly that no issue is likely to satisfy that standard (Nexgen Objection at 17), the ANDA holders' requests for hearing and objections to the proposed order do not dispute that the active ingredient, dosage form, strength, route of administration, indication, and patient population are the same for the original prescription MiraLAX product approved in NDA 20–698, the prescription generic PEG 3350 products, and OTC MiraLAX approved in NDA 22–015, as reflected on the products' labeling. Contrary to their assertions, the Agency is not construing substantial and genuine issue of fact narrowly. Rather, any data or information presented by the ANDA holders purporting to establish facts that do not relate to the factors set forth in the ANPRM and NOOH is immaterial because those are the factors that are relevant to determining if there is a meaningful difference between the products. In addition, the factors the Agency set forth as relevant to determining a meaningful difference between the products largely align with those the Agency relied upon in approving the PEG 3350 ANDAs (see 21 U.S.C. 355(j)(2)(A)(i) to (v)). Under these circumstances, it would be difficult for the ANDA holders to raise a genuine and substantial issue of fact requiring a hearing. Considering the relevant issues in this proceeding, the evidence submitted combined with the mere assertions of fact advanced by the PEG 3350 ANDA holders is insufficient to raise a genuine and substantial issue of fact requiring a hearing. The Commissioner therefore denies the PEG 3350 ANDA holders' request for a hearing and is entering summary judgment (§§ 12.24(b)(1) and (2), and 314.200(g)).

B. New Evidence Submitted With the Objections to the Proposed Order

In addition to submitting evidence intended to support its arguments in its request for hearing, Nexgen's objection to CDER's proposed order included new evidence and allegations. Nexgen maintains the new information and allegations raise genuine and substantial issues of fact requiring a hearing. The new information includes medical literature describing the use of PEG 3350 for chronic constipation and for a duration longer than 14 days, and literature discussing the physician's role in PEG 3350 use. Also included in the Objection are allegations that FDA was long ''aware'' of the tension between the safe duration of use period for OTC laxatives and the use of laxatives for prolonged periods in certain populations with physician supervision. Nexgen also alleges for the first time that OTC MiraLAX has a new indication because FDA's approval letter referenced required pediatric studies for OTC MiraLAX. Nexgen also raises allegations regarding: additional active ingredients for which FDA has permitted simultaneous prescription and nonprescription products; the lack of a labeling comprehension study and advisory committee meeting prior to approval of OTC MiraLAX; a U.S. Department of Health and Human Services (HHS) announcement of a grant to study PEG 3350 in the pediatric population; and the cost of OTC MiraLAX. Nexgen submitted survey results of physician perceptions of the OTC and prescription MiraLAX labeling, data on reported adverse events for MiraLAX after the OTC approval, and data on continued sales of prescription MiraLAX (Nexgen Objection at 23–43; Nexgen Objection Exhibits 5–7).

Under § 314.200(c), an applicant who wishes to participate in a hearing shall file the studies on which the person relies to justify a hearing within 60 days after the date of publication of the notice of opportunity for hearing. FDA will not consider data or analyses submitted after that 60-day timeframe when determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the

date of the notice of opportunity for hearing and the results of the studies were not available within 60 days after the date of publication of the notice. Under those circumstances, the person requesting a hearing shall list all studies in progress, the results of which the person intends later to submit in support of the request for a hearing. Additionally, such person must submit a copy of the complete protocol, a list of participating investigators, and a brief status report of the studies within 60 days of the notice of hearing. Further, FDA may consider studies submitted outside the 60-day timeframe when the person requesting a hearing makes a showing of an inadvertent omission and hardship (§ 314.200(c)(1) and (2)).

In the preamble to 21 CFR 130.14, the predecessor to § 314.200, FDA rejected a comment suggesting that FDA should permit later submission of material ''not known'' to exist at the time a request for hearing is due. FDA stated on numerous occasions in the past, persons requesting a hearing have subsequently supplemented that request with multiple submissions of data and information culled from the literature and other sources, all of which were available at the time of the original request for hearing. This has resulted in lengthy delays while the newly submitted information has been assessed. In the interest of administrative efficiency, it is essential that this type of continuous submission be precluded. Accordingly, the new regulations require that any submission of existing information be made within the 60-day time period permitted in the regulations. (39 FR 9750 at 9757.) Likewise, in the preamble to the predecessor to part 12, FDA stated it would be impracticable to permit supplementation at any time prior to the Commissioner's ruling on an objection or request for hearing, for the Commissioner would then be required to defer his ruling whenever supplemental material was received. This would seriously disrupt the process of ruling on objections and requests, would frustrate efforts of persons to respond in support of denial of a hearing, and could prolong action indefinitely. (41 FR 51706 at 51707, November 23, 1976.)

In its request for a hearing, Nexgen stated, ''Nexgen is submitting herein substantial facts and legal analyses controverting FDA's position, and intends to supplement this information in its '60 day' submission pursuant to 21 CFR 12.22 and 314.200.'' (Nexgen Comment at 2). Regarding the new information and allegations Nexgen submitted in its Objection, Nexgen made no attempt to supplement its request for hearing in a manner that comports with the requirements of § 314.200(c)(2). Nexgen did not show that the information includes data derived from well-controlled studies that began before the date of the notice of opportunity for hearing and that the results were not available within 60 days of the date of publication of the notice. Nexgen did not list the studies in progress, nor did it submit the protocols, the participating investigators, or a status report of the studies. Nexgen made no showing that any of the data or analyses or cited publications are derived from well-controlled studies. Even if FDA were to consider information not derived from well-controlled studies submitted after 60 days, Nexgen made no attempt to inform FDA that it would be submitting the results of a telephonic survey, adverse event data, labeling analysis of products for which FDA has permitted simultaneous prescription and nonprescription marketing, cost data, or continued sales data for prescription MiraLAX. Additionally, Nexgen did not show that the new information and allegations submitted in the Objections were not included in its Request for Hearing due to an inadvertent omission and hardship. Nexgen's failure to submit this new evidence in conformance with § 314.200 gives the Commissioner sufficient reason to decline to review it.

Even if the Commissioner were to consider the submissions in Nexgen's objection, Nexgen's new information and analyses are not relevant to the issue of whether there is a meaningful difference between the prescription and nonprescription versions of MiraLAX approved by FDA such that PEG 3350 could be marketed simultaneously in both a prescription and nonprescription MiraLAX product. The data and analyses submitted by Nexgen, such as the physician survey, studies of PEG 3350 for chronic constipation, the approval process for OTC MiraLAX, adverse event reports for MiraLAX, sales data for prescription MiraLAX, the cost of OTC MiraLAX, and HHS funding to study PEG 3350 in the pediatric population, are not related to the factors set forth in the ANPRM and the NOOH as material to determining meaningful difference. In light of the requirements in § 314.200 for submitting data and analyses after the 60-day deadline, FDA's rationale for imposing restrictions on the submission of data and analyses after 60 days, and the lack of relevance of this information, the Commissioner will not further consider the information Nexgen and Breckenridge submitted with their objections to the proposed order.

C. Legal Arguments Offered by the ANDA Holders

The ANDA holders have failed to raise a genuine and substantial issue of fact that requires a hearing, and a hearing will not be granted on issues of law (§ 12.24(b)(1)). In addition, the Commissioner does not find the arguments advanced by the PEG 3350 ANDA holders persuasive and is entering summary judgment against them. The Commissioner will address each argument and assertion made by the PEG 3350 ANDA holders in support of their hearing requests to explain the finding of summary judgment.

The arguments addressed in section III.C of this order challenge the statutory and regulatory requirements of the FD&C Act that govern prescription and nonprescription marketing status, the withdrawal of approval of a drug application, generic drugs and exclusivity, and FDA enforcement. The arguments challenge the regulatory requirements of the Administrative Procedure Act (APA) and FD&C Act with regard to notice and comment rulemaking. The arguments also challenge the statutory and regulatory requirements for summary judgment. As such, they are legal arguments, which do not raise a genuine and substantial issue of fact. Thus, these arguments cannot form the basis for granting a hearing (see §§ 12.24(b)(1) and 314.200(g)). In addition, these arguments do not have any legal merit.

1. The Agency's Authority Under Section 503(b)(4)(B) of the FD&C Act

Nexgen, Paddock, and Gavis all submitted arguments regarding the Agency's authority under section 503(b)(4)(B) of the FD&C Act. Specifically, they argue that because their ANDAs were approved as prescription products, they are required to bear the ''Rx only'' symbol and therefore cannot be deemed misbranded under section 503(b)(4)(B) of the FD&C Act (Nexgen Comments at 37–39). As the basis for this argument, they suggest that the provisions in section 503(b)(1)(A) are independent of those in section 503(b)(1)(B) of the FD&C Act, and a drug is a prescription drug if it is covered under section 503(b)(1)(B), regardless of whether it is covered under section 503(b)(1)(A) (Nexgen Comments at 38; Gavis Comments at 002; Paddock Comments at 6). Thus, they contend that once a drug is approved as prescription under section 503(b)(1)(B) of the FD&C Act, it is

always prescription and that status cannot be taken away, regardless of a change from prescription to nonprescription status of the RLD.

Likewise, they argue that the Durham-Humphrey Amendments (Pub. L. 82–215 (1951)) were not intended to address the situation in which a prescription drug product is forced to change to nonprescription because a separate NDA for the same active ingredient was approved as a nonprescription product (Nexgen Comments at 39–40). They further argue that if Congress intended generic prescription drugs to become misbranded immediately when their referenced products are approved for nonprescription use, it should have written that explicitly into the FD&C Act (Gavis Comments at 003; Paddock Comments at 6; Nexgen Comments at 39–40).

A basic rule of statutory construction is that ''a statute is to be read as a whole . . . since the meaning of statutory language, plain or not, depends on context.'' (*King* v. *St. Vincent's Hosp.,* 502 U.S. 215, 220 (1991) (citations omitted).) ''A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme . . . .'' (*United Savings Ass'n* v. *Timbers of Inwood Forest Associates,* 484 U.S. 365, 371 (1988) (citations omitted)). In line with the notion that the statute should be read in a holistic manner, congressional silence on a particular point does not lend more credence to one interpretation if much of the evidence would point to another interpretation. ''An inference drawn from congressional silence certainly cannot be credited when it is contrary to all other textual and contextual evidence of congressional intent.'' (See *Burns* v. *United States,* 501 U.S. 129, 136 (1991) (internal citation omitted).) Further, where Congress does not explicitly include language addressing a particular situation, it is appropriate for FDA to form an interpretation of the proper application of the statute based on the legislative history (see *Wilder* v. *Virginia Hosp. Ass'n,* 496 U.S. 498, 515 (1990) (referencing to Senate report for evidence of ''the primary objective'' of the Boren amendment to the Medicaid law)).

The ANDA holders' argument that once a product is approved as a prescription product, it is always a prescription product, cannot withstand a holistic reading of section 503(b) of the FD&C Act. Section 503(b)(3) states that FDA may ''remove drugs subject to section 505 [of the FD&C Act] from the requirements of [section 503(b)(1)] . . . when such requirements are not necessary for the protection of the public health.'' On its face, the statute authorizes the Secretary to exempt a product from the prescription-dispensing requirements when such requirements are not necessary for the protection of the public health. Further, section 503(b)(3) of the FD&C Act references 503(b)(1) in its entirety and thus applies to drugs that are limited by an application approved under section 505 of the FD&C Act to prescription use under section 503(b)(1)(B). FDA set forth this interpretation when it issued § 310.200 in 1963 (28 FR 6377, June 20, 1963). That regulation states that any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling. (§ 310.200(b).) Therefore, the ANDA holders' general contention that once a product is approved as a prescription product under section 503(b)(1)(B) of the FD&C Act, it can never lose its prescription status, is incorrect.

Section 503(b)(4) of the FD&C Act describes when a drug product is required to bear the ''Rx only'' symbol on its label and when a drug product may not bear the ''Rx only'' symbol. Under section 503(b)(4)(A), any drug product that is subject to 503(b)(1) ''shall be deemed misbranded if at any time prior to dispensing the label of the drug fails to bear . . . the symbol 'Rx only'.'' Under section 503(b)(4)(B) of the FD&C Act, any drug product that is not subject to 503(b)(1), *i.e.,* a nonprescription product, shall be deemed to be misbranded if it bears the ''Rx only'' symbol on its label any time prior to the dispensing of the drug product. The purpose of section 503(b)(4) of the FD&C Act is to eliminate the marketing of both prescription and nonprescription versions of the same drug product at the same time (see Pub. L. 82–215 (1951)).

While considering the Durham-Humphrey Amendments, Congress noted that retail pharmacists shelved one and the same drug product made by various manufacturers, but with different labels. Some drug products bore prescription labeling while the same drug product manufactured by a different firm bore nonprescription labeling, leading to confusion for both pharmacists and the public. (See H.R. Rep. No. 82–700, at 3 (1951); S. Rep. No. 82–946, at 2 (1951); 97 Cong. Rec. 9235 (1951); see also 97 Cong. Rec. 9321 (1951).) Congress stated that the purpose of the amendments was to change that ''uncertain situation'' into a ''certain situation.'' (See 97 Cong. Rec. 9330 (1951).) The amendments were also meant to ''relieve retail pharmacists and the public from burdensome and unnecessary restrictions on the dispensing of drugs that are safe for use without the supervision of a physician.'' (S. Rep. No. 82–946, at 1–2 (1951); see also 97 Cong. Rec. 9235 (1951).)

If section 503(b)(4) of the FD&C Act were construed the way Nexgen, Paddock, and Gavis describe, the Durham-Humphrey Amendments would be rendered meaningless. If a prescription generic drug product were allowed to remain on the market by virtue of its approval as a prescription product, which approval was based, among other things, on its bioequivalence to an RLD, despite that RLD's switch from prescription to nonprescription, there would be simultaneous marketing of prescription and nonprescription versions of the same drug product. This result conflicts with a holistic reading of section 503(b) of the FD&C Act. Further, this result would negate a central purpose of the Durham-Humphrey Amendments as set forth in the legislative history: avoiding confusion for pharmacists and the public.

Additionally, the ANDA holders' argument with respect to Congress's failure to include specific language in the FD&C Act describing the exact situation in which the PEG 3350 ANDA holders find themselves is not persuasive. In the absence of express statutory language, FDA is permitted to put forth a reasonable interpretation of the statute. The courts have long held that FDA's interpretation of the FD&C Act governs as long as it is ''a permissible construction of the statute.'' (See *Chevron, U.S.A., Inc.* v. *Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842–44(1984); *Novartis Pharm. Corp.* v. *Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006) (''FDA interpretations of the FDCA receive deference''); cf. *Pharmanex* v. *Shalala*, 221 F.3d 1151, 1160 (10th Cir. 2000) (FDA's interpretation that a ''new drug'' includes active ingredients as well as finished drug products is entitled to deference); *Nat'l Pharm. Alliance* v. *Henney*, 47 F. Supp. 2d 37, 39–40 (D.D.C. 1999) (because Congress's use of ''drug'' in section 505 did not clearly speak to the relevant issue, courts must defer to FDA's interpretation).) As described above, Congress expressed

clear concerns about the same products being marketed as both prescription and nonprescription products and the ensuing confusion for both pharmacists and the public at large. FDA's interpretation of the application of the Durham-Humphrey Amendments is not only a permissible construction of section 503(b) of the FD&C Act when reading that section as a whole, but a logical interpretation in light of the legislative history behind the amendments. Additionally, based on those concerns, Congress could not have intended the interpretation that the ANDA holders put forth.

Furthermore, the PEG 3350 ANDA holders' interpretation of section 503(b)(4) of the FD&C Act is inconsistent with that held by the United States Court of Appeals for the Seventh Circuit (Seventh Circuit). The PEG 3350 ANDA holders were the Defendants-Appellees in a case under section 43(a)(1)(B) of the Lanham Act (15 U.S.C. 1125(a)(1)(B)) concerning the marketing of generic prescription PEG 3350 products, which was appealed to the Seventh Circuit after the District Court dismissed the case pending a decision by FDA regarding the misbranding of their products (*i.e.,* the publication of this notice). In its opinion, the Seventh Circuit upheld the lower court's decision and clearly explained that ''the Food, Drug, and Cosmetic Act does not permit both by-prescription-only and over-the-counter versions of the same drug to be sold at the same time.'' (*Schering-Plough Healthcare Products, Inc.* v. *Schwarz Pharma, Inc.*, 586 F.3d 500, 505 (7th Cir. 2009) (citing section 503(b)(4) of the FD&C Act).) The Seventh Circuit also explained that, in light of this provision of the FD&C Act, ''the FDA is conducting a proceeding to determine whether [the PEG 3350 ANDA products] are misbranded now that there is an over-the-counter version of the drug . . . [and] if the FDA determines that they are 'the same,' the result will be that the generic drug can no longer be sold.'' (Id.).

In this case, CDER concluded, and the Commissioner affirms, that there is not a meaningful difference between the prescription and nonprescription versions of MiraLAX; *i.e.,* that they are essentially the ''same.'' And, once a drug product is fully switched from prescription to nonprescription use, the previous prescription drug product may no longer be legally marketed as per section 503(b) of the FD&C Act, as the prescription product would be misbranded under section 503(b)(4)(B). Had Braintree continued to market prescription MiraLAX following FDA's approval of OTC MiraLAX, the prescription MiraLAX would have been misbranded. It follows that the PEG 3350 ANDA products that reference prescription MiraLAX and that were approved based upon a finding that they met the requirements of section 505(j)(2)(A)(i) to (v) and (j)(4) of the FD&C Act cannot avoid being misbranded under section 503(b)(4) and § 310.200(d) simply because they were initially approved as prescription drugs and continue to be marketed as prescription products.

2. The Agency's Authority Under Section 505(e) of the FD&C Act

a. False or misleading. Nexgen and Paddock submitted comments arguing that the prescription version of the labeling is not false or misleading; therefore, the Agency does not have the authority to withdraw the product under section 505(e) of the FD&C Act. Nexgen and Paddock argue that the PEG 3350 labeling is not false or misleading because it still meets the standards under which it was initially approved as a prescription drug product referencing NDA 20–698. They maintain that the approval of their products as prescription drugs did not depend upon PEG 3350's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use. Rather, they maintain that their PEG 3350 products are entitled to prescription status under section 503(b)(1)(B) of the FD&C Act because the ANDA required that their products be dispensed by prescription. They also contend that because the NOOH provides no evidence of new information that would indicate that the labeling is false or misleading, section 505(e)(3) of the FD&C Act does not apply (see Nexgen Comments at 41; Paddock Comments at 9–10).

These legal arguments are based upon an incorrect assertion that the products are not misbranded under section 503(b)(4) of the FD&C Act. In this instance, neither criterion under 503(b)(1) applies to the generic PEG 3350 products. FDA previously determined, at the time OTC MiraLAX was approved, that the supervision of a licensed practitioner is no longer necessary for the use of MiraLAX and that no prescription indications remained. After FDA made that determination with regard to the RLD, the legal status of the RLD as a prescription product and the medical and scientific basis underlying the approval of both the RLD and the generic PEG 3350 products as prescription drugs no longer existed. Where, as here, the legal and scientific underpinnings of the approval of the generic PEG 3350 products as prescription drugs have ceased to exist, FDA concludes that section 503(b)(1)(B) of the FD&C Act no longer applies to those products. This interpretation is supported by a reading of section 503(b) as a whole and is consistent with the purpose of the statute as set forth in the legislative history, as discussed in the above subsection of this order. In addition, the labeling of the ANDA PEG 3350 products is false or misleading. By bearing the ''Rx only'' symbol, the labeling implies that the products can be dispensed safely only with a licensed practitioner's prescription. Yet, FDA has determined that MiraLAX can be used safely and effectively in the nonprescription setting and specifically does not meet the criteria in 503(b)(1) of the FD&C Act. In section III. D. of this order, FDA has determined that the generic PEG 3350 products are the same drug product as nonprescription MiraLAX (*i.e.,* there is no meaningful difference between them) for purposes of determining whether they are misbranded under section 503(b)(4) of the FD&C Act. Thus, the contention that the generic prescription labeling is not false or misleading because the applications were originally approved as prescription products is without merit.

Because the labeling for the PEG 3350 prescription products is false or misleading, the Agency has the authority to withdraw approval of the products under section 505(e)(3) of the FD&C Act. The ''new information'' in this case is the October 2006 approval of MiraLAX as an OTC drug, the change in status of MiraLAX from prescription to nonprescription, and the fact that the PEG 3350 ANDA holders have not submitted new ANDAs referencing OTC MiraLAX and including the same OTC labeling as the RLD after receiving written notice from FDA. Accordingly, the standard for withdrawal in section 505(e)(3) of the FD&C Act has been met.

b. Written notice. Schwarz submitted comments arguing that the April 20, 2007, letters are not sufficient ''written notice'' under the FD&C Act to justify the NOOH. Schwarz argues that because neither the Secretary, nor anyone with properly delegated authority, provided written notice to Schwarz, the April 20, 2007, letter does not constitute an advisory opinion or represent the formal position of FDA. Further, Schwarz claims that there is no evidence that Schwarz did not attempt to correct the issues identified in the April 20, 2007, letter. Because of this, Schwarz contends that FDA has not satisfied the prerequisites to withdrawal under

section 505(e)(3) of the FD&C Act and the NOOH is invalid (Schwarz Comments at 2–3).

This argument is unavailing. Section 505(e) states that the Secretary may, ''after due notice and opportunity for hearing to the applicant,'' withdraw approval of a drug application if the Secretary finds that the labeling of such drug 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. Schwarz's assertions regarding the April 20, 2007, letter are unavailing, as even if the Commissioner were to assume that the Buehler letter failed to satisfy the requirements of section 505(e), the NOOH itself also satisfies this requirement.

The NOOH issued in October 2008 proposed the withdrawal of the PEG 3350 ANDAs on the basis of the switch of MiraLAX from Rx to OTC. The NOOH noted that the FD&C Act does not permit both Rx and OTC versions of the same drug product to be marketed at the same time. Under the FD&C Act, a drug to which the prescription dispensing requirements do not apply (*i.e.,* an OTC drug) shall be deemed misbranded if at any time prior to its dispensing, the label of the product bears the ''Rx only'' symbol. The NOOH explained that the ANDA products' labels, which bear the ''Rx only'' symbol, are false or misleading because the same PEG 3350 product was approved for OTC use. Thus the NOOH, which was issued by the Associate Commissioner for Policy and Planning pursuant to delegated authority,[8] also satisfies the requirement in section 505(e) of the FD&C Act that there be written notice specifying the matter complained of.

Contrary to Schwarz's suggestion, there is nothing in the statute that requires written notice to ''justify'' the NOOH; the statute only requires written notice as a prerequisite to the withdrawal itself. The NOOH did not withdraw the applications; it merely initiated this proceeding during which the applicants were given ample opportunity to contest the proposed withdrawals. The Commissioner is withdrawing approval of the applications via this order, and the NOOH serves as written notice prior to this withdrawal under section 505(e) of the FD&C Act.[9]

3. The Agency's Authority Under Hatch-Waxman

Paddock's comments contend that the Hatch-Waxman amendments do not authorize FDA to withdraw approval of an ANDA for nonsafety or noneffectiveness reasons. In fact, Paddock argues, by removing the prescription PEG 3350 products from the market, FDA is effectively awarding Braintree 6 years of exclusivity for its prescription product, which contravenes the Hatch-Waxman Amendments in section 505(c) and (j) of the FD&C Act. Paddock further argues that FDA's award of 3 years of exclusivity to OTC MiraLAX must have been based on studies in a new patient population and thus contravenes the proposal to find that there is not a meaningful difference between the prescription and OTC products (Paddock Comments at 5–6).

These allegations make incorrect statements about the Agency's authority under the FD&C Act regarding withdrawal of generic drug products and granting of market exclusivity. The Hatch-Waxman Amendments established new section 505(j) of the FD&C Act, which sets forth the ANDA approval process for generic drugs. The NOOH proposed withdrawal based upon the second sentence of section 505(e) of the FD&C Act, which explicitly references section 505(j), and vests the Secretary with the authority to withdraw an ANDA whenever new information establishes that ''the labeling of such drug . . . is false or misleading in any particular.'' The prescription PEG 3350 ANDAs are misbranded under section 503(b)(4)(B) of the FD&C Act and FDA's regulations because they are marketed for prescription use at the same time as a nonprescription product that FDA determines in this order is not meaningfully different. In this case, the use of the ''Rx only'' symbol on the labeling of the prescription PEG 3350 products is false or misleading because it implies that the products are required to be dispensed only with a prescription; whereas FDA has determined that the same product does not meet the criteria in section 503(b)(1) of the FD&C Act and can be used safely and effectively in the nonprescription setting.

FDA did not award Braintree 6 years of exclusivity for its prescription product. Braintree received 3 years of exclusivity under section 505(j)(5)(F) of the FD&C Act when the initial approval of prescription MiraLAX was supported by new clinical studies essential to its approval conducted by or on behalf of Braintree. It also received 3 years of exclusivity under the same provision when the OTC switch NDA was approved because Braintree supported its OTC MiraLAX application with new clinical studies conducted by or on behalf of Braintree that were essential to its approval. These are two separate awards of exclusivity earned by Braintree under the criteria set forth in the FD&C Act. Contrary to Paddock's contention, there were two separate bases for granting two 3-year periods of exclusivity, as is often the case when products switch from prescription to nonprescription status.

4. Arguments Regarding the Administrative Procedure Act

a. Notice and comment rulemaking. Paddock argues that the Agency's withdrawal of the Rx PEG 3350 ANDAs following MiraLAX's switch from Rx to OTC would violate the APA when MiraLAX's switch was not accomplished through the notice and comment rulemaking process. Paddock argues that the Durham-Humphrey Amendments preclude withdrawal of a generic product based on a change of the RLD to nonprescription status unless the RLD's prescription status was changed through rulemaking (Paddock Comments at 2–3). Therefore, Paddock contends that because the Agency did not engage in notice and comment rulemaking to change the status of MiraLAX from prescription to nonprescription, it does not have the authority to withdraw approval of the PEG 3350 ANDAs (Paddock Comments at 2–3, 7). Paddock further argues that the approval of OTC MiraLAX and the later decision to propose withdrawal of

[8] The Secretary delegated authority to the Commissioner, with authority to redelegate, all functions vested in the Secretary under the FD&C Act, as set forth in the FDA Staff Manual Guide, Volume II, Number 1410.10 (effective May 18, 2005). Available at: *https://web.archive.org/web/20070701125239/http://www.fda.gov:80/smg/1410_10.html* (accessed December 15, 2017). At the time the NOOH was issued, the Commissioner had redelegated the authority to perform all functions of the Commissioner to certain specified officials including the Associate Commissioner for Policy and Planning, as set forth in the FDA Staff Manual Guide, Volume II, Number 1410.21 (effective May 15, 2007). Available at: *https://web.archive.org/web/20070705185904/http://www.fda.gov:80/smg/1410_21.html* (accessed December 15, 2017).

[9] The ANDA holders have received additional notice prior to this withdrawal order that their products' labeling was false or misleading, as required by section 505(e) of the FD&C Act. In May 2014, Dr. Janet Woodcock, CDER Director, wrote to the ANDA holders and attached a copy of the proposed order, which specified CDER's basis for concluding that the prescription MiraLAX labeling is false or misleading. The ANDA holders have not corrected the misbranding within a reasonable time of receiving Dr. Woodcock's letter. In May 2014, Dr. Woodcock had the properly delegated authority to take regulatory actions for drugs for human use for which approved applications submitted under section 505 of the FD&C Act are in effect. See FDA Staff Manual Guide 1410.104 ¶ 1.A (effective June 12, 2012). Available at: *https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM336918.pdf.*

the prescription PEG 3350 ANDAs from the market is essentially a legislative rule issued without notice and comment in violation of the APA (Paddock Comments at 7–8). In addition, Paddock argues that because the Agency has never defined how it assesses a meaningful difference, it is in effect issuing a legislative rule without engaging in notice and comment rulemaking (Paddock Comments at 19).

These allegations are inaccurate regarding the Agency's authority under the FD&C Act and the APA, neither of which requires the issuance of regulations before FDA can determine that a drug no longer meets the criteria at section 503(b)(1) of the FD&C Act. Paddock seemingly relies upon section 503(b)(3), which describes one procedure for exempting a drug from the prescription drug requirements of section 503(b)(1) of the FD&C Act. Specifically, section 503(b)(3) provides that FDA may, by regulation, remove a drug from the prescription dispensing requirements in section 503(b)(1) of the FD&C Act when the prescription status mandated by its NDA approval is no longer ''necessary for the protection of the public health.'' FDA has interpreted section 503(b) of the FD&C Act to allow the Agency to switch a drug product from prescription to nonprescription by approving an NDA submitted by a sponsor seeking such a change. In practice, FDA has exercised that authority and changed the status of numerous products from prescription to nonprescription through the submission of NDAs.

Further, in the absence of express statutory language requiring rulemaking, government agencies possess broad discretion in deciding whether to proceed by general rulemaking or case-by-case adjudication. (See, *e.g.*, *NLRB* v. *Bell Aerospace*, 416 U.S. 267, 293–94 (1974) (stating that ''the choice made between proceeding by general rule or by individual, *ad hoc* litigation is one that lies primarily in the informed discretion of the administrative agency.'' (internal citation omitted)); see generally *Cellnet Commc'n, Inc.* v. *FCC*, 965 F.2d 1106, 1111 (D.C. Cir. 1992) (reviewing the FCC's refusal to initiate a rulemaking and stating that ''an agency's refusal to initiate a rulemaking is evaluated with a deference so broad as to make the process akin to non-reviewability.'').) While the Agency may proceed through rulemaking, FDA also has the authority to exempt a drug from the prescription dispensing requirements without rulemaking. Switching a product through the NDA holder's submission of an NDA is an example of the Agency exercising its authority to proceed on a case-by-case basis.

As noted above, Paddock argues that withdrawal of the PEG 3350 ANDAs in the absence of notice and comment rulemaking constitutes a legislative rule. Under section 505(e) of the FD&C Act, FDA may withdraw approval of applications through adjudication, as the Agency is doing here; therefore, FDA's withdrawal of the PEG 3350 ANDAs does not constitute a legislative rule. Further, the issue of whether an FDA action involving an interpretation of the FD&C Act constitutes a legislative rule has been previously considered. In a matter challenging FDA's implementation of the pediatric exclusivity provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA), one of the arguments maintained that the ''Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act'' was a legislative rule that should have been enacted through notice and comment rulemaking. To determine whether the rule in that case was legislative or interpretive, the court used the four-part test from *American Mining Congress* v. *Mine Safety & Health Admin.*, 995 F.2d 1106 (D.C. Cir. 1993). The court first asked ''whether in the absence of the rule there would not be an adequate legislative basis for . . . agency action.'' (*Nat'l Pharm. Alliance* v. *Henney,* 47 F. Supp. 2d 37, 41 (D.D.C. 1999).) The court reasoned that, ''[FDAMA] on its face provides all the 'legislative basis' that is necessary for the agency's action,'' (Id.) and did not reach the remaining questions. As explained in section III.C.1 of this order, Congress explicitly added the Durham-Humphrey Amendments to the FD&C Act to eliminate the marketing of both prescription and nonprescription versions of the same drug product at the same time. Thus, as with FDAMA, sections 503 and 505(e) of the FD&C Act provide the legislative basis for FDA to withdraw the PEG 3350 ANDAs; therefore, FDA's withdrawal action does not constitute a legislative rule. To the extent that Paddock argues that FDA's interpretation of meaningful difference, as set forth in the NOOH and ANPRM, is a legislative rule, applying the *American Mining Congress* four-part test again supports that FDA's interpretation does not constitute a legislative rule. As explained earlier in section I.B of this order, in the 2005 **Federal Register** notice referenced above, FDA explained that the Agency has interpreted the language in section 503(b)(1) and (4) of the FD&C Act to allow marketing of the same active ingredient in products that are both prescription and nonprescription, assuming some meaningful difference exists between the two that makes the prescription product safe only under the supervision of a licensed practitioner (70 FR 52050 at 52051). FDA noted such a difference could be, for example, in indication, strength, route of administration, and/or dosage form. This is a permissible interpretation of the FD&C Act by FDA (see, *e.g.*, *Shalala* v. *Guernsey Mem'l Hosp.*, 514 U.S. 87, 110 (1995) (5–4 decision) (O'Connor, J., dissenting)). The interpretation of ''meaningful difference'' does not require notice and comment rulemaking because the Durham-Humphrey Amendments provide an adequate legislative basis on its face to make such an interpretation.

b. Burden of proof. Paddock argues that the Agency also violates the APA in its application of evidentiary requirements with regard to summary judgment. Paddock argues that the APA places the burdens of persuasion and production on the party seeking an order, which in this case is the Secretary (Paddock Comments at 14). Here, Paddock contends that the Agency has to present evidence that the labeling of the prescription PEG 3350 products is false and misleading and that FDA's action to withdraw the ANDAs is based on new information (Paddock Comments at 14).

It is inappropriate, Paddock argues, for the Agency to issue a summary judgment order absent a hearing because the APA only authorizes a hearing officer to do so, and the Agency should be the party demonstrating that there is no genuine and substantial issue of fact (Paddock Comments at 16). If the Agency proceeds as it plans to according to the NOOH and issues an order for summary judgment, Paddock argues, it would be acting as prosecutor, judge, and jury, which is not authorized under the APA (Paddock Comments at 16).

Furthermore, both Nexgen and Paddock request that the Agency make all of the data from the clinical studies in the nonprescription MiraLAX NDA (22–015) available to the PEG 3350 ANDA holders (Nexgen Comments at 40 n. 37; Paddock Comments at 17–19; Nexgen Objection at 76–77). Not doing so, they claim, deprives them of due process because the data cited in the NOOH is not sufficient to understand the basis upon which FDA is acting to remove the PEG 3350 ANDAs from the market. Paddock argues that, under Rule 56(f) of the Federal Rules of Civil Procedure (FRCP), it has the right to review the protocols and data

underlying the OTC MiraLAX approval (Paddock Comments at 17–19).

These allegations mischaracterize the Agency's authority to issue summary judgment orders as set forth under the FD&C Act, its implementing regulations, and the APA, and as reflected in case law. The Agency is authorized under section 505(e) of the FD&C Act to withdraw a drug from the market, after notice and opportunity for a hearing, if its labeling is false and misleading. In addition, FDA's regulations set forth a regulatory procedure for withdrawing approval of drug marketing applications under 505(e) that is designed to provide due process, including notice and opportunity for a hearing, to application holders (see § 314.200(a)). FDA's regulations governing formal evidentiary public hearings set forth the grounds upon which a hearing may be denied and summary decision granted (see § 12.24). FDA regulations explicitly require the person requesting a hearing to show that the criteria in § 12.24(b) for granting a hearing are met. Likewise, where FDA serves a proposed order denying a hearing, the burden remains on the person requesting the hearing to respond with sufficient data, information, and analysis to justify a hearing (§§ 12.24 and 314.200(g)).

In fact, these administrative procedures have been previously upheld by the Supreme Court (*see Hynson*, 412 U.S. at 622 (''we find FDA hearing regulations unexceptionable on any statutory or constitutional ground.'')). Likewise, the courts have held that summary judgment is available to FDA if hearing requests fail to raise a genuine and substantial issue of fact. (*See Hynson*, 412 U.S. at 621 (''We cannot impute to Congress the design of requiring, nor does due process demand, a hearing when it appears conclusively from the applicant's 'pleadings' that the application cannot succeed.''); *Hess & Clark,* 495 F.2d at 983 (''When the FDA issues a Notice of Opportunity for Hearing, its summary judgment procedures are available if the requesting party fails to raise material issues of fact.'').) Contrary to Paddock's contentions, FDA is authorized to act as the final arbiter on issues of summary judgment. In issuing the predecessor regulation to § 314.200, FDA rejected comments asserting that an Administrative Law Judge should determine whether there is an issue of fact justifying a hearing. FDA noted that the same legal arguments were raised in the pharmaceutical industry briefs in *Hynson* and were rejected by the Supreme Court holding that the present summary judgment procedures met all statutory and constitutional requirements (39 FR 9750 at 9754). Not all of the constraints inherent in Rule 56 of the FRCP apply to this proceeding. (*See Smithkline Corp.* v. *FDA*, 587 F.2d 1107, 1119 (D.C. Cir. 1978) (''The Supreme Court has made clear, however, that, because these circumstances do not involve the Seventh Amendment right to a trial by jury, we need not engage in the sharp limitations on summary judgment required by Rule 56 of the Federal Rules of Civil Procedure.''); *Copanos,* 854 F.2d at 518 (''It is well settled that this provision does not guarantee the applicant a hearing in all circumstances; the agency may by regulation provide for summary withdrawal of approvals. . . .'').)

Based on the requirements of the FD&C Act, FDA's regulations, and the APA, Paddock and the other PEG 3350 ANDA holders have been afforded an appropriate opportunity to justify a hearing on the factual basis for the proposed withdrawal of approval for the ANDAs. They have been given specific instructions as to the type and detail of evidence required to support a request for hearing. As explained elsewhere in this order, the ANDA holders' approval relies on FDA's prior safety and efficacy findings for the RLD. The issue for resolution in this proceeding is whether there is a meaningful difference between OTC MiraLAX and the prescription PEG 3350 products as approved by FDA. Whether or not FDA should have approved MiraLAX Rx or MiraLAX OTC in the first place is not at issue here. Due process does not require FDA to provide the underlying data supporting the approval of prescription or OTC MiraLAX. The Agency is not obligated to provide the PEG 3350 ANDA holders additional or more detailed information with regard to its issuance of the NOOH.

5. Other Legal Arguments or Claims

Nexgen argues in its request for a hearing that FDA has never taken enforcement action to require the withdrawal of a prescription drug product simply because it lacks a meaningful difference from a later-approved nonprescription drug product (Nexgen Comments at 43). Thus, they contend that ''*FDA has no regulatory standards in place and no enforcement history to cite as a body of law establishing the foundation or the basis for its extraordinary proposed withdrawal*'' of the prescription PEG 3350 ANDAs (Nexgen Comments at 43 (emphasis in original)).[10]

This argument does not have any legal merit. It is within FDA's purview to determine when and what enforcement actions are appropriate regarding specific drug products, taking into account Agency resources and public health priorities. Such individual enforcement-related decisions have no bearing on the lawfulness of the marketing of any particular product. Even if FDA were enforcing provisions of the FD&C Act it had not previously, FDA is not estopped from enforcing those provisions (*see Scott Paper Co.* v. *Marcalus Mfg. Co.*, 326 U.S. 249, 257 (1945); *Donovan* v. *Daniel Marr & Son, Co.*, 763 F.2d 477, 484 (1st Cir. 1985); *United States* v. *Undetermined Quantities of Clear Plastic Bags of an Article of Drug for Veterinary Use*, 963 F. Supp. 641, 646–647, *aff'd*, No. 97–3467, 1998 U.S. App. LEXIS 9320, at *3–4 (6th Cir. May 4, 1998); *United States* v. *789 Cases of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1296–97 (D.P.R. 1992)). Companies marketing drug products in the United States have the responsibility to ensure that their products are safe and effective and marketed in compliance with the law. Any product, including a product that is misbranded under the FD&C Act, which is being marketed illegally is subject to enforcement action at any time.[11]

Gavis submitted comments arguing that changing their prescription PEG 3350 product to nonprescription status would open them up to product liability in many States because they would not have the benefit of the learned intermediary defense, which exists for prescription products (Gavis Comments at 005). Nexgen argues for the first time in its objection that the ANDA holders could be subject to design defect liability for use beyond 7 days and misbranding charges for promoting use beyond 7 days. Nexgen also maintains that physicians may be subject to tort

[10] Counsel for Nexgen, Buchanan, Ingersoll & Rooney PC, also raised this issue in a Citizen Petition to the Agency (unrelated to the subject of this notice). See Docket No. FDA–2009–P–0589, Citizen Petition from Edward John Allera, Request to Confirm Dihydrocodeine Bitartrate as Generally Recognized as Safe and Effective for Use as a Liquid Antitussive in Prescription Cough/Cold Drug Products, dated December 1, 2009. The Agency denied the Citizen Petition in its entirety noting that ''The fact that FDA has not taken enforcement action against particular products in the past has no bearing on the lawfulness of the marketing of such products. FDA is not estopped from enforcing the requirements of the FD&C Act because the Agency has not previously enforced those requirements with respect to certain unapproved and violative products.'' (See Response to Citizen Petition FDA–2009–P–0589, issued March 9, 2012.)

[11] FDA, Guidance for FDA Staff and Industry Marketed Unapproved Drugs Manual of Compliance Policy Guides 440.100 at 5–6 (2011), available at *https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm.*

liability for instructing patients to use OTC MiraLAX for a duration longer than 7 days (Nexgen Objection at 77–78).

Potential liability issues are not among the factors FDA considers in determining whether an active ingredient may be simultaneously marketed in a prescription and nonprescription product. With regard to the decision to approve OTC MiraLAX, the Agency does not consider individual State tort law liability in its decisions regarding the safety and efficacy of drug products and whether the criteria for prescription products at section 503(b)(1) of the FD&C Act are met. As a matter of Federal law, FDA determines when approving an NDA whether a product meets the criteria for prescription drugs in the FD&C Act at section 503(b), or whether it can be safely and effectively marketed as a nonprescription product.

D. Evidence and Arguments Regarding Meaningful Difference Between the Prescription and Nonprescription PEG 3350 Products

As noted in section III.A, the PEG 3350 ANDA holders submitted evidence and arguments to support the contention that there is a meaningful difference between the prescription and nonprescription PEG 3350 products and assert that FDA is incorrect in proposing to withdraw the prescription version from the market. The evidence and arguments submitted by the PEG 3350 ANDA holders are further addressed in this section.

1. Duration of Use

Despite the fact that FDA considered the change of MiraLAX from prescription to nonprescription to be a ''full'' switch (and MiraLAX is no longer a RLD eligible to be marketed on a prescription basis), Nexgen, Gavis, and Paddock all assert that the difference in duration of use between the prescription and nonprescription versions of the PEG 3350 labeling constitutes a meaningful difference between the two products.

TABLE 3—LABELING REGARDING DURATION OF USE FOR PRESCRIPTION AND NONPRESCRIPTION PEG 3350

	Prescription MiraLAX	Nonprescription MiraLAX
Duration of Use	This product should be used for 2 weeks or less or as directed by a physician.	Use no more than 7 days. Stop use and ask a doctor if you need to use a laxative for longer than 1 week.

Nexgen and Gavis both argue that the words ''or as directed by a physician'' in the prescription MiraLAX labeling can be construed to mean that the PEG 3350 ANDA prescription products can be prescribed by a physician for an indefinite period of time or for chronic use; whereas the wording of the nonprescription MiraLAX labeling implies that FDA determined that use of PEG 3350 for longer than 7 days is unsafe for the consumer without supervision of a practitioner licensed by law (Gavis Comments at 003–004; Nexgen Comments at 6). Thus, they assert that because the prescription ANDA products are labeled for a longer duration of use with physician oversight, those products must be dispensed pursuant to prescription. They argue that because the PEG 3350 ANDAs are approved for prescription use, they should be allowed to remain on the market for those patients who need physician supervision (Gavis Comments at 003–004; Nexgen Comments at 8–9).

Furthermore, Nexgen and Gavis assert that the data submitted as part of the NDA for nonprescription MiraLAX support long-term use of the product, and withdrawing the prescription PEG 3350 ANDAs from the market would leave patients without a long-term option (see Gavis Comments at 004–005). Paddock and Nexgen claim that the data supporting the application for nonprescription use show that consumers taking PEG 3350 will experience increasing levels of effectiveness between 10 days and 1 month of use (Paddock Comments at 24; Nexgen Comments at 9; Nexgen Objection at 49–58). They believe this change in effectiveness over time is a material difference between the prescription and nonprescription products and shows that longer-term use with physician supervision is medically necessary (Nexgen Comments at 12; Paddock Comments at 20). Furthermore, Nexgen argues that the studies used to support the nonprescription MiraLAX NDA were conducted in chronically constipated patients and were designed to evaluate chronic use over the long term (Nexgen Comments at 14–15; Nexgen Objection at 49–58).

Nexgen also contends that FDA arbitrarily chose 7 days as a duration of use for the nonprescription MiraLAX product. This duration of use, Nexgen argues, was not based on FDA's medical judgment, but instead was a recommended time for OTC laxatives generally (Nexgen Comments at 7; Nexgen Objection at 56–57). Paddock agrees and claims that the statements in the NOOH are contrary to the recommendation in the TFM [12] on OTC laxatives (50 FR 2124 at 2131, January 15, 1985)), which states that ''constipation lasting more than 1 week could be a sign of a more serious condition for which proper diagnosis and treatment may be warranted. Therefore, the 1-week use limitation warning will be retained for bulk-forming laxatives as well as all other OTC laxative drug products,'' which Paddock believes indicates that the Agency found there to be a significant difference between 1- and 2-weeks duration of use (Paddock Comments at 22–23). Nexgen maintains that FDA must address at a hearing why it approved a 7-day duration of use consistent with the TFM in light of the NDA studies and literature (Nexgen Objection at 56–57). The ANDA holders' arguments regarding duration of use are not persuasive.

When FDA approved nonprescription MiraLAX, it considered the change from prescription to nonprescription to be complete, *i.e.,* no prescription indications remained. As set forth explicitly in the approved labeling, both the prescription and nonprescription products are indicated for occasional constipation, not chronic constipation, and the duration of use must be read in concert with that approved indication. Thus, FDA did not consider there to be any meaningful differences between the prescription and nonprescription labeling, and FDA considered any minor wording changes to simply be due to the different audiences (*i.e.,* learned intermediary versus lay consumer) and the difference in setting (*i.e.,* use with a physician's supervision versus consumer self-directed use).

Although the words ''or as directed by a physician'' in the prescription ANDA labeling may be interpreted as contemplating extended use, in the prescription setting a physician would have been involved in making that determination. Thus, according to the

[12] *See generally* 21 CFR part 330 (describing the public rulemaking process resulting in the establishment of standards (drug monographs) for an OTC therapeutic drug class).

labeling, a physician may choose, in his or her discretion as a medical professional, to prescribe the product for longer than 2 weeks. Contrary to the arguments posited by the ANDA holders, this recognition of physician discretion did not change the approved indication to chronic constipation. In any event, the nonprescription product also recognizes such discretion, so in that regard the products are the same, as well. Nonprescription MiraLAX describes a shorter duration of use and recommends seeing a physician if the patient needs to use a laxative for longer than 7 days, and, if so, a physician can direct the OTC consumer to continue using the product for a longer duration.

Although the studies supporting the approval of both the prescription and nonprescription versions of MiraLAX were of a longer duration than the duration of use for which the nonprescription product is labeled, when evaluating nonprescription labeling FDA determines what it believes to be the appropriate duration of use before recommending consumers seek assistance from a physician. The studies themselves are only one aspect of that determination. Furthermore, for approvals of both prescription and nonprescription products generally, long-term studies are often used to establish safety of the product. (See ''Guidance for Industry: Premarketing Risk Assessment,'' available at *https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126958.pdf*.) For nonprescription MiraLAX, the purpose of the longer duration of the studies was to assess the safety of the product for use in the OTC setting in which the potential exists for consumers to use the product repeatedly without consulting a physician.

FDA acknowledges that the study designs used in the trials that supported the change from prescription to nonprescription status were similar to study designs that could be used to support an indication of chronic idiopathic constipation, which is a long-term use indication that FDA would likely consider to be a prescription use. While the trials conducted to support the approval of MiraLAX as a nonprescription product were sufficiently long in duration to potentially have supported an indication for chronic idiopathic constipation (in addition to occasional constipation), such an indication was not sought by the sponsor. Because Braintree did not seek a chronic idiopathic constipation indication as a prescription product, and the ANDA prescription products were not approved for and are not labeled for that use, any argument that the studies support this use, or that their approvals should not be withdrawn because the product is used off-label, is irrelevant.

In determining whether a complete change from prescription to nonprescription status was appropriate, FDA found that there was no evidence in the three studies submitted in the MiraLAX NDA for nonprescription use that showed a different efficacy or safety profile in the treated population, compared with the studies that supported the prescription indication. With regard to the ANDA holders' assertions that the data supporting the nonprescription use demonstrates increased efficacy between 14 days and 1 month, the trials for the original prescription product were not designed to evaluate comparative efficacy over time. Therefore, there is no evidence from the studies that were used to support the approval of the prescription indication that establishes that MiraLAX is most effective when used for more than 7 days as the PEG 3350 ANDA holders claim. As to the longer-term studies supporting the nonprescription approval, as explained above, FDA considered the longer-term studies for nonprescription MiraLAX primarily to provide safety information. Specifically, these studies confirm that the drug would still be considered safe if a consumer chose to use it repeatedly before seeking advice from a physician. The studies cannot be used to support the assertions made by the PEG 3350 ANDA holders that the prescription product is most effective when used for a longer period of time. As reflected in their respective labeling, both products were expected to be effective in producing a bowel movement in less than 7 days, further confirming that there is no meaningful difference with respect to duration of use.

The ANDA holders also challenge decisions made during the course of FDA approval of OTC MiraLAX. They maintain that FDA's decision, made at the time of the OTC approval, to include a 7-day duration of use in the OTC labeling was arbitrary and was not based on FDA's medical judgment. As discussed above, the ANDA holders are not entitled to a hearing with regard to the decision to approve OTC MiraLAX or to decisions related to the content of the OTC label; those decisions are not at issue in this proceeding. Based on its studies and analyses submitted to support the nonprescription MiraLAX NDA, Braintree's proposed nonprescription labeling contained a 14-day duration of use, like the labeling for the prescription product. However, FDA, in conducting its own analysis, determined that the appropriate duration of use for the nonprescription MiraLAX product was 7 days with an instruction to consult a physician after that time. FDA determined that the 7-day duration of use was appropriate for a consumer self-medicating in the nonprescription setting and concluded that the nonprescription labeling should be consistent with earlier FDA determinations for other nonprescription laxatives. FDA issued a TFM for nonprescription laxative products in 1985. In this proposed regulation, the Agency agreed with the advisory panel regarding duration of use for laxatives in the OTC setting. The panel had previously stated that the reason for this recommendation is that a sudden change in bowel habits may be due to serious disease (*e.g.,* cancer, stricture), and the continued use of a laxative may delay diagnosis of such conditions. The panel is of the opinion that the available scientific evidence shows that very few indications warrant the use of any laxative beyond 1 week, except under the advice of a physician (40 FR 12902 at 12906, March 21, 1975). In the preamble to the TFM, FDA stated that ''the [A]gency considers the recommended 1-week limitation on the use of laxatives to be a necessary warning for the safe use of these products.'' (50 FR 2124 at 2130). This decision regarding the appropriate duration of use for laxative products in the OTC setting was not arbitrary, as the ANDA holders contend, but rather was based on FDA's scientific judgment regarding laxative products and its determination regarding how best to protect and promote the health of consumers using laxatives in the OTC setting. In any event, however, this decision regarding the OTC label was not based on any meaningful difference between the prescription and nonprescription products.

Gavis and Nexgen also attempt to fashion an argument out of a typographical error in the NOOH (Nexgen Comments at 5–6; Gavis Comments at 003–004). FDA wrote in the NOOH that the prescription indication is the following: ''This product should be used for 2 weeks or less as directed by a physician.'' The correct wording of the ANDA prescription labeling is, ''This product should be used for 2 weeks or less *or* as directed by a physician'' (emphasis added to indicate omitted word). Gavis and Nexgen both argue that FDA's conclusion that there is no meaningful difference is faulty because they contend that the Agency relied on the misstated indication for the prescription

PEG 3350 labeling. The Commissioner acknowledges that FDA unintentionally omitted the word ''or'' from the description of the ANDA prescription labeling in the NOOH. No meaning should be ascribed to this omission. FDA's analysis was based on the actual ANDA prescription labeling.

Nexgen also argues that the approval of nonprescription MiraLAX was an ''Initial Marketing of a Drug Product OTC'' and not an ''Rx to OTC Switch'' under the Center for Drug Evaluation and Research's Manual of Policies and Procedures (MAPP) 6020.5. Similar to their arguments described above, Nexgen contends that an ''Rx to OTC switch'' did not occur because the nonprescription MiraLAX has a different duration of use from the prescription product, which they suggest points to a meaningful difference between the two (Nexgen Comments at 16). Further, Nexgen accuses FDA of making an ''after-the-fact effort to revise or re-write the actual history relating to the OTC application and its review, apparently to rationalize its unfounded and unprecedented proposed enforcement action [withdrawing the PEG 3350 ANDAs]'' (Nexgen Comments at 17). Nexgen maintains that the switch of MiraLAX from prescription to nonprescription was not a complete switch because OTC MiraLAX was approved under a different NDA number, while, for other products, FDA has effectuated a partial switch with a new NDA and a complete switch with a supplemental NDA (Nexgen Objection at 44–46). Nexgen also maintains that the switch was not a complete switch because Breckenridge's prescription ANDA was approved only a few months prior to approval of OTC MiraLAX, Nexgen's prescription ANDA was approved 10 days prior to the approval of OTC MiraLAX, and the prescription MiraLAX NDA was not withdrawn until March 2009 (Nexgen Objection at 46).

These arguments have no validity. Nexgen's characterizations of FDA's actions are unfounded and incorrect. In assessing whether section 503(b)(4) allows the same active ingredient in products that are both prescription and nonprescription, FDA considers the products' approved indication, strength, route of administration, dosage form, and patient population and not the definitions in MAPP 6020.5 or MAPP processes that may have been followed prior to the approval. Facts related to the timing of a generic prescription PEG 3350 approval and the withdrawal of the prescription NDA likewise are not relevant to those considerations. While Braintree's NDA for nonprescription MiraLAX has a different NDA number, the issuance of a new NDA number is an administrative issue, which is irrelevant to the question of whether there is a meaningful difference between the prescription and nonprescription versions. Despite the difference in NDA numbers, FDA did consider the nonprescription MiraLAX NDA to be an ''Rx to OTC switch'' according to the MAPP.

In sum, the Commissioner has concluded that that there is not a meaningful difference between the prescription and nonprescription products based on the duration of use. The Commissioner does not find the arguments advanced by the PEG 3350 ANDA holders on this topic persuasive and is entering summary judgment against them.

2. Difference in Patient Populations

Nexgen, Gavis, and Paddock also submitted comments regarding the use of PEG 3350 in high-risk populations. They argue that their prescription approvals should not be withdrawn because, in their opinion, the supervision of a licensed practitioner is necessary for the safe and effective use of this drug in high-risk populations (Nexgen Comments at 26–30). They believe that patients in higher-risk populations cannot self-diagnose and self-treat their constipation. Therefore, they argue that the product should be dispensed upon a prescription and that a physician should be involved in the care of such patients (Paddock Comments at 24–26).

Furthermore, they do not believe that the nonprescription product can be used correctly by all of the patients that regularly use PEG 3350 and contend that eliminating the prescription version promotes self-medication by chronically ill individuals (Nexgen Comments at 47; Paddock Comments at 20). Specifically, they argue that the studies submitted to support the approval of MiraLAX for nonprescription use do not reflect how the product will be used in high-risk populations because high-risk subjects were excluded from the study population (Nexgen Comments at 21; Paddock Comments at 24). The studies excluded children and patients with a history of heart failure, diabetes, kidney failure, gastrointestinal disease, and surgeries or obstruction. Paddock argues that these groups represent large segments of the population who need laxative therapy (Paddock Comments at 24). In addition, Nexgen, Paddock, and Gavis note that subpopulations like children and the elderly require close monitoring when using laxatives and are at risk when taking a nonprescription product (Paddock Comments at 25; Gavis Comments at 007; Nexgen Comments at 31–33).

Finally, Nexgen notes that FDA failed to consider the needs of pediatric patients in its analysis. The prescription labeling stated that ''safety and effectiveness in pediatric patients has not been established''; whereas, the nonprescription labeling states, ''children 16 years of age or under: ask a doctor.'' Nexgen argues that the nonprescription labeling fails to consider that a physician's supervision is required for use in children. Nexgen also conjectures that by allowing Braintree to defer pediatric studies until 2016, FDA contemplated use of nonprescription MiraLAX in children (Nexgen Comments at 7–8).

FDA disagrees with the PEG 3350 ANDA holders' argument that there should be a prescription version of PEG 3350 available. As an initial matter, the ANDA holders' allegations regarding potential misuse by chronically ill individuals are simply a new iteration on their prior arguments about an off-label use of MiraLAX: Chronic constipation associated with these chronic illnesses. The data submitted by Braintree met the statutory and regulatory criteria for changing the product's status from prescription to nonprescription. In making this determination, FDA found that the product is safe and effective for use for self-medication as directed in the proposed nonprescription labeling. In this instance, and with all other nonprescription drug products, the labeling describes the patient population for which the product was found to be safe and effective, and suggests that other populations, such as children, should consult a physician. Nonprescription labeling is designed to assist consumers in appropriate self-selection and use. In addition, the nonprescription labeling is designed to instruct consumers regarding when they should seek the advice of a physician. Further, a physician is free to instruct a patient on how and whether to use a nonprescription product.

FDA disagrees with the contention that nonprescription MiraLAX is unsafe for use by elderly patients. In fact, the long-term clinical studies conducted to support the approval of MiraLAX as a nonprescription product enrolled a significant number of patients aged 65 years or older. In one study, 25 percent of the patients were over 65 years old, and in another study, 38 percent of

patients were over 65 years old.[13] The ANDA holders present their experts' observations related to the risk of MiraLAX use in the elderly but do not challenge the results of these studies. Furthermore, the risk information in the prescription labeling on geriatric use (''In geriatric nursing home patients a higher incidence of diarrhea occurred at the recommended 17 g dose. If diarrhea occurs MiraLAX should be discontinued'') is reflected in the risk information in the nonprescription ''Drug Facts'' label (''When using this product you may have loose, watery, more frequent stools; Stop use and ask a doctor if . . . [bullet] you get diarrhea''). Based on available data and information, FDA determined that the product is safe and effective for use in geriatric patients without a prescription if used as directed in the approved labeling and disagrees with Nexgen and Paddock's contentions that only having a nonprescription version available puts elderly patients at risk.

With regard to pediatric patients, the approved nonprescription MiraLAX labeling, like the prescription labeling, indicates that the product is for those 17 and older and explains that children under 16 should consult with a physician. No randomized, controlled studies were performed to properly assess the efficacy and safety of nonprescription MiraLAX in pediatric patients. In the absence of such data, it is common for nonprescription labeling to include age cutoffs and instruct consumers to talk to their doctor. Based on a particular patient's medical condition, a physician can choose to direct him or her on how to use a nonprescription product.

3. Difference in Labeling

Nexgen and Paddock also argue that removing the prescription PEG 3350 products from the market would deprive physicians of important information that is included in the prescription labeling but not in the nonprescription labeling. Nexgen argues that the quality of information provided in the prescription labeling and package insert is helpful in treating high-risk patients (Nexgen Comments at 21). Paddock notes that the package insert more fully discusses the efficacy, safety, and risk profile of PEG 3350 for long-term use and in high-risk patients (Paddock Comments at 20). Nexgen maintains that FDA's TFM for laxative products proposed to require professional labeling for OTC laxatives (Nexgen Objection at 72). These differences, they argue, constitute a meaningful difference between the products and require that prescription PEG 3350 remain on the market.

It is true that prescription labeling contains more detailed information than is included on nonprescription products (see §§ 201.57 and 201.66 (21 CFR 201.57 and 201.66)). However, when FDA determines that a product meets the statutory and regulatory criteria for changing its status from prescription to nonprescription, the new nonprescription labeling is designed for consumer use as per § 201.66. Prescription labeling is designed to inform medical practitioners and thus contains more information than OTC labeling. Such additional detail would not be appropriate or useful in the OTC setting. Because FDA considered the change from prescription to nonprescription status to be a ''full'' switch, the prescription labeling is no longer appropriate. The fact that the prescription labeling is more detailed does not establish a meaningful difference between the prescription and nonprescription versions.

The factors FDA generally considers in determining whether there is a meaningful difference are indication, strength, route of administration, population, and dosage form. As the labeling for the prescription and nonprescription PEG 3350 products shows, they have the same indication, strength, route of administration, population, and dosage form. As explained in the NOOH, if FDA were to include the differences between prescription and nonprescription labeling requirements as a factor in determining whether there is a meaningful difference sufficient to allow the same active ingredient to be marketed in prescription and nonprescription products, FDA would never be able to exempt a drug product from the prescribing requirements of section 503(b). This result would be in contravention of the plain language of section 503 of the FD&C Act and the purpose of Congress in enacting that provision. Further, Nexgen's contention that FDA proposed to require professional labeling for nonprescription laxatives in the TFM for those products fails to establish a meaningful difference between the prescription and nonprescription PEG 3350 products.[14]

4. Other Active Ingredients Marketed in Prescription and Nonprescription Drug Products Simultaneously

Nexgen and Paddock do not agree that the examples FDA cited in the NOOH of active ingredients that are simultaneously marketed in prescription and nonprescription drugs that FDA considers to be meaningfully different (ranitidine hydrochloride (HCl), omeprazole, and ibuprofen) can be distinguished from PEG 3350. In addition, Nexgen and Paddock identified other examples of active ingredients that are simultaneously marketed in prescription and nonprescription products (butenafine HCl, terbinafine HCl, cimetidine, and loperamide) that they believe are analogous to PEG 3350. They argue that all of the examples of active ingredients being simultaneously marketed for prescription and nonprescription uses have less significant differences in conditions of use than those between the prescription and nonprescription versions of MiraLAX (Paddock Comments at 2 and 21; Nexgen Comments at 49–53). Furthermore, Nexgen argues that in the examples FDA cited in its NOOH, each of the active ingredients has a prescription version because of a need for continued physician oversight to treat certain patient populations. In this way, they contend, those products are analogous to the prescription PEG 3350 products. Thus, they argue that the ANDA PEG 3350 approvals should be retained to ensure the intervention and supervision of a physician of certain patients for which physicians commonly prescribe PEG 3350 (geriatric patients, pediatric patients, patients with chronic constipation) and for whom a serious disease or condition is the cause of constipation. They argue that, although PEG 3350 is not approved for chronic use and pediatric patients, FDA must consider that PEG 3350 is commonly prescribed for these uses (Nexgen Comments at 49–50). Nexgen also argues that meaningful differences exist between the prescription and nonprescription labels of MiraLAX and ranitidine products because the prescription labeling for the prescription MiraLAX and ranitidine includes information describing dosing in elderly patients, while the OTC labeling for both products does not (Nexgen Comments at 50).

Nexgen and Paddock's arguments that FDA's determinations regarding whether there are meaningful differences between the prescription and nonprescription versions of ranitidine HCl, omeprazole, and

[13] Ruyi He, GI Team Leader AP Comments on NDA 22–015, dated August 14, 2006.

[14] Should a physician wish to access more detailed information about the efficacy, safety, and risk profile of nonprescription MiraLAX for long-term use and/or use in high-risk patients, such information is available in the medical literature.

ibuprofen do not support the conclusion that the prescription PEG 3350 products also have meaningful differences from nonprescription MiraLAX. Nexgen's and Paddock's meaningful difference arguments largely compare uses for which the ANDA holders assert PEG 3350 is commonly prescribed, but for which it is not approved, (*e.g.,* pediatric patients and patients with chronic constipation) with indications for which ranitidine HCl, omeprazole, and ibuprofen are approved. Because this proceeding to withdraw approval of the Rx PEG 3350 products focuses on whether such products as approved by FDA are meaningfully different than OTC MiraLAX, such arguments regarding unapproved uses of PEG 3350 are irrelevant in this proceeding. Other arguments are relevant to the issue of whether any laxative product should be approved OTC (*e.g.,* constipation may be caused by a serious underlying condition) and not relevant to the issue of whether there is a meaningful difference between the prescription and nonprescription products as approved by FDA.

The ANDA holders' reliance on FDA's decision to allow simultaneous prescription and nonprescription marketing of other active ingredients is misplaced because FDA makes these decisions on a case-by-case basis, based upon the merits of the individual application before the Agency. Nevertheless, the Commissioner will address the examples of simultaneous marketing raised by the ANDA holders. Furthermore, the permitted simultaneous prescription and nonprescription marketing of active ingredients, such as butenafine HCl (Mentax Rx and Lotrimin Ultra), terbinafine HCl (Lamisil), cimetidine, and loperamide are distinguishable from the prescription PEG 3350 products. Unlike MiraLAX, the differences in the cited examples are meaningful for the reasons set forth in this section. Moreover, none of the examples cited below rely upon duration of use alone to support the simultaneous marketing of Rx and OTC products. While some of the Rx and OTC products discussed below do have different durations of use, there is also an additional, more fundamental difference between the Rx and OTC products discussed below, such as different indication, patient population, or dose.

a. Butenafine HCl. The active ingredient, butenafine HCl, is an antifungal agent for which safety and efficacy have been established for the topical treatment of a variety of superficial dermal infections (tinea corporis, tinea cruris (jock itch), interdigital tinea pedis (athlete's foot), and tinea versicolor (a fungal infection of the skin resulting in small, discolored patches)) due to susceptible organisms. FDA considers some of these indications to require the involvement of a practitioner licensed by law and thus to meet the standard for requiring a prescription under section 503(b)(1) of the FD&C Act, while others do not. The active ingredient is marketed with the tradename Mentax as a prescription product, and with the tradename Lotrimin Ultra as a nonprescription product. The indications for the active ingredient butenafine HCl Rx and butenafine HCl OTC are set out in table 4.

TABLE 4—DIFFERENCES BETWEEN THE PRESCRIPTION AND NONPRESCRIPTION VERSIONS OF DRUG PRODUCTS WITH THE ACTIVE INGREDIENT BUTENAFINE HCl AND BUTENAFINE HCl

	Mentax (butenafine HCl) (Rx)	Lotrimin Ultra (butenafine HCl) (OTC)
Indication	Indicated for the topical treatment of the dermatologic fungal infection, tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *P. orbiculare*).	Indicated for the treatment of athlete's foot (tinea pedis) and jock itch (tinea cruris) in consumers 12 years and older. Consumers less than 12 years old are directed to ask a doctor.

Tinea versicolor, the prescription indication, is usually diagnosed based on a medical history and physical examination. The symptoms may resemble other skin conditions and require the expertise of a physician for diagnosis using an ultraviolet light or other professional diagnostic tools. In contrast, FDA considers the indication for the treatment of athlete's foot and/or jock itch to be conditions that a consumer can self-diagnose and self-treat.

Thus, FDA determined that the prescription indication requires the supervision of a practitioner licensed by law and meets the criteria at section 503(b)(1) of the FD&C Act, while the nonprescription indications did not meet the criteria at section 503(b)(1). Thus, the differences in the indications for the active ingredient, butenafine HCl creams are meaningful in that the conditions for which they are indicated require different levels of expertise to diagnose and treat.

b. Terbinafine HCl. The active ingredient terbinafine HCl is an antifungal agent that is administered either orally or topically. It is marketed as a prescription product under the tradename Lamisil Gel and as a nonprescription product under the tradename Lamisil Cream.[15] Like the last example, the indications for the two products are different as explained in table 5.

TABLE 5—DIFFERENCES BETWEEN PRESCRIPTION TERBINAFINE HCl AND NONPRESCRIPTION TERBINAFINE HCl

	Lamisil DermGel Rx	Lamisil Cream OTC
Indication	For the treatment of tinea (pityriasis) versicolor due to *M. furfur,* tinea pedis (athlete's foot), tinea corporis (ringworm) or tinea cruris (jock itch) due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum*.	For the treatment of athlete's foot (tinea pedis), tinea corporis (ringworm) and jock itch (tinea cruris) in consumers 12 years and older. Consumers less than 12 years old are directed to ask a doctor.

[15] The Rx Gel (NDA 20–846) has been discontinued.

As noted in table 5, the nonprescription version of Lamisil (cream) is used for the treatment of athlete's foot (tinea pedis), ringworm (tinea corporis), and jock itch (tinea cruris)—common conditions a consumer can self-diagnose and self-treat. The prescription version of Lamisil is indicated for the treatment of tinea versicolor, which requires the expertise of a physician to diagnose and treat (as discussed above). Similar to butenafine HCl discussed in section III.D.4.a., the differences in the indication of Rx versus OTC terbinafine HCl are meaningful in that the conditions for which they are indicated require different levels of expertise to diagnose and treat (as discussed above).

c. Loperamide. Loperamide is an oral antidiarrheal agent marketed under the trade name Imodium as a nonprescription product. Loperamide prolongs the transit time of the intestinal contents. It reduces fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Table 6 sets out the differences between the indication, dosage, and duration of use for loperamide Rx versus loperamide OTC.

TABLE 6—DIFFERENCES BETWEEN LOPERAMIDE Rx AND LOPERAMIDE OTC

	Loperamide Rx (Imodium) 2 milligram (mg) capsule	Loperamide OTC Loperamide (Imodium) 2 mg caplet
Indication	Indicated for the control and symptomatic relief of acute nonspecific diarrhea and chronic diarrhea associated with inflammatory bowel disease. It is also indicated for reducing the volume of discharge from ileostomies.	Used for the control of symptoms of diarrhea, including travelers' diarrhea.
Dose	The recommended daily dose in adults should not exceed 16 mg (8 capsules). In children, the dosing is based on age and weight range. Following the first treatment day, it is recommended that subsequent doses (1 mg/10 kg body weight) be administered only after a loose stool; total daily dosage should not exceed recommended dosages for the first day.	The recommended daily dose in adults and children over 12 years of age should not exceed 8 mg (4 capsules) in 24 hours. In children, the dosing is based on age and weight range (different from that of the Rx labeling).
Duration of Use	There is no specified limit in the duration of use	Patients are directed to stop use and ask a doctor if symptoms get worse or diarrhea lasts for more than 2 days.

Prescription loperamide is indicated for the control and symptomatic relief of acute nonspecific diarrhea and chronic diarrhea associated with inflammatory bowel disease and for reducing the volume of discharge from ileostomies. These conditions require the diagnostic skills and treatment intervention of a physician. In comparison, OTC loperamide is indicated for the treatment of diarrhea, including traveler's diarrhea, which can be self-diagnosed and treated. In addition, the total daily dose is 8 mg for OTC loperamide and 16 mg for Rx loperamide, and there are differences in dosing for children. Finally, the OTC version has a recommended duration of use of only 2 days, whereas the Rx version is used to treat chronic conditions for an unlimited period of time under the supervision of a physician.

The differences between Rx and OTC loperamide are meaningful in that the conditions for which they are indicated require different levels of expertise to diagnose and treat. In addition, they are dosed at different levels.

d. Cimetidine. Cimetidine is an oral H_2-receptor antagonist used mainly for treating acid-related gastrointestinal disorders. It is marketed as Tagamet. Table 7 sets out the differences between the dosage, indication, and duration of use for cimetidine Rx versus cimetidine OTC.

TABLE 7—DIFFERENCES BETWEEN CIMETIDINE Rx AND CIMETIDINE OTC

	Cimetidine Rx	Cimetidine OTC
Indication	Indicated for the treatment of acid-related gastrointestinal disorders such as gastroesophageal reflux disease (GERD) and duodenal ulcers.	Relief of heartburn associated with acid indigestion and sour stomach; prevention of heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain foods and beverages.
Dosage	200 mg–1600 mg as adjusted to individual patient needs	200 mg up to 2 times per day as needed to relieve heartburn.
Duration of Use	2–3 times per day for 4–12 weeks. Indication specific	No longer than 14 days unless directed by a physician.

The conditions for which cimetidine Rx is indicated require a physician for diagnosis and treatment; they cannot be self-diagnosed and are not appropriate for self-treatment. They are also treated at a significantly higher dose (*e.g.,* 400 to 1600 mg per day for 4 to 8 weeks; 800 mg twice a day for 12 weeks) and at a much longer duration (up to 12 weeks) than the OTC drug product with the same active ingredient.

Cimetidine OTC is indicated to relieve or prevent heartburn associated with acid indigestion and sour stomach that occurs after eating or drinking certain food or beverages, a condition that patients can self-diagnose and self-treat. Unlike cimetidine Rx, it is not indicated to be used on a regular dosing regimen to treat a permanent medical condition such as GERD or duodenal ulcers. Rather, the OTC product is used on an ''as needed'' basis to prevent or relieve a symptom, so consumers could take one or two doses (200 to 400 mg) on a day they experience heartburn. The OTC labeling limits use to no more than 2 weeks.

The Rx and OTC versions of cimetidine have meaningful differences in that the conditions for which they are indicated require different levels of expertise to diagnose and treat, and they

have different dosage strengths, durations of use, and indications.

e. Omeprazole. Omeprazole is a proton pump inhibitor used mainly for treating acid-related gastrointestinal disorders. It is marketed as PRILOSEC. Table 8 sets out the differences between the dosage, indication, and duration of use for omeprazole Rx versus omeprazole OTC.

TABLE 8—DIFFERENCES BETWEEN OMEPRAZOLE RX AND OMEPRAZOLE OTC

	Omeprazole Rx	Omeprazole OTC
Indication	Indicated for the treatment of conditions that require profound inhibition of gastric acid secretion, such as treatment of GERD and maintenance of healing of erosive esophagitis in both adult and pediatric patients, and especially the treatment of hypersecretory conditions.	Indicated for the treatment of frequent heartburn occurring 2 or more days a week.
Dosage	20 mg–60 mg. Indication specific	20 mg.
Duration of Use	Ranges from once daily for 4 weeks to an open-ended duration. Indication specific.	No more than 14 days and not more often than every 4 months unless directed by a physician.

The conditions for which Rx omeprazole is indicated require the supervision of a physician for diagnosis and treatment. Depending on the indication, treatment duration could be months and even years. In the particular instance of the treatment of symptomatic GERD, the recommended dose is 20 mg daily for up to 4 weeks and of the treatment of erosive esophagitis due to acid-mediated GERD, the recommended dose is 20 mg once daily for 4 to 8 weeks. The Rx version allows titrating upward to achieve efficacy, especially for pathological hypersecretory conditions.

On the other hand, omeprazole OTC is approved for the treatment of frequent heartburn (defined as occurring 2 or more days per week). This product is to be taken once a day (every 24 hours) every day for 14 days. The product labeling notes that it may take 1 to 4 days for full effect, although some people may get complete relief of symptoms within 24 hours. The consumer is instructed not to take the drug for more than 14 days or use more than one course every 4 months unless otherwise directed by a doctor.

The Rx and OTC versions of omeprazole have meaningful differences in that the conditions for which they are indicated require different levels of expertise to diagnose and treat, and they have different durations of use and indications.

f. Ranitidine HCl 150 mg. Ranitidine HCl is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is marketed as ZANTAC. It comes in a wide variety of strengths, but the 150 mg strength tablet is the only formulation that is marketed as both Rx and OTC. Table 9 sets out the differences between the dosage, indication, and duration of use for 150 mg ranitidine HCl Rx versus ranitidine OTC.

TABLE 9—DIFFERENCES BETWEEN RANITIDINE HCl RX AND RANITIDINE HCl OTC

	150 mg Ranitidine HCl Rx	150 mg Ranitidine HCl OTC
Indication	Pediatric patients (1 month to 16 years): Treatment of duodenal and gastric ulcers, maintenance of healing of duodenal and gastric ulcers, and treatment of GERD and erosive esophagitis. Adult patients: Multiple indications related to duodenal ulcer, gastric ulcer, GERD, erosive esophagitis, and pathological hypersecretory conditions.	Relieves heartburn associated with acid indigestion and sour stomach. Prevents heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain foods and beverages.
Dosage	Pediatric patients: Dose varies based on body weight; dose frequency is one to two times per day, depending on the indication. Adult patients: One to four times per day, depending on the indication.	Adults and children 12 years and over: To relieve symptoms, swallow 1 tablet with a glass of water. To prevent symptoms, swallow 1 tablet with a glass of water 30 to 60 minutes before eating food or drinking beverages that cause heartburn. Can be used up to twice daily (do not take more than 2 tablets in 24 hours). Children under 12 years: Ask a doctor.
Duration of Use	Indication specific. For most indications, duration is open-ended.	Stop use and ask a doctor if your heartburn continues or worsens or if you need to take this product for more than 14 days.

OTC ranitidine HCl is indicated for conditions that the patient may self-diagnose and self-treat and because of the ability to self-diagnose and self-treat, the dosing is on an ''as needed'' basis to prevent or relieve a symptom. For example, a consumer could take one or two doses (150 to 300 mg) on a day they experience heartburn. The OTC product limits time for which a consumer should use the product without consulting a doctor. In addition, the OTC product is only approved for use in adults and children 12 and over.

On the other hand, Rx ranitidine HCl is indicated for the treatment of more serious acid- related gastrointestinal disorders such as GERD and duodenal ulcers, which require a physician to diagnose. These conditions are chronic and require treatment over an extended period of time under the supervision of a physician. Further, the Rx ranitidine HCl is approved for use in children as young as 1 month old. Nexgen acknowledges that Rx ranitidine HCl remains approved because, among other reasons, it is indicated for much more severe medical conditions than the OTC ranitidine HCl (Nexgen Comments at

50). Nevertheless, Nexgen argues that the labeling for prescription PEG 3350 and ranitidine addresses use in elderly patients, which does not appear in the OTC labeling. Such labeling differences result from the differences in the labeling requirements for prescription (§ 201.57) and OTC (§ 201.66) products. Such differences were not set forth in the ANPRM or the NOOH for this proceeding as a factor that FDA would consider in determining that there is a meaningful difference such that the same active ingredient could be marketed in both a prescription and nonprescription product. Unlike OTC MiraLAX and Rx PEG 3350, the Rx and OTC versions of 150 mg ranitidine HCl have meaningful differences in that the conditions for which they are indicated require different levels of expertise to diagnose and treat, and they have different indications, durations of use, dosages, and indicated patient populations.

g. Ibuprofen. Ibuprofen is a nonsteroidal anti-inflammatory drug used as an analgesic for relief of symptoms of, including but not limited to, arthritis, fever, inflammation, and dysmenorrhea. Ibuprofen is marketed under multiple brand names, including ADVIL and MOTRIN, and comes in multiple dosage forms. Tables 10a and 10b set out the differences in indication, dosing, and duration of use of the 100 mg/5 mL suspension for Rx versus OTC use and the meaningful differences in the 400 mg Rx tablet and the 200 mg OTC tablet.

TABLE 10a—DIFFERENCES BETWEEN IBUPROFEN SUSPENSION Rx AND IBUPROFEN SUSPENSION OTC

	Ibuprofen 100 mg/5 mL suspension Rx	Ibuprofen 100 mg/5 mL suspension OTC
Indication	Pediatric Patients: For reduction of fever in patients aged 6 months up to 2 years of age. For relief of mild to moderate pain in patients aged 6 months up to 2 years of age. For relief of signs and symptoms of juvenile arthritis. Adult Patients: For treatment of primary dysmenorrhea. For relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.	Pediatric Patients (age 2–11): Relieves minor aches and pains due to the common cold, flu, sore throat, headache, and toothache. Reduces fever (stop use and ask a doctor if: Fever or pain gets worse or lasts more than 3 days)
Dosage	Pediatric Patients: Doses vary depending on the condition being treated, but the recommended maximum daily dose in treating any of the conditions is 40mg/kg. Adult Patients: The dose of ibuprofen oral suspension should be tailored to each patient, and may be lowered or raised from the suggested doses depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.	The dosage depends on the child's age and weight. An attached dosing chart informs the consumer how large of a dose the child should receive.
Duration of use	Ranges from as necessary to an open-ended daily dosage.	No more than 3 days unless directed by a doctor.

TABLE 10b—DIFFERENCES BETWEEN IBUPROFEN TABLET Rx AND IBUPROFEN TABLET OTC

	Ibuprofen 400 mg tablet Rx	Ibuprofen 200 mg tablet OTC
Indication	Indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, relief of mild to moderate pain, and treatment of primary dysmenorrhea.	Indicated for the temporary relief of minor aches and pains due to: Headache, minor pain of arthritis, backache, menstrual cramps, muscular aches, toothache, and the common cold. Indicated to temporarily reduce fever.
Dosage	Patients should use the lowest effective dose for the shortest duration consistent with patient treatment goals. After observing the response to initial therapy, the dose and frequency should be adjusted to suit an individual patient's needs. Do not exceed 3200 mg total daily dose. Rheumatoid arthritis and osteoarthritis suggested dosage: 1200 mg–3200 mg daily. Mild to moderate pain suggested dosage: 400 mg every 4 to 6 hours as necessary for relief of pain. Dysmenorrhea suggested dosage: 400 mg every 4 hours as necessary for relief of pain.	Adults and children 12 years and older, take one caplet every 4 to 6 hours while symptoms persist. If pain does not respond to one caplet, two caplets may be used. Do not exceed six caplets in 24 hours, unless directed by a doctor.
Duration of use	Shortest duration consistent with individual patient treatment goals.	Stop and ask a doctor if pain gets worse or lasts more than 10 days, or fever gets worse or lasts more than 3 days.

Both Rx ibuprofen forms allow for high doses to treat rheumatoid arthritis and juvenile arthritis, as well as other chronic conditions. The ibuprofen Rx suspension also allows for titration of doses to treat pain of varying severity in adults who cannot swallow pills and for pediatric patients depending on the severity of the symptoms. Neither Rx ibuprofen form limits the duration of use in patients. The labeled instructions to titrate the dosage and use the product for an unlimited duration support the necessity of physician oversight with both Rx ibuprofen forms.

On the other hand, the ibuprofen OTC suspension product has fixed age and weight range dosing divisions, does not exceed 15 mg/kg per dose, does not allow for dose titration, and limits use to 3 days. The ibuprofen OTC tablet label recommends a maximum daily dose of 1200 mg, whereas the ibuprofen

Rx tablet allowed for up to 3200 mg daily, for certain conditions. The ibuprofen OTC tablet also limits use to 3 or 10 days, for certain conditions. Finally, both OTC ibuprofen forms are indicated for less severe and non-chronic conditions. Because the ibuprofen 100 mg/5 mL suspension Rx and OTC products and the ibuprofen Rx and OTC tablet products differ in the indications, dosage, and durations of use depending upon the indication, they are meaningfully different.

Unlike the meaningful differences in the examples provided in section III.D.4, and for the reasons discussed in other parts of this section, FDA does not consider there to be a meaningful difference between the prescription PEG 3350 products and the nonprescription MiraLAX product. The Commissioner finds that the meaningful differences between the other active ingredients that are marketed in drug products that are both prescription and nonprescription products described in section III.D.4 are distinguishable from the nonmeaningful differences between the prescription PEG 3350 products and the nonprescription MiraLAX product. The examples cited by the PEG 3350 ANDA holders significantly differ in one or more of their indications, dosage, or target population. In addition to these differences, some also have a different duration of therapy. All of these drugs were initially approved as prescription products, and then subsequently the active ingredients were also approved for use in a nonprescription product for different indications, or sometimes a subset of, the prescription indications—unlike MiraLAX where no different prescription indications remain. By definition, prescription products are approved for use for indications for which consumers cannot self-diagnose or self-treat, thus requiring the supervision of a licensed practitioner, *i.e.,* the prescription standard in section 503(b) of the FD&C Act is met. In the case of nonprescription MiraLAX, it is not indicated for any conditions that consumers cannot self-diagnose or self-treat, and thus does not meet the standard in section 503(b) of the FD&C Act.

5. Other Objections

Other objections raised by the PEG 3350 ANDA holders regarding their contention that there is a meaningful difference between the prescription PEG 3350 products and nonprescription MiraLAX include those related to the wording of the indication, the exclusivity granted to Braintree, and the cost of OTC MiraLAX.

Gavis and Nexgen argue that the prescription ANDA PEG 3350 labeling states that the product is for the ''treatment'' of occasional constipation; whereas, nonprescription MiraLAX is for ''reliev[ing]'' occasional constipation. Gavis contends that nonprescription MiraLAX ''relieves'' constipation, rather than treating it, which is a meaningful difference requiring the prescription product to remain on the market (Gavis Comments at 006; Nexgen Objection at 66). Nexgen notes that ''treats'' and ''relieves'' may not be used interchangeably under FDA's regulation for OTC drug products at 21 CFR 330.1(i) (Nexgen Objection at 66). The NOOH explained that the approved OTC MiraLAX labeling uses the word ''relieves'' to ensure consistency with other OTC monograph laxative products. As noted, FDA, in considering whether there is a meaningful difference, compares the active ingredient, dosage form, strength, route of administration, indications, and patient population. In this case, because both the OTC and Rx products are indicated for occasional constipation, the different terms ''relieves'' and ''treats'' do not constitute a meaningful difference.

Paddock also argues that granting Braintree 3 years of exclusivity under section 505(j)(5)(F) of the FD&C Act indicates that there are meaningful differences between the prescription PEG 3350 labeling and the nonprescription MiraLAX labeling because the clinical data submitted to support nonprescription MiraLAX was in different populations (Paddock Comments at 2). In Paddock's opinion, 3-year exclusivity would only be authorized if the data were the result of ''new clinical investigations,'' which would indicate that nonprescription MiraLAX is different from the prescription PEG 3350 products (Paddock Comments at 6). It is true that Braintree conducted new clinical investigations to support its NDA for nonprescription MiraLAX. However, contrary to Paddock's contentions, the basis of approval for the prescription product consisted of two studies, 851–3 and 851–6, which demonstrated that at least one-third of subjects taking 17 g of MiraLAX per day have a bowel movement by Day 1, and at least three-fourths have a first bowel movement by Day 3. The three studies submitted in the nonprescription NDA, studies 851–CR1, 851–ZCC, and 851–CR3, did not show a different efficacy or safety profile in the treated populations when compared with the studies submitted in support of the prescription NDA (851–3 and 851–6). The three studies submitted with the nonprescription NDA simply provided evidence that nonprescription MiraLAX would be safe if used repeatedly over time in an OTC setting. As noted in section III.C.3, Braintree earned 3 years of exclusivity for the new clinical studies it conducted that supported approval of its OTC switch NDA. In the Commissioner's opinion, the fact that clinical data was necessary to provide assurance that nonprescription availability of the product was safe does not, in and of itself, support the contention that the product is meaningfully different from the previously approved prescription product. Sponsors of nonprescription drug products frequently perform additional studies that FDA concludes are essential to support a change from prescription to nonprescription status, such as actual use studies, for which they may receive exclusivity (if the statutory criteria for exclusivity are met).

Paddock also notes that removing the prescription PEG 3350 products from the market will nearly triple the cost of the product for the average insured patient (Paddock Comments at 2). Paddock maintains that this predicted cost increase is because consumers with insurance may pay less out of pocket for prescription drugs than for nonprescription drugs, and the exclusivity granted to Braintree for the nonprescription product would create a monopoly if all competing prescription products were withdrawn from the market (Paddock Comments at 30). Paddock and Nexgen argue that withdrawal of approval for prescription PEG 3350 products will reduce the availability of the products due to the absence of Medicaid and health insurance coverage (Nexgen Comments at 43; Paddock Comments at 30; Nexgen Objection at 41). Nexgen challenges FDA's conclusion in the draft order that cost is not a relevant consideration in this proceeding (Nexgen Objection at 42).

These arguments are irrelevant. In this instance, the prescription PEG 3350 products may no longer be lawfully marketed. In the ANPRM and NOOH, FDA set forth the factors it generally considers in determining whether the same active ingredient may be marketed in a prescription and nonprescription product: Issues related to the cost of drug products are not a relevant consideration.

Nexgen maintains that FDA should stay the withdrawal of the ANDAs pending the finalization of the TFM for OTC laxatives and FDA issuing a response on a pending citizen petition

submitted by Nexgen (Nexgen Objection at 78–82). According to Nexgen, its pending citizen petition requests that FDA find that the prescription MiraLAX NDA was not withdrawn for reasons of safety and efficacy and to declare Nexgen's prescription ANDA as the new RLD drug for prescription PEG 3350 products (Objection at 79). It is not necessary to finalize the TFM for OTC laxatives or to respond to Nexgen's pending citizen petition prior to the withdrawal of the ANDAs. As discussed elsewhere in this order, the OTC MiraLAX labeling is consistent with the TFM for OTC laxatives with respect to the use of the phrase ''relieves'' versus ''treats'' and the instruction to ''use no more than 7 days'' and ''Stop use and ask a doctor if . . . you need to use a laxative for longer than 1 week.'' However, this labeling does not change the factors relevant to determining whether there is a meaningful difference between the prescription and nonprescription PEG 3350 products. If an order is entered withdrawing the approval of the ANDAs, the issues raised in the citizen petition will be moot.

Nexgen complains that FDA largely based its draft proposed order on a January 2013 letter from Merck rather than more carefully reviewing and responding to each argument raised by the ANDA holders, rendering the order suspect (Nexgen Objection at 75–76). In fact, both the Merck letter and the draft proposed order were written in response to the issues and evidence submitted by the ANDA holders. The draft proposed order provided a lengthy analysis addressing the arguments and evidence submitted by the ANDA holders. The fact that the draft proposed order ultimately reached the same conclusion urged by the NDA holder (and the result proposed by CDER in the NOOH) does not render that order ''suspect.''

In sum, the Commissioner believes that the change in prescription to nonprescription status was a complete switch. In addition, the Commissioner concludes that there is not a meaningful difference between the prescription and nonprescription products approved by FDA based on the arguments discussed in this section. The Commissioner finds that the ANDA holders have failed to raise a genuine and substantial issue of fact regarding a meaningful difference between prescription and nonprescription MiraLAX that requires a hearing. The Commissioner does not find the arguments advanced by the PEG 3350 ANDA holders on the topics discussed in this section persuasive and is entering summary judgment against them.

IV. Findings and Order

Based upon the above, the Commissioner finds that the PEG 3350 ANDA holders have failed to raise a genuine and substantial issue of fact requiring a hearing in their responses to the NOOH. A hearing, therefore, is not required under § 12.24(b). The PEG 3350 ANDA holders did not submit any specifically identified reliable evidence demonstrating that a hearing is necessary. Other evidence submitted was not material to the issues in this proceeding. Even if the Commissioner were to accept these factual assertions as having some weight, such evidence does not present a sufficient area of disagreement to require an evidentiary hearing. Rather, the evidence is ''so one-sided that [FDA] must prevail as a matter of law.'' (See *Anderson* v. *Liberty Lobby, Inc.*, 477 U.S. 242, 252 (1986).)

In addition to finding that the ANDA holders have failed to raise a genuine and substantial issue of fact that requires a hearing, the Commissioner does not find the arguments advanced by the PEG 3350 ANDA holders persuasive and is entering summary judgment against them under § 314.200(g). There is no meaningful difference between the ANDA holders' PEG 3350 products and OTC MiraLAX. The labeling of the ANDA holders' PEG 3350 products is false and misleading because it bears the ''Rx only'' symbol when FDA has determined in approving OTC MiraLAX that the drug can be used safely and effectively in the nonprescription setting and does not meet the criteria for a prescription drug in 503(b)(1) of the FD&C Act. This false and misleading labeling was not corrected within a reasonable time after receipt of written notice from FDA. Therefore, under section 505(e) of the FD&C Act and under authority delegated to the Commissioner, the PEG 3350 ANDA holders' requests for a hearing are denied.

It is ordered, that pursuant to section 505(e) of the FD&C Act (21 U.S.C. 355(e)), that approval of the following ANDAs: ANDA 76–652 held by Kremers Urban Pharmaceuticals, Inc.; ANDA 77–736 held by Breckenridge Pharmaceutical, Inc.; ANDA 77–706 held by Nexgen Pharma, Inc. (formerly known as Anabolic Laboratories, Inc.); ANDA 77–893 held by Paddock Laboratories, LLC.; and ANDA 77–445 held by Teva Pharmaceutical, USA; and all amendments and supplements to them, be and hereby are withdrawn, effective May 2, 2018.

Dated: March 22, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–1141]

Mallinckrodt Inc. et al.; Withdrawal of Approval of Five New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of five new drug applications (NDAs) from multiple applicants. The holders of the applications notified the Agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Approval is withdrawn as of May 2, 2018.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6248, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications under the process in § 314.150(c) (21 CFR 314.150(c)). The applicants have also, by their requests, waived their opportunity for a hearing. Withdrawal of approval of an application or abbreviated application under § 314.150(c) is without prejudice to refiling.

Application No.	Drug	Applicant
NDA 006383	Methadone Hydrochloride (HCl) Powder, 50 grams (g)/bottle, 100 g/bottle, and 500 g/bottle.	Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, MO 63042.