Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: March 20, 2014.

Jill Hartzler Warner,

Acting Associate Commissioner for Special Medical Programs.

[FR Doc. 2014–06766 Filed 3–26–14; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2011–N–0021]

AbbVie Inc., et al.; Proposal To Withdraw Approval of Abbreviated New Drug Applications for Prescription Pain Medications Containing More Than 325 Milligrams of Acetaminophen; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity to request a hearing on the Agency's proposal to withdraw approval of abbreviated new drug applications (ANDAs) from multiple sponsors for prescription pain medications containing more than 325 milligrams (mg) of acetaminophen. The basis for this proposal is that the Agency has determined that fixed-combination prescription drugs containing more than 325 mg of acetaminophen per dosage unit (tablet or capsule) do not provide a sufficient margin of safety to protect the public against the serious risk of acetaminophen-induced liver injury.

DATES: Submit written requests for a hearing by April 28, 2014; submit data and information in support of the hearing request by May 27, 2014.

ADDRESSES: Identify your requests for a hearing, supporting data, and other comments with Docket No. FDA–2011–N–0021 and submit this information to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Rachel Turow, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6236, Silver Spring, MD 20993–0002, 301–796–5094.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 14, 2011 (76 FR 2691), FDA published a notice announcing its plans to reduce the maximum dosage unit strength of acetaminophen in prescription drug products. The notice announced FDA's conclusion that, based on a reevaluation of the relative risks and benefits of prescription acetaminophen products, fixed-combination prescription drugs containing more than 325 mg of acetaminophen per dosage unit (tablet or capsule) do not provide a sufficient margin of safety to protect the public against the serious risk of acetaminophen-induced liver injury. Accordingly, we asked product sponsors to limit the maximum amount of acetaminophen per dosage unit to 325 mg and, for those products containing more than 325 mg of acetaminophen per dosage unit, to submit requests that FDA withdraw approval of their applications under § 314.150(d) (21 CFR 314.150(d)). FDA asked that all such requests be made before January 14, 2014, after which date the Agency would use its authority under section 505(e) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(e)) to initiate approval withdrawal proceedings for any prescription drug products containing more than 325 mg of acetaminophen per dosage unit that remain on the market. The full text of that notice is provided in this document, and provides a detailed description and analysis of the specific facts resulting in today's action.

FDA did not receive a request for withdrawal of approval of an application containing more than 325 mg of acetaminophen per dosage unit from one sponsor. In addition, FDA received requests for withdrawal of approval of applications for products containing more than 325 mg of acetaminophen per dosage unit for which sponsors either submitted requests under § 314.150(c) or failed to cite a relevant regulatory provision. FDA contacted all of these sponsors on multiple occasions to ask that they submit a request that FDA withdraw approval of their applications under § 314.150(d), but they failed to respond.

With respect to those applications for which FDA received no request for withdrawal, FDA is proceeding under § 314.150(a) and (b) to withdraw approval. With respect to requests for withdrawal of approval submitted under § 314.150(c), the Agency notes that because FDA has made a determination under § 314.150(a) that approval of these applications should be withdrawn for reasons of safety, application holders may not withdraw their applications pursuant to § 314.150(c). The text of § 314.150(c) expressly precludes withdrawal of an application under the subsection if FDA has made a safety determination under § 314.150(a). Similarly, when a request for withdrawal is made without a citation to any regulation, FDA is not appropriately notified that an application holder has voluntarily waived the opportunity for a hearing. Accordingly, FDA has determined to proceed with withdrawal of approval of applications for which sponsors either submitted requests under § 314.150(c) or failed to cite a relevant regulatory provision pursuant to the withdrawal procedures outlined in §§ 314.150 (a) and (b).

Table 1 lists the applications for products for which FDA received no request for withdrawal, a request for withdrawal citing § 314.150(c), or a request for withdrawal with no regulatory citation.

TABLE 1—APPLICATIONS FOR FIXED-COMBINATION PRESCRIPTION DRUGS CONTAINING MORE THAN 325 MG OF ACETAMINOPHEN PER DOSAGE UNIT THAT HAVE NOT BEEN VOLUNTARILY WITHDRAWN AS OF JANUARY 14, 2014

Application No.	Drug product(s)	Applicant or holder	Reason
ANDA 40117	Vicodin HP (Acetaminophen and Hydrocodone Bitartrate Tablets), 660 mg/10 mg.	AbbVie Inc., 1 N. Waukegan Rd., North Chicago, IL 60064.	Submitted a voluntary request for withdrawal under § 314.150(c).
ANDA 88058	Vicodin (Acetaminophen and Hydrocodone Bitartrate Tablets), 500 mg/5 mg.	AbbVie Inc	Submitted a voluntary request for withdrawal under § 314.150(c).
ANDA 89736	Vicodin ES (Acetaminophen and Hydrocodone Bitartrate Tablets), 750 mg/7.5 mg.	AbbVie Inc	Submitted a voluntary request for withdrawal under § 314.150(c).

TABLE 1—APPLICATIONS FOR FIXED-COMBINATION PRESCRIPTION DRUGS CONTAINING MORE THAN 325 MG OF ACETAMINOPHEN PER DOSAGE UNIT THAT HAVE NOT BEEN VOLUNTARILY WITHDRAWN AS OF JANUARY 14, 2014—Continued

Application No.	Drug product(s)	Applicant or holder	Reason
ANDA 89166	SYNALGOS–DC–A (Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Capsules), 356.4 mg/30 mg/16 mg.	Leitner Pharmaceuticals LLC, 340 Edgemont Ave., Bristol, TN 37620.	Did not submit a voluntary request for withdrawal.
ANDA 40366	Acetaminophen and Hydrocodone Bitartrate Oral Solution, 500 mg/15 mL; 7.5 mg/15 mL.	Nesher Pharmaceuticals USA LLC, 13910 St. Charles Rock Rd., Bridgeton, MO 63044.	Submitted a voluntary request for withdrawal under § 314.150(c).
ANDA 40182	Acetaminophen and Hydrocodone Bitartrate Oral Solution, 500 mg/15 mL; 7.5 mg/15 mL.	Pharmaceutical Associates, Inc., 201 Delaware St., Greenville, SC 29605.	Submitted a voluntary request for withdrawal, but failed to cite the appropriate regulatory provision.
ANDA 40825	Acetaminophen and Hydrocodone Bitartrate Tablets, 500 mg/5 mg.	Ranbaxy Laboratories Inc., C/O Ranbaxy Inc., 600 College Rd. East, Princeton, NJ 08540.	Submitted a voluntary request for withdrawal, but failed to cite the appropriate regulatory provision.
ANDA 40824	Acetaminophen and Hydrocodone Bitartrate Tablets, 500 mg/10 mg.	Ranbaxy Laboratories Inc., C/O Ranbaxy Inc., 600 College Rd., East, Princeton, NJ 08540.	Submitted a voluntary request for withdrawal, but failed to cite the appropriate regulatory provision.
ANDA 40822	Acetaminophen and Hydrocodone Bitartrate Tablets, 750 mg/7.5 mg.	Ranbaxy Laboratories Ltd., C/O Ranbaxy Inc., 600 College Rd. East, Ste. 2100, Princeton, NJ 08540.	Submitted a voluntary request for withdrawal, but failed to cite the appropriate regulatory provision.
ANDA 040637.	Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Tablets, 712.8 mg/60 mg/32 mg.	West-Ward Pharmaceutical Corp., 435 Industrial Way West, Eatontown, NJ 07724.	Submitted a voluntary request for withdrawal, but failed to cite the appropriate regulatory provision.

Under section 505(e) of the FD&C Act (21 U.S.C. 355(e)) and § 314.150(a) (21 CFR 314.150(a)), and under authority delegated to her by the Commissioner of Food and Drugs, the Director, Center for Drug Evaluation and Research (CDER), has evaluated the information discussed in this notice and in the January 14, 2011, **Federal Register** notice and, on the grounds stated, is proposing to withdraw approval of the applications listed in table 1 of this document and all amendments and supplements thereto for unit dose strengths greater than 325 mg. This proposal is made on the grounds that, based on consideration of new evidence together with the evidence available to FDA when the applications were approved, the drugs are no longer safe for use under the conditions of use upon the basis of which they were approved.

Therefore, in accordance with section 505(e) of the FD&C Act and §§ 314.150 and 314.200 (21 CFR 314.150(a) and 314.200)), notice is given to the holders of the ANDAs listed in table 1, and to all other interested persons, that FDA is hereby providing the holders the opportunity to request a hearing to show why approval of the applications listed should not be withdrawn.

Any holder that decides to seek a hearing must file: (1) On or before April 28, 2014, a written notice of appearance and request for a hearing; and (2) on or before May 27, 2014, the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of material fact that requires a hearing to resolve, as specified in § 314.200.

Any other interested person may also submit comments on this notice on or before May 27, 2014. The procedures and requirements governing this notice of opportunity for a hearing, notice of participation and request for a hearing, information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 and in 21 CFR part 12.

The failure of a holder to file a timely written notice of participation and request for a hearing, as required by § 314.200, constitutes an election by that holder not to avail itself of the opportunity to request a hearing concerning the action proposed and constitutes a waiver of any contentions concerning the legal status of that holder's drug products. In such instance, FDA intends to withdraw approval of the applications and to take other appropriate action. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

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

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

The following is the text of the January 14, 2011, **Federal Register** notice entitled ''Prescription Drug Products Containing Acetaminophen; Actions to Reduce Liver Injury From Unintentional Overdose.''

I. Acetaminophen Drug Products and Liver Injury

Acetaminophen is the generic name of a drug used in many over-the-counter (OTC) oral pain-relievers such as Tylenol, and in prescription combination drug products such as Vicodin and Percocet. Acetaminophen is one of the most widely used drugs in the United States in both prescription and OTC products. This notice applies only to acetaminophen-containing drug products that are labeled for prescription use and marketed under approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs). OTC acetaminophen drug products are not affected by this notice.[1]

[1] FDA continues to monitor the occurrence of adverse events associated with both prescription

Continued

All acetaminophen-containing prescription products are combinations with other drug ingredients, primarily opioids in various strengths. These other drug ingredients include the opioids hydrocodone bitartrate (e.g., Vicodin), oxycodone hydrochloride, (e.g., Percocet), codeine phosphate (e.g., Tylenol with Codeine), dihydrocodeine, tramadol hydrocholoride, and pentazocine hydrochloride, as well as butalbital (a barbiturate) and caffeine (a stimulant).[2] General references to ''acetaminophen combinations'' or ''acetaminophen combination products'' in this notice refer to all such products. There are no prescription drug products that contain only acetaminophen.

Prescription combination drugs account for approximately 20 percent of the total acetaminophen drug market, and include some of the most widely prescribed and sold prescription drug products in the United States. (The remaining 80 percent of the acetaminophen drug market consists of OTC products.) Acetaminophen-hydrocodone combinations account for more than half of all prescriptions for acetaminophen combination drug products in the United States, and for many years, have also been the most-prescribed products in the U.S. retail market (Ref. 1). Unlike other drugs commonly used to reduce pain and fever (e.g., nonsteroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, and naproxen), at recommended doses acetaminophen does not cause gastro-intestinal discomfort and/or bleeding. However, despite its wide use, long acceptance, and therapeutic utility, acetaminophen does pose risks. Acetaminophen overdose can cause liver damage (hepatotoxicity), ranging in severity from abnormalities in liver function to acute liver failure (ALF), and even death (Ref. 1). Acetaminophen overdose has become the leading cause of ALF as well as a leading cause of death from ALF in the United States (Refs. 2–4). Based on extrapolation from regional results in the first population-based study of ALF conducted in the United States, an estimated national total of 1,600 cases of ALF may occur each year (Ref. 3).

Acetaminophen-induced liver injury is caused by the effects of a toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI) that is produced when acetaminophen is broken down by the body (Ref. 5). With low doses of acetaminophen, the amount of NAPQI produced is low and an individual's body usually has sufficient intracellular glutathione levels to bind to the NAPQI and prevent toxicity (Ref. 6). With higher acetaminophen levels and greater NAPQI production, NAPQI binds to liver proteins, causing cellular injury that can lead to liver failure and death (Refs. 4, 7).

The likelihood and severity of liver injury is influenced by the amount of acetaminophen that is ingested and the ability of an individual's liver to effectively remove it from the body. In most cases, glutathione levels are more than sufficient to conjugate the small amount of NAPQI produced by therapeutic doses of acetaminophen (Ref. 6). However, some people may have increased risk for liver injury following exposure to therapeutic doses or overdoses of acetaminophen due to reduced glutathione stores, induced cytochrome P450 enzymatic activity, or states of oxidative stress. Increased risk may be associated with a wide variety of conditions, such as Acquired Immune Deficiency Syndrome, chronic alcoholism, acute excess alcohol use, and use of anticonvulsant or antituberculosis medications (Refs. 8–9). Acetaminophen poisoning is treated with the drug N-acetylcysteine (NAC), which helps prevent toxicity by inactivating NAPQI. However, NAC does not reverse liver cell damage that has already occurred (Ref. 10).

The public health burden of acetaminophen-associated overdoses has been estimated using data from a variety of national databases and other resources.[3] A summary of data from four different surveillance systems indicates that there were an estimated 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths per year related to acetaminophen-associated overdoses during the 1990s (Ref. 10). Within these estimates, unintentional acetaminophen overdose accounted for nearly 25 percent of the emergency department visits, 10 percent of the hospitalizations, and 25 percent of the deaths (Ref. 10).

Prescription products contribute significantly to the toll of liver damage from both unintentional and intentional acetaminophen overdoses. For example, in the study of ALF patients by Larson et al., 63 percent of the unintentionally overdosed subjects and 18 percent of intentionally overdosed subjects had taken prescription acetaminophen combination products prior to injury (Ref. 4). According to data from the Toxic Exposure Surveillance System (now named the National Poison Data System (NPDS)), 30 percent of all acetaminophen-associated calls to poison centers in 2005 involved prescription acetaminophen combination products (41,999 of 138,602 calls). Prescription acetaminophen combination products were involved in approximately 44 percent of acetaminophen-associated calls that resulted in serious injury (1,470 of 3,310 calls) and 48 percent (161 of 333 calls) of acetaminophen associated calls that resulted in fatalities (Ref 11).[4]

In addition, there is a high incidence of cases of unintentional acetaminophen overdose, which should be preventable. In a population-based study of ALF conducted in the United States, 45 percent of adult ALF cases were associated with acetaminophen use and 55 percent of those were related to unintentional overdose (Ref. 3). In another study, similarly, approximately half of the cases of acetaminophen-induced ALF were due to unintentional overdose (Ref. 4).

There is no single factor that accounts for the high incidence of unintentional acetaminophen overdose. Multiple distinct factors appear to contribute to the problem, including the following:

- Given the large number and wide array of OTC and prescription acetaminophen products and indications, consumers may unintentionally overdose by taking more than one acetaminophen product at the same time without realizing that acetaminophen is a common ingredient.
- Patients may be unaware that their prescription pain relief products contain

and OTC acetaminophen products. Any action relating to additional safety measures for OTC acetaminophen products will be taken separately from this notice, through rulemaking as part of the ongoing OTC monograph proceeding for internal analgesic drug products.

[2] The opioid ingredient propoxyphene has also been widely used in combination with acetaminophen under the brand name Darvocet as well as in many generic products. On November 19, 2010, FDA announced that Darvocet was being voluntarily withdrawn from the market at FDA's request due to significant safety concerns about propoxyphene. FDA also requested that makers of generic propoxyphene-acetaminophen combination products withdraw their products from the market. Additional information about the status of propoxyphene-containing drug products can be found on FDA's Web site at *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm233800.htm*.

[3] These include, among others: Emergency department data from the National Electronic Injury Surveillance System All Injury Program and the National Hospital Ambulatory Medical Care Survey-Emergency Department; hospitalization data from the National Hospital Discharge Survey; and mortality data from the National Multiple Cause of Death File.

[4] The NPDS data include all acetaminophen-related calls, including calls relating to both prescription and OTC products, and calls that do not involve liver damage. ''Serious injury'' includes, but is not limited to, serious liver damage caused by acetaminophen.

acetaminophen because the ingredient is often identified on pharmacy drug containers only as ''APAP,'' an acronym based on the chemical name of acetaminophen (N-acetyl-para-aminophenol), or by an abbreviation such as ''ACET.'' Such terms are not generally understood by the public to mean that a product contains acetaminophen.

- Patients may take more than the maximum number of labeled or prescribed doses seeking additional therapeutic benefit, unaware that they are taking too much acetaminophen.
- Experts agree that taking a large amount of acetaminophen over a short period of time causes liver injury, but a specific threshold dose for toxicity has not been established and may not be the same for all persons. Based on available information, we cannot currently identify all of the factors that might increase an individual's risk of acetaminophen toxicity, particularly at doses near the current recommended total daily dose of 4,000 mg per day (Refs. 5 and 7).
- NAC, the antidote for acetaminophen poisoning, is most effective when given in the first 8 hours after an acute overdose and has been shown to have benefit up to 24 hours and possibly later (Ref. 10). Victims of unintentional acetaminophen overdose may not be treated within that time because the symptoms of liver damage can take several days to emerge, even in severe cases, and are not readily associated by patients or clinicians with acetaminophen poisoning (Ref. 5).
- Patients do not realize that acetaminophen can cause severe liver injury if the recommended dose is exceeded. In 2004, FDA launched a public education program to help inform consumers about the potential for acetaminophen to cause liver injury. Since that time, FDA has provided materials for use in a wide variety of media and tailored for users of both prescription and OTC acetaminophen products. The continued occurrence of liver injury associated with prescription acetaminophen combinations notwithstanding those efforts suggests that additional interventions are needed.

II. FDA's Acetaminophen Safety Initiatives

FDA has been working to reduce the incidence of acetaminophen-related liver injury since the early 1990s, when the scope of the problem began to become evident. In addition to the scientific activities described in section I of this document, we have been active in acetaminophen safety education for consumers and health care professionals. In particular, we are currently working with the National Association of State Boards of Pharmacy, to urge state authorities to adopt rules replacing the term ''APAP'' and other abbreviations with ''acetaminophen'' on pharmacy containers. Our dedicated Web page on acetaminophen safety provides access to educational information along with links to additional scientific and regulatory resources. This information can be viewed at *http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm.*

Most importantly, as the Federal Agency responsible for the science-based regulatory oversight of drug products, we have continued to identify and pursue additional regulatory measures to reduce the risk of acetaminophen-induced liver injury. Rulemaking initiatives to date have focused largely on OTC acetaminophen products under our ongoing monograph proceeding for OTC internal analgesic, anti-inflammatory and antipyretic drug products. In 2002, we conducted a comprehensive review of the available data on acetaminophen and liver injury. The data were presented for consideration by the Non-Prescription Drug Advisory Committee (2002 Advisory Committee)[5] whose members unanimously agreed that the evidence of risk associated with the unintentional overdose of acetaminophen warranted labeling changes.[6] The 2002 Advisory Committee also considered whether a lower dose that would be safe for alcohol users or other sensitive subpopulations could be identified, but concluded that current data were insufficient for this purpose.[7] Based in part on the 2002 Committee's recommendations, in 2009 the Agency issued a new final rule requiring specific liver injury warnings and related labeling for OTC acetaminophen drugs (final rule, 74 FR 19385, April 29, 2009 and technical amendment, 74 FR 61512, November 25, 2009).

In 2007, the Director of CDER convened a multidisciplinary working group in CDER to update, review, and report on the full range of medical data and to propose additional regulatory options for both prescription and OTC acetaminophen drug products. On June 29 and 30, 2009, FDA held a joint meeting of the Drug Safety and Risk Management Advisory Committee, the Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee (2009 Advisory Committee) to consider the collected data and related public testimony and make recommendations concerning further regulatory options for both prescription and OTC acetaminophen drugs. Detailed information on the 2009 Advisory Committee's deliberations and the evidence it considered are available on FDA's Web site at *http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm.* After reviewing and discussing the evidence presented, the 2009 Advisory Committee recommended a range of additional regulatory actions such as adding a boxed warning to prescription acetaminophen products, withdrawing prescription combination products from the market, or reducing the amount of acetaminophen in each dosage unit.[8]

FDA has determined that reducing the dosage unit strength of acetaminophen in prescription products is necessary to reduce the risk of liver injury associated with prescription acetaminophen combinations, and to ensure safe use of acetaminophen combinations. FDA is issuing this notice as the first step towards implementing this change. In deciding to take this step, we considered the 2009 Advisory Committee's recommendations and the Agency's evaluation of the available

[5] Meeting of the Non-Prescription Drug Advisory Committee with members from the Anesthetic and Life Support Drugs Advisory Committee, Arthritis Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Gastrointestinal Drugs Advisory Committee, September 19 and 20, 2002, (2002 Advisory Committee). Detailed information on this meeting can be viewed electronically at *http://www.fda.gov/ohrms/dockets/ac/cder02.htm#NonprescriptionDrugs.*

[6] 2002 Advisory Committee Transcript, September 19, 2002, discussion at 160–182.

[7] 2002 Advisory Committee Transcript, *supra* at 182–221.

[8] Among other recommendations, 24 of the 37 Advisory Committee members recommended reducing the amount of acetaminophen per single adult dose in OTC products to 650 milligrams per dose (i.e., two 325 mg tablets or capsules). With respect to prescription products, the Advisory Committee overwhelmingly voted to require a boxed warning for prescription acetaminophen combinations, and slightly more than half favored eliminating prescription acetaminophen combinations entirely (with the option of prescribing single-entity opioids instead). While not offered as a voting option, the alternative of reducing the amount of acetaminophen per dosage unit in prescription combination products was recommended by a number of Advisory Committee members. See FDA, Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee To Address the Public Health Problem of Liver Injury Related to the Use of Acetaminophen in Both Over-the-Counter and Prescription Drugs, June 30, 2009, at 658–672 (Vote on Question 2), 771–801 (Vote on Question 7), 802–842 (Vote on Question 9 and Discussion of Question 11).

data on both prescription and OTC products. The data and the 2009 Advisory Committee's recommendations on OTC products are relevant to prescription acetaminophen combinations for several reasons. The mechanism of acetaminophen-related liver injury is the same for both OTC and prescription drug products. In addition, while the range of acetaminophen strengths is much greater for prescription than for OTC products, the most widely used acetaminophen dosage unit in both prescription and OTC products is 500 mg. All acetaminophen products likewise share the same maximum recommended daily dose (4,000 mg). As a result, our safety evaluation of prescription acetaminophen products draws on the common body of evidence and expert advice about all acetaminophen products, as well as important factors that are specific to the prescription products and how they are used.

III. FDA's New Safety Measures for Prescription Acetaminophen Drug Products

A. Safety Labeling Changes

Consistent with the advice of the 2009 Advisory Committee, FDA today is issuing letters to holders of approved NDAs and ANDAs (if the same drug approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(b)) is not currently marketed) for prescription acetaminophen drugs, notifying them of the need to modify the labeling of prescription acetaminophen drugs to reflect new safety information about acetaminophen and liver toxicity. Our authority for this action is section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which was added to the FD&C Act by the Food and Drug Administration Amendments Act of 2007. This provision authorizes FDA to require certain holders of approved new drug applications to make safety-related labeling changes based on new safety information that becomes available after approval of the drug.[9]

The letters issued today propose that the sponsors of prescription acetaminophen drugs make various modifications to their drugs' approved labeling, including adding the following as a boxed warning:

Hepatotoxicity

[DRUG NAME] contains acetaminophen and [INGREDIENT]. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, often in combination with other acetaminophen-containing products.

The safety labeling changes will be required for all prescription drug products containing acetaminophen. In accordance with section 505(o)(4)(B) of the FD&C Act, within 30 days of the date of the letters, the holders of approved applications for prescription acetaminophen drugs must submit to FDA a supplement proposing labeling changes that reflect the new safety information about acetaminophen and liver toxicity, or a statement detailing the reasons why such a change is not warranted.

However, we do not believe that these safety labeling changes alone will adequately address the ongoing problem of liver injury associated with prescription acetaminophen combinations. Accordingly, we are taking additional steps to reduce the amount of exposure to acetaminophen from these products, as described in the following discussion.

B. Limiting the Amount of Acetaminophen in Prescription Combination Products

1. How and Why We Are Limiting Acetaminophen Content

In light of the information described previously, we have re-evaluated the relative risks and benefits of prescription acetaminophen products and have concluded that acetaminophen prescription drugs containing more than 325 mg of acetaminophen per dosage unit (tablet or capsule) do not provide a sufficient margin of safety to protect the public against the serious risk of acetaminophen-induced liver injury. Accordingly, we are asking product sponsors to limit the maximum amount of acetaminophen per dosage unit of the combination product (''acetaminophen strength'') to 325 mg. We are basing this change on multiple considerations, including the following:

- The significant contribution made by prescription products to the continued and unacceptably high incidence of acetaminophen-related liver injury;
- The need to establish an adequate margin of safety given the current inability to identify precise toxicity thresholds and/or specific populations for whom currently recommended dosages are not safe;
- The high potential for unintentional overdosing; and
- The lack of evidence from which to conclude that the benefit of increased pain relief or dosing convenience from higher acetaminophen strengths outweighs the risk of liver damage from unintentional overdose.

The intended effect of reducing the amount of acetaminophen to 325 mg per dosage unit is to reduce the potential for exceeding the toxic threshold of the drug that could cause liver injury. This change is intended to reduce the risk of unintentional acetaminophen overdose by providing an additional margin of safety for all users, including individuals who, for a variety of reasons (e.g., existing liver disease, chronic alcohol use) are particularly susceptible to liver injury from acetaminophen. The change is consistent with the fundamental principle that the benefit-to-risk ratio of a drug must be considered in determining safety and effectiveness, and the safety of a drug can only be established if its benefits outweigh its known and potential risks. Additionally, as discussed in the following section, many acetaminophen combinations are already approved at the 325-mg acetaminophen strength and thus can provide a basis for further generic approvals at the new maximum dosage unit strength.

It is not possible, based on currently available information, to quantify precisely to what extent reducing the maximum acetaminophen strength of acetaminophen combination drugs will reduce the incidence of liver injury. However, data from Larson et al. (Ref. 4) suggest that the effect could be considerable. In that study, the median dose of acetaminophen taken by 77 people with an unintentional overdose was 7,500 mg per day. Assuming that they took 500 mg tablets (currently the most common prescription and OTC dosage strength), the total median dose for this group from taking the same number (15) of 325-mg tablets or capsules would have been only 4,875 mg, a level at which death or liver failure is unlikely to occur in most people.

2. How FDA Is Implementing the Limitation on Acetaminophen Strength

We have identified prescription acetaminophen drug products and product sponsors potentially affected by this notice based on information in the list of *Approved Drug Products With Therapeutic Equivalence Evaluations*

[9] Section 505(o)(4) of the FD&C Act also establishes the procedures for implementing safety labeling changes. The procedures include an opportunity for application holders to question the need for or specific wording of the labeling changes.

(the Orange Book).[10] Table 1 of this document provides an overview of approved new drug applications for currently marketed acetaminophen combination products grouped according to their active ingredients and acetaminophen strengths.[11]

TABLE 2—OVERVIEW OF CURRENTLY MARKETED PRESCRIPTION ACETAMINOPHEN PRODUCTS

Ingredient combination	N*—All Acetaminophen strengths	Acetaminophen strengths ≤325 mg	N*—Acetaminophen strengths ≤ 325 mg	Acetaminophen strengths >325 mg	N*—Acetaminophen strengths >325
Acetaminophen; Butalbital.	4	325 mg; 50 mg Tablets.	2	650 mg; 50 mg Tablets.	1.
				650 mg; 50 mg Capsules.	1.
			Total: 2		Total: 2.
Acetaminophen; Butalbital; Caffeine.	16	300 mg; 50 mg; 40 mg Capsules.	1	500 mg; 50 mg; 40 mg Tablets.	6.
		325 mg; 50 mg; 40 mg Tablets.	6	500 mg; 50 mg; 40 mg Capsules.	1.
		325 mg; 50 mg; 40 mg Capsules.	1	750 mg; 50 mg; 40 mg Tablet.	1.
			Total: 8		Total: 8.
Acetaminophen Codeine Phosphate.	24	300 mg; 15 mg Tablets.	6	None	0.
		300 mg; 30 mg Tablets.	10		
		300 mg; 60 mg Tablets.	8		
			Total: 24		Total: 0.
Acetaminophen; Hydrocodone.	88	300 mg; 5 mg Tablets	1	400 mg; 5 mg Tablets	1.
		300 mg; 7.5 mg Tablets.	1	400 mg; 7.5 mg Tablets.	1.
		300 mg; 10 mg Tablets.	1	400 mg; 10 mg Tablets.	1.
		325 mg; 2.5 mg Tablets.	1	500 mg; 2.5 mg Tablets.	4.
		325 mg; 5 mg Tablets	5	500 mg; 5 mg Tablets	12.
		325 mg; 7.5 mg Tablets.	5	500 mg; 7.5 mg Tablets.	7.
		325 mg; 10 mg Tablets.	7	500 mg; 10 mg Tablets.	7.
			Total: 21		
				500 mg; 5 mg Capsules.	2.
				650 mg; 5 mg Tablets	1.
				650 mg; 7.5 mg Tablets.	7.
					7.
					6.
					9.
					2.
					Total: 67.
Acetaminophen; Hydrocodone.	.....	300 mg; 5 mg Tablets	1	400 mg; 5 mg Tablets	1.
		300 mg; 7.5 mg Tablets.	1	400 mg; 7.5 mg Tablets.	1.
		300 mg; 10 mg Tablets.	1	400 mg; 10 mg Tablets.	1.
		325 mg; 2.5 mg Tablets.	1	500 mg; 2.5 mg Tablets.	4.
		325 mg; 5 mg Tablets	5	500 mg; 5 mg Tablets	12.
		325 mg; 7.5 mg Tablets.	5	500 mg; 7.5 mg Tablets.	7.
		325 mg; 10 mg Tablets.	7	500 mg; 10 mg Tablets.	7.
			Total: 21		

[10] Detailed Orange Book listings, including specific application numbers and sponsors, can be viewed electronically by accessing FDA's Web site at *http://www.accessdata.fda.gov/scripts/cder/ob*, selecting ''Search by Active Ingredient,'' and entering ''acetaminophen'' in the search form.

[11] The figures in table 1 of this document do not include approved applications for combination products that are subject to the recently announced market withdrawal due to safety concerns related to propoxyphene. The table also excludes various approved combinations that are not currently marketed. These include: Acetaminophen; butalbital; caffeine; codeine (1 approved application with acetaminophen strength ≤325 mg); acetaminophen; caffeine; dihydrocodeine bitartrate (5 applications with acetaminophen strengths >325 mg;) acetaminophen; codeine phosphate (1 application with acetaminophen strength over 325 mg); acetaminophen; hydrocodone in solution dosage form (3 applications with acetaminophen strengths ≤325 mg; 6 with acetaminophen strengths >325 mg).

TABLE 2—OVERVIEW OF CURRENTLY MARKETED PRESCRIPTION ACETAMINOPHEN PRODUCTS—Continued

Ingredient combination	N *—All Acetaminophen strengths	Acetaminophen strengths ≤325 mg	N *—Acetaminophen strengths ≤ 325 mg	Acetaminophen strengths >325 mg	N *—Acetaminophen strengths >325
				500 mg; 5 mg Capsules.	2.
				650 mg; 5 mg Tablets	1.
				650 mg; 7.5 mg Tablets.	7.
				650 mg; 10 mg Tablets.	7.
				660 mg; 10 mg Tablets.	6.
				750 mg; 7.5 mg Tablets.	9.
				750 mg; 10 mg Tablets.	2.
					Total: 67.
Acetaminophen; Oxycodone HCl.	49	300 mg; 2.5 mg Tablets.	1	400 mg; 2.5 mg Tablets.	1.
		300 mg; 5 mg Tablets	1	400 mg; 5 mg Tablets	1.
		300 mg; 7.5 mg Tablets.	1	400 mg; 7.5 mg Tablets.	1.
		300 mg; 10 mg Tablets.	1	400 mg; 10 mg Tablets.	1.
		325 mg; 2.5 mg Tablets.	2	500 mg; 5 mg Tablets	1.
		325 mg; 5 mg Tablets	8	500 mg; 75 mg Tablets.	5.
		325 mg; 7.5 mg Tablets.	4	500 mg; 10 mg Tablets.	1.
		325 mg; 10 mg Tablets.	5	500 mg; 5 mg Capsules.	8.
		325 mg/5 ml; 5 mg/5 ml Oral Solution.	2	650 mg; 5 mg Tablets	4.
			Total: 25	650 mg; 10 mg Tablets.	1.
					Total: 24.
Acetaminophen; Pentazocine HCl.	2	None	0	650 mg; EQ 25 mg BASE Tablets.	2.
			Total: 0		Total: 2.
Acetaminophen; Tramadol HCL.	6	325 mg; 37.5 mg Tablets.	6		0.
			Total: 6	None	Total: 0.
	Grand Total: 189		Total: 86		Total: 103.

* N = number of approved applications.

As shown in table 1 of this document, there are 7 different prescription acetaminophen combinations currently marketed under a total of 189 approved active applications. The applications are held by a total number of 26 sponsors. Products with approved acetaminophen strengths of 325 mg or less per dosage unit (''lower acetaminophen strengths'') account for slightly fewer than half (86) of the approved applications but are much less widely marketed and prescribed than products with higher acetaminophen strengths.

We anticipate that drug sponsors who request that FDA withdraw approval of their higher acetaminophen strength applications under § 314.150(d) (21 CFR 314.150(d)) will wish to market the same combination of active ingredients with lower acetaminophen strength. For example, a sponsor that requests that FDA withdraw approval of its application for 500 mg of acetaminophen combined with 5 mg of hydrocodone in tablet dosage form presumably would want to remain on the market with a tablet product containing 5 mg of hydrocodone and no more than 325 mg of acetaminophen. Such a change will not require submission of an application by sponsors who already have approved applications for the lower strength product, as often is the case. However, sponsors who do not already have such approval would need to develop a new formulation with the lower acetaminophen strength, submit an appropriate application, and obtain FDA approval before marketing.

We anticipate that in virtually all cases the fastest and least burdensome route to approval for new lower acetaminophen strength versions of existing higher acetaminophen strength products will be through new ANDA submissions using another manufacturer's existing lower acetaminophen strength product as the reference listed drug (RLD).[12] For nearly all of the higher acetaminophen strength combinations, there is at least one

[12] For historical reasons, virtually all currently approved applications for prescription acetaminophen combination products are ANDAs rather than NDAs. Unlike NDAs, which may be supplemented to reflect changes in unit dosage strength or other product characteristics, products marketed under an approved ANDA must maintain the same strength as the RLD. Accordingly, if the acetaminophen strength of such a product is reformulated from, e.g., 500 mg to 325 mg, a new ANDA listing either an appropriate RLD having the new lower strength or an appropriate approved suitability petition as described in § 314.94(a)(3)(iii), must be approved before the reformulated product may be marketed.

appropriate RLD with an acetaminophen strength at or below 325 mg in the Orange Book. For a small minority of higher acetaminophen strength combinations, there is no approved lower acetaminophen strength product with the same active ingredients that could serve as the RLD. We believe that reformulations of these products, however, could be approved as ANDAs upon approval of an ANDA suitability petition (see section 505(j)(2)(C) of the FD&C Act and § 314.93 (21 CFR 314.93)) permitting the submission of an ANDA for a drug product that is not identical to the RLD in an active ingredient or unit dosage strength, or could be approved as NDAs following submission of applications with appropriate clinical studies.

We are establishing a timeframe for responding to this notice that takes into account the estimated time needed for sponsors to obtain necessary approvals and begin to market new products with lower acetaminophen strengths. We believe that a period of 3 years from publication of this notice in the **Federal Register** will provide adequate time for drug sponsors to prepare to withdraw existing products with higher acetaminophen strengths, and to develop and obtain approval for lower acetaminophen strength versions of those products. We also anticipate that this will provide sufficient time for drug sponsors with approved lower acetaminophen strength products to expand their production to meet the expected increase in demand for lower acetaminophen strength products when the higher strength products become unavailable.

We strongly encourage sponsors of combination prescription products with acetaminophen strengths greater than 325 mg to submit requests for withdrawal of those products' approved applications under § 314.150(d) within the 3-year period described previously. Sponsors who intend to seek approval of one or more new products with acetaminophen strengths of 325 mg or less are encouraged to submit appropriate applications for such products in time to obtain approval within the same period. To that end, we welcome inquiries and requests for consultation from sponsors relating to specific existing or proposed products in connection with this notice. Any such requests from sponsors of currently approved products affected by this notice should be made as correspondence under the affected application(s) and should reference this notice.

We are issuing this notice because we believe that voluntary action on the part of product sponsors to reduce the acetaminophen strengths of prescription acetaminophen combinations can achieve the needed increase in patient safety substantially sooner and with less burden on public and private resources than alternative regulatory measures. However, FDA has authority under section 505(e)(2) of the FD&C Act to withdraw approval of an NDA or ANDA if the Agency determines that the ''* * * drug is not shown to be safe for use under the conditions of use upon the basis of which the drug was approved * * *'' based on consideration of ''* * * new evidence * * * together with the evidence available to [FDA] when the application was approved * * *.'' FDA regulations describe the procedures for withdrawing approval of an application. (See § 314.150 and 21 CFR 314.151, 314.200, 314.201, and 314.235). We intend to use our authority under section 505(e) of the FD&C Act to initiate withdrawal proceedings for any prescription acetaminophen combination products with acetaminophen strengths greater than 325 mg that remain on the market 3 years after the date of publication of this notice.

IV. References

FDA has verified the Web site address in this reference section, but we are not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.

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10. Nourjah, P. et al, ''Estimates of Acetaminophen (Paracetamol)-induced Overdoses in the United States,'' Pharacoepidemiological Drug Safety, 6: 406–409, 2006.
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Dated: March 24, 2014.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 2014–06802 Filed 3–26–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2011–N–0021]

Actavis Totowa LLC, et al.; Withdrawal of Approval of Abbreviated New Drug Applications for Prescription Pain Medications Containing More Than 325 Milligrams of Acetaminophen

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 108 abbreviated new drug applications (ANDAs) for prescription pain medications containing more than 325 milligrams (mg) of acetaminophen. The holders of these ANDAs have voluntarily requested that approval of these applications be withdrawn and have waived their opportunity for a hearing.

DATES: Effective March 27, 2014.

FOR FURTHER INFORMATION CONTACT: Rachel Turow, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6236, Silver Spring, MD 20993–0002, 301–796–5094.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 14, 2011 (76 FR 2691), FDA announced its plans to reduce the maximum dosage unit strength of acetaminophen in prescription drug products. The notice