United States in support of the U.S. Armed Forces' operation during some period of time from September 11, 2001, to termination of SFAR 100–2;

(b) The person's flight instructor certificate, airman written test report, or inspection authorization expired some time between September 11, 2001, and 6 calendar months after returning to the United States or termination of SFAR 100–2, whichever is earlier; and

(c) The person complies with § 61.197 or § 65.93 of this chapter, as appropriate, or completes the appropriate practical test within 6 calendar months after returning to the United States, or upon termination of SFAR 100–2, whichever is earlier.

3. *Required documents.* The person must send the Airman Certificate and/or Rating Application (FAA Form 8710–1) to the appropriate Flight Standards District Office. The person must include with the application one of the following documents, which must show the date of assignment outside the United States and the date of return to the United States:

(a) An official U.S. Government notification of personnel action, or equivalent document, showing the person was a civilian on official duty for the U.S. Government outside the United States and was assigned to a U.S. Armed Forces' operation some time between September 11, 2001, to termination of SFAR 100–2;

(b) Military orders showing the person was assigned to duty outside the United States and was assigned to a U.S. Armed Forces' operation some time between September 11, 2001, to termination of SFAR 100–2 ; or

(c) A letter from the person's military commander or civilian supervisor providing the dates during which the person served outside the United States and was assigned to a U.S. Armed Forces' operation some time between September 11, 2001, to termination of SFAR 100–2.

4. *Expiration date.* This Special Federal Aviation Regulation No. 100–2 is effective until further notice.

PART 63—CERTIFICATION: FLIGHT CREWMEMBERS OTHER THAN PILOTS

■ 4. The authority citation for part 63 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701–44703, 44707, 44709–44711, 45102–45103, 45301–45302.

PART 65—CERTIFICATION: AIRMEN OTHER THAN FLIGHT CREWMEMBERS

■ 5. The authority citation for part 65 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701–44703, 44707, 44709–44711, 45102–45103, 45301–45302.

Issued in Washington, DC, on February 22, 2010.

J. Randolph Babbitt,

Administrator.

[FR Doc. 2010–4580 Filed 3–3–10; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

RIN 0910—AG00

[Docket Nos. FDA–1981–N–0114 and FDA–1992–N–0049] (formerly Docket Nos. 1981N–0114A and 1992N–0311)

Classification of Benzoyl Peroxide as Safe and Effective and Revision of Labeling to Drug Facts Format; Topical Acne Drug Products for Over-The-Counter Human Use; Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: We, the Food and Drug Administration (FDA), are issuing this final rule to include benzoyl peroxide as a generally recognized as safe and effective (GRASE) active ingredient in over-the-counter (OTC) topical acne drug products. In addition, this final rule includes new warnings and directions required for OTC acne drug products containing benzoyl peroxide. We are also revising labeling for OTC topical acne drug products containing resorcinol, resorcinol monoacetate, salicylic acid and/or sulfur to meet OTC drug labeling content and format requirements in a certain FDA regulation. This final rule is part of our ongoing review of OTC drug products and represents our conclusions on benzoyl peroxide in OTC acne drug products.

DATES: *Effective Date*: This rule is effective on March 4, 2011.

Compliance Date: The compliance date for products containing resorcinol, resorcinol monoacetate, salicylic acid, and/or sulfur subject to 21 CFR part 333 is March 4, 2015. The compliance date for products containing benzoyl peroxide subject to 21 CFR part 333 with annual sales less than $25,000 is March 2, 2012. The compliance date for products containing benzoyl peroxide subject to part 21 CFR part 333 with annual sales of $25,000 or more is March 4, 2011.

FOR FURTHER INFORMATION CONTACT: Matthew R. Holman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, MS 5411, Silver Spring, MD 20993, 301–796–2090.

SUPPLEMENTARY INFORMATION:

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I. Glossary

- ANPR: Advance Notice of Proposed Rulemaking
- CFR: Code of Federal Regulations
- CHPA: Consumer Healthcare Products Association (formerly Nonprescription Drug Manufacturers Association)
- Committee: Dermatologic Drugs Advisory Committee
- FDA: Food and Drug Administration
- FR: **Federal Register**
- GRASE: Generally Recognized as Safe and Effective
- NDA: New Drug Application—an application submitted to FDA to market a new drug under section

505 of the Federal Food, Drug, and Cosmetic Act (21 CFR part 314)
- OTC: Over-the-Counter—medicines sold without a prescription
- Panel: Advisory Review Panel on OTC Antimicrobial (II) Drug Products
- SKU: Stock Keeping Unit—an identifier that is used by merchants to permit the systematic tracking of products and services offered to customers
- TPA: 12-O-tetradecanoylphorbol 13-acetate—a powerful tumor promoter
- U.S.C.: United States Code—compilation of Federal laws
- UVA: Ultraviolet A radiation—ultraviolet radiation with a wavelength between 400 and 320 nanometers
- UVB: Ultraviolet B radiation—ultraviolet radiation with a wavelength between 320 and 280 nanometers
- UVR: Ultraviolet radiation—UVC, UVB, and UVA radiation (1–400 nanometers)
- We: Food and Drug Administration

II. Purpose of this Final Rule

This final rule establishes conditions under which OTC drug products containing benzoyl peroxide for the topical treatment of acne are GRASE and not misbranded. In the **Federal Register** of January 15, 1985 (50 FR 2173), we published a proposed rule in which 2.5 to 10 percent benzoyl peroxide is proposed GRASE for the topical treatment of acne (the 1985 proposed rule). In the **Federal Register** of August 7, 1991 (56 FR 37622), we issued a proposed rule which proposed to classify benzoyl peroxide as category III (i.e., "more-data-needed") instead of category I (GRASE) based on safety concerns that arose at that time (the 1991 proposed rule). Following the 1991 proposed rule, new data were submitted to address our safety concerns. After reviewing the data, we now conclude that benzoyl peroxide can be adequately labeled to minimize the risks associated with benzoyl peroxide while delivering effective acne treatment. Therefore, we are classifying benzoyl peroxide as category I in this final rule.

In addition, this final rule requires that OTC acne drug products containing benzoyl peroxide, resorcinol, resorcinol monoacetate, salicylic acid, and/or sulfur be relabeled. We revised the warnings and directions for these products such that they meet the content and format requirements in § 201.66 (21 CFR 201.66). When the final rule for these products was established in 1991, we had not yet established § 201.66. The revisions necessary to comply with the requirements of § 201.66 were minimal.

III. Past FDA Actions or Activities Related to this Final Rule

In the **Federal Register** of March 23, 1982 (47 FR 12430), we published an ANPR to establish a monograph for OTC topical acne drug products (the 1982 ANPR). The 1982 ANPR included the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products (the Panel). The Panel concluded that benzoyl peroxide, in concentrations of 2.5 to 10 percent, is safe and effective for OTC topical use to treat acne. The Panel recognized that benzoyl peroxide is a dose-dependent skin irritant that can also lead to sensitization. Therefore, the Panel recommended the following warnings be included in labeling:
- Do not use benzoyl peroxide on very sensitive skin.
- Keep benzoyl peroxide products away from the eyes, lips, and mouth.
- Benzoyl peroxide may bleach hair or dye fabric.

The 1985 proposed rule proposed conditions under which OTC topical acne drug products are GRASE and not misbranded. We agreed with the Panel's recommendations, and the 1985 proposed rule proposed that 2.5 to 10 percent benzoyl peroxide is GRASE for the treatment of acne. The 1985 proposed rule also proposed requiring the benzoyl peroxide warnings recommended by the Panel.

In the **Federal Register** of August 16, 1991 (56 FR 41008), we issued a final rule for OTC topical acne drug products (the 1991 final rule). In the 1991 final rule, we established conditions under which OTC topical acne drug products, except those containing benzoyl peroxide, are GRASE and not misbranded. We also issued the 1991 proposed rule which proposed to classify benzoyl peroxide as category III instead of category I (GRASE) based on safety concerns. Category III means that we need more data before we can properly classify benzoyl peroxide as GRASE. This proposed classification of benzoyl peroxide as Category III came after considering new safety data and information suggesting that benzoyl peroxide may initiate tumor formation and promote tumor development in animals. We stated in the 1991 proposed rule that it is unclear whether these findings in animals can be extrapolated to humans. We also stated that further studies were necessary to adequately assess the tumor promotion and carcinogenic potential of benzoyl peroxide. In the meantime, we noted that manufacturers could continue to market acne drug products containing benzoyl peroxide until the safety issues were resolved.

To help us resolve the safety issues, we requested comments on the safety of these products, stating that we would discuss these issues with an Advisory Committee (Committee) shortly after the 1991 proposed rule published. In 1992, a few months after the 1991 proposed rule published, we discussed the available benzoyl peroxide safety and efficacy data at an Advisory Committee meeting. The Committee made the following recommendations:
- New photocarcinogenicity studies on benzoyl peroxide should be conducted.
- Current animal safety data regarding benzoyl peroxide should be conveyed in labeling.
- Acne drug products containing benzoyl peroxide should stay on the market while new studies are being performed.

The Committee's recommendations applied to both prescription and OTC acne drug products.

During the Advisory Committee meeting, industry representatives stated that published studies in mice showed no evidence of benzoyl peroxide being photocarcinogenic (Refs. 1 and 2). However, the Committee concluded that the studies were insufficient to determine whether benzoyl peroxide is carcinogenic. The Committee indicated that the studies were inconclusive because none of the studies used sufficient numbers of mice and the mice should have been observed over their entire lifespan. Therefore, the Committee unanimously agreed that a new photocarcinogenicity study should be conducted.

The Committee recommended, by a four-to-three vote (with one abstention), that the known safety data regarding the tumor promoting potential of benzoyl peroxide should be communicated to consumers. Because this data was inconclusive, the Committee unanimously agreed that the word "cancer" should not be included in the labeling of acne drug products containing benzoyl peroxide. The Committee was concerned that the word "cancer" would cause consumers to avoid using these products (even though the data were inconclusive). The Committee did not believe the data adequately demonstrated that benzoyl peroxide was unsafe, and they recognized that benzoyl peroxide is effective in treating acne. Therefore, the Committee unanimously recommended that acne drug products containing benzoyl peroxide should remain on the

market while the additional safety studies were being conducted.

In the **Federal Register** of February 17, 1995 (60 FR 9554), we issued a proposed rule for all OTC and prescription acne drug products containing benzoyl peroxide in which we agreed with all of the Committee's recommendations (the 1995 proposed rule). When stating the need for additional safety studies, we noted that the Nonprescription Drug Manufacturers Association (since renamed Consumer Healthcare Products Association (CHPA)) was conducting photocarcinogenicity studies at that time. We also proposed labeling to communicate the results of the animal studies. The labeling included warnings and directions that would appear in the Drug Facts box of OTC acne drug products containing benzoyl peroxide. In addition, we proposed requiring package inserts for OTC and prescription acne drug products containing benzoyl peroxide. We requested that manufacturers voluntarily implement the proposed labeling as soon as possible. As recommended by the Committee, the proposed package inserts included the word "tumor" but not "cancer." We also agreed with the Committee that these drug products should stay on the market. To support this position, we discussed human epidemiological studies conducted at that time suggesting that the use of benzoyl peroxide does not increase the risk of facial skin cancer in humans (Refs. 3 and 4).

IV. FDA's Conclusions on Safety

We now conclude that benzoyl peroxide, in concentrations of 2.5 to 10 percent, is GRASE for the OTC topical treatment of acne. This conclusion is based on safety data that we received and evaluated since publication of the 1995 proposed rule that proposed classifying benzoyl peroxide as Category III. As recommended by the Committee, these new data include studies examining the carcinogenic and photocarcinogenic potential of benzoyl peroxide. In addition to discussing these new studies in this section of the document, we provide a summary of earlier studies discussed in previous OTC acne drug product rulemakings. We believe the combined results of the earlier and new studies support the GRASE finding for benzoyl peroxide (see section IV.G of this document).

A. Genotoxicity

In the 1991 proposed rule, we discussed studies suggesting that benzoyl peroxide may be genotoxic (56 FR 37622 at 37627 and 37628). Genotoxic substances are capable of causing genetic mutations and chromosomal changes that can contribute to the development of tumors and possibly cancer. Six in vitro studies examining deoxyribonucleic acid (DNA) breaks in various mammalian cells were reviewed in the 1991 proposed rule. Benzoyl peroxide was shown to produce DNA breaks in five of the six studies. In addition, the 1991 proposed rule reviewed six Ames tests. The Ames test is a standard biological assay to assess the mutagenic potential of chemical compounds using the bacteria *Salmonella typhimurium* or *Escherichia coli*. Five of the tests demonstrate that benzoyl peroxide is not mutagenic, while one demonstrates it is a weak mutagen. Finally, we discussed three other in vitro genotoxicity studies in the 1991 proposed rule. One study suggests that benzoyl peroxide is not mutagenic, while two studies suggest that it is a weak mutagen.

Even though some of the in vitro studies suggest that benzoyl peroxide may be a weak mutagen, the negative studies along with the overall genotoxicity profile do not warrant concluding that benzoyl peroxide is a genotoxic agent. In accordance with ICH S2A Guidelines (the guidelines), a single positive result in any genotoxicity assay does not necessarily mean that the test compound poses a genotoxic hazard to humans (Ref. 5). The guidelines state that "any in vitro positive test result should be evaluated for its biological relevance." We believe that the positive genotoxicity results are likely due to the oxidative DNA damage caused by benzoyl peroxide, which has been shown in numerous studies (Refs. 6, 7, and 8). In humans, there are oxidative repair mechanisms that would likely prevent benzoyl peroxide from causing DNA damage (Ref. 9). Therefore, we believe there is no significant biological relevance of the mixed results from the in vitro genotoxicity studies.

B. Tumor Promotion Wth Chemical Initiation

In the 1991 proposed rule, we discussed concerns that benzoyl peroxide may be a tumor promoter in the presence of a chemical tumor initiator (56 FR 37622 at 37631). A tumor promoter increases tumor formation and growth as well as conversion of benign tumors to malignant tumors after exposure to a tumor initiator (e.g., a chemical or UV radiation). However, a tumor promoter is not a carcinogen and exposure to a tumor promoter alone will not cause cancer. In the 1991 proposed rule, we reviewed animal studies examining the ability of benzoyl peroxide to act as a tumor promoter in the presence of a chemical tumor initiator. The tumor promoter studies were conducted by applying a known tumor initiator at the beginning of a study and then later applying the suspected tumor promoter, benzoyl peroxide, at multiple times throughout the remainder of the study. Because tumor promotion was observed in almost all the studies, we concluded that benzoyl peroxide is a skin tumor promoter, in the presence of a chemical tumor initiator, in more than one strain of mice and other laboratory animals (56 FR 37622 at 37631). We continue to believe that benzoyl peroxide is a tumor promoter in animals when combined with a chemical tumor initiator.

C. Tumor Promotion with Ultraviolet Initiation

In the 1991 proposed rule, we discussed a tumor promotion study in which ultraviolet (UV) radiation was the initiator (56 FR 37622 at 37629). The backs of albino hairless mice were irradiated three times per week for 8 weeks. After completion of the UV irradiation cycles, benzoyl peroxide was applied to the backs 5 times per week for 50 weeks. In this study, benzoyl peroxide was not a tumor promoter with UV initiation.

There were no other UV initiation tumor promoter studies until after publication of the 1995 proposed rule, when CHPA submitted a new study entitled "The Skin Tumor Promoting Potential of Benzoyl Peroxide Carbopol Gel Following UVR Initiation in SKH-1 Albino Mice" (Ref. 10). The study compares benzoyl peroxide's tumor promoting capability on mice exposed to UV radiation to that of a known chemical tumor promoter, 12-O-tetradecanoylphorbol 13-acetate (TPA). Six groups of mice were irradiated for 6 weeks (5 days per week) with a daily dose of 0.2 joules per square centimeter ultraviolet B (UVB, 290–320 nanometers) radiation. Another six groups of mice were not exposed to UVB radiation. After a 1-week rest period, benzoyl peroxide or TPA were applied on the mice as outlined in table 1 of this document. Acetone was also applied because TPA was dissolved in acetone, so acetone was a control. The test materials were applied to the backs and sides of the mice. The mice were treated for 40 weeks and then observed for a 12-week treatment-free period.

TABLE 1.—TREATMENT GROUPS IN UV INITIATION TUMOR PROMOTER STUDY OF ALBINO MICE

	Treatment Groups[1,2]											
	1	2	3	4	5	6	7	8	9	10	11	12
UVB irradiation	-	-	-	-	-	-	+	+	+	+	+	+
Benzoyl peroxide	-	0.1%	1.5%	5%	-	-	-	0.1%	1.5%	5%	-	-
TPA in acetone	-	-	-	-	+	-	-	-	-	-	+	-
Acetone	-	-	-	-	-	+	-	-	-	-	-	+

[1] + Denotes the presence of UVB radiation, TPA, or acetone.
[2] - Denotes the absence of UVB radiation, TPA, or acetone.

The study authors assessed tumor promotion ability by comparing two endpoints in mice treated with vehicle and those treated with benzoyl peroxide as follows: (1) The percent of mice with tumors and (2) the number of tumors per mouse. At the end of the study, the percent of mice with tumors was the same in the vehicle-treated group (Group 7) and the group treated with 0.1 percent benzoyl peroxide (Group 8). The percent of mice with tumors in the groups treated with 1.5 or 5 percent benzoyl peroxide (Groups 8 and 9) was much higher than the vehicle or 0.1 percent groups. The number of tumors per mouse in the groups treated with 1.5 or 5 percent benzoyl peroxide (Groups 8 and 9) was much higher than the vehicle or 0.1 percent groups. The results from this study suggest that benzoyl peroxide causes tumor promotion in a dose-dependent manner.

The results from the study submitted in 1995 by CHPA and the study discussed in the 1991 proposed rule produced contradictory results. Therefore, it is difficult to draw any final conclusions regarding tumor promotion with benzoyl peroxide in the presence of UV radiation from these two studies. As with the genotoxicity studies, the biological relevance of the tumor promotion studies results needs to be determined. Drug dosing in tumor promoter studies does not reflect actual human use conditions, making it difficult to interpret the results and extrapolate to human use. The relevance of the animal tumor promoter study results to human safety can only be determined by carcinogenicity and photocarcinogenicity studies for benzoyl peroxide (see sections IV.D and E of this document).

D. Carcinogenicity

We have reviewed a number of animal studies examining the carcinogenic potential of benzoyl peroxide and conclude that benzoyl peroxide is not a carcinogen. In the ANPR, the Panel cites data from two dermal animal carcinogenicity studies and a report to support their conclusion that benzoyl peroxide is not a carcinogen (47 FR 12430 at 12443 to 12444). In the 1991 proposed rule, we stated that "* * *[a] definitive study to assess the complete carcinogenicity of benzoyl peroxide has not, as yet, been conducted" (56 FR 37622 at 37630). In that document, we state that benzoyl peroxide did not produce cancer in the following studies conducted on mice and rats that were not reviewed by the Panel (56 FR 37622 at 37623 to 37626):

- Four studies using oral administration
- Three studies using subcutaneous administration
- Five studies using topical administration

We explain that, because these studies were not of a sufficient duration, they were not sufficient to assess the carcinogenicity of benzoyl peroxide. We state that long-term (i.e., over the entire animal lifespan) carcinogenicity studies need to be conducted in two rodent species to understand whether benzoyl peroxide is a carcinogen with a long latency period (56 FR 37622 at 37631).

After publication of the 1995 proposed rule, we collaborated with CHPA to develop carcinogenicity study protocols (Refs. 11 through 14). In 2001, CHPA submitted a mouse and a rat carcinogenicity study (Ref. 15). Both studies were conducted using a carbopol benzoyl peroxide gel administered topically for 2 years. Neither study demonstrated that benzoyl peroxide is carcinogenic. In the mouse study, benzoyl peroxide was applied at doses of 1, 5, and 15 milligrams (mg) per mouse once daily to 6 square centimeters (cm^2) on the dorsal skin. In the rat study, benzoyl peroxide was applied at doses of 5, 15, and 45 mg per rat once daily to 12 cm^2 on the dorsal skin. The mice and rats were sacrificed at 52 weeks (interim sacrifice) or 104 weeks, and complete necropsies were performed. Both studies show that benzoyl peroxide had no effect on survival, body weight, food consumption, or gross pathology, and neither produced any evidence of systemic toxicity. The dosing used in the study (0.17, 0.83, and 2.5 mg per cm^2) probably represents the dosing used by humans under actual use conditions. Because these studies were well-designed and conducted for the animals' lifespan, we believe they adequately exclude the possibility that benzoyl peroxide is a carcinogen with a short or long latency period.

E. Photocarcinogenicity

Our review of a photocarcinogenicity study submitted after the 1995 proposed rule suggest that benzoyl peroxide is not a photocarcinogen. The design of photocarcinogenicity studies is similar to that of the tumor promoter studies discussed in the previous section of this document but differ in the exposure to UV radiation. The tumor promoter studies are designed so that animals are exposed to UV radiation for a short time and then exposed to benzoyl peroxide (in the absence of UV radiation) for nearly the animals' entire lifespan. Photocarcinogenicity studies involve exposure to UV radiation and benzoyl peroxide simultaneously for the animals' lifespan.

The 1991 proposed rule did not include a discussion of any photocarcinogenicity studies because none were available at the time. Two published photocarcinogenicity studies in mice, whose results had been reviewed at the 1992 Advisory Committee meeting, were discussed in the 1995 proposed rule. The studies showed no evidence that benzoyl peroxide is a photocarcinogen. The Advisory Committee, however, concluded that the studies were not adequate to fully resolve this issue because they did not include sufficient numbers of mice and they did not collect data throughout the animals' lifespan. We agreed with the Advisory Committee and requested new

photocarcinogenic studies in the 1995 proposed rule.

In 1999, CHPA submitted a study examining the photocarcinogenic potential of benzoyl peroxide in mice (Ref. 10). The study is entitled "12-Month Topical Study to Determine the Influence of Benzoyl Peroxide on Photocarcinogenesis in Albino Hairless Mice Crl: SKH1(hr/hr)BR." The mice received single daily doses of UV radiation along with 0, 5, 15, and 50 mg per milliliter benzoyl peroxide carbopol gel. The mice were dosed daily, Monday through Friday. On Monday, Wednesday, and Friday, the benzoyl peroxide was applied before irradiation. On Tuesday and Thursday, the benzoyl peroxide was applied after irradiation. Treatment was continued for 40 weeks, and then the mice were observed for an additional 12 weeks (52 weeks total). The number of tumors was recorded each week. This study shows a slight enhancement of UV-mediated skin tumorigenesis by benzoyl peroxide at the low and mid doses. However, no enhancement was apparent at the high dose, as the number of tumors was similar to that in the control group. Because increased doses of benzoyl peroxide did not produce greater numbers of tumors, the study suggests that benzoyl peroxide is not photocarcinogenic in mice.

F. Epidemiological Data

There have been several epidemiological studies conducted that provide information about whether there is a link between the use of benzoyl peroxide to tumor development, as discussed in the 1991 proposed rule (56 FR 37622 at 37629 and 37630). None of the studies clearly associate the use of benzoyl peroxide with the development of skin cancer in humans. The largest of these studies evaluated 870 subjects who developed skin cancer and 1,250 control subjects who did not develop skin cancer (matched for age, sex, and geographic location) (Ref. 4). The study authors concluded that the past history of acne was the second strongest correlation to the development of basal cell carcinoma, with a family history of cancer being the strongest correlation. Although the authors suggested that there may be a relationship between benzoyl peroxide use and skin cancer, data about subject use of acne treatments was not collected (e.g., whether subjects had used benzoyl peroxide). We are not aware of any relevant epidemiological studies published since 1991. Therefore, we do not have any epidemiological evidence demonstrating that benzoyl peroxide is a carcinogen in humans.

G. Overall Conclusion

We are classifying benzoyl peroxide as GRASE. This conclusion is supported by the animal studies that suggest benzoyl peroxide is not carcinogenic or photocarcinogenic. Although some of the studies suggest that benzoyl peroxide is a tumor promoter with chemical initiators in animals, three studies demonstrate that benzoyl peroxide is not carcinogenic or photocarcinogenic in animals. We believe these three studies are more meaningful than the conflicting tumor promoter studies.

As explained in this section of the document, we believe that consideration of all the findings supports the GRASE status of benzoyl peroxide. Even though benzoyl peroxide is known to be a skin irritant and sensitizer in humans (47 FR 12430 at 12444), we believe, with adequate labeling, these risks can be minimized in such a way that benzoyl peroxide is safe to use for acne.

There were two safety signals that concerned us when we proposed to classify benzoyl peroxide as category III (i.e., more data needed to determine safety) instead of GRASE:

- The ability of benzoyl peroxide to be a weak mutagen in vitro, and
- The tumor promotion potential of benzoyl peroxide in the presence of a chemical initiator in animals

No new safety signals have been identified since the 1991 proposed rule, despite the conduct of additional studies. We conclude that the additional rodent carcinogenicity and photocarcinogenicity studies conducted since the proposed rule justify a GRASE determination in spite of the mutagenic and tumor promoter potential of benzoyl peroxide.

Although genotoxicity studies are useful, findings that a drug is mutagenic in these studies does not necessarily lead to a determination that the drug is unsafe. Genotoxicity studies are often preliminary studies in drug development that help provide a framework for how to proceed with future studies. Positive results with genotoxicity studies show that a drug has the potential to be a mutagen, thereby contributing to the development of tumors and possibly cancer. Consistent with the guidelines (Ref. 5), the genotoxicity study findings led to animal studies to determine the biological relevance of the evidence that benzoyl peroxide may be a weak mutagen in vitro. The animal studies subsequently conducted consist of animal tumor promotion, carcinogenicity, and photocarcinogenicity studies.

The tumor promotion studies demonstrate that benzoyl peroxide is a tumor promoter in the presence of a chemical initiator. It is unclear from the studies whether benzoyl peroxide is a tumor promoter in the presence of UV radiation (as an initiator) because two studies are contradictory. As with the genotoxicity studies, the biological relevance of the tumor promotion studies results needs to be determined. Tumor promoter studies are not generally relied on solely in place of carcinogenicity studies. Drug dosing in tumor promoter studies does not reflect actual human use conditions, making it difficult to interpret the results and extrapolate to human use. The relevance of the animal tumor promoter study results to human safety can only be determined by carcinogenicity and photocarcinogenicity studies for benzoyl peroxide.

Carcinogenicity studies are the most reliable non-clinical studies that can be extrapolated to humans for determining the long-term or chronic safety. These studies are conducted with topical application of benzoyl peroxide with and without UV irradiation (i.e., both carcinogenicity and photocarcinogenicity studies). Dermal carcinogenicity and photocarcinogenicity studies best represent actual use conditions for benzoyl peroxide. They are the benchmark for determining the carcinogenic potential of a drug. We believe that the negative findings in the carcinogenic and photocarcinogenic studies support a GRASE conclusion for benzoyl peroxide because they are more relevant to humans under conditions of actual use than genotoxicity or tumor promotion studies.

V. FDA's Conclusions on Labeling

In addition to the labeling required for all OTC topical acne drug products, we are now requiring labeling that provides information related specifically to benzoyl peroxide. We are only requiring carton labeling and not consumer package insert labeling for benzoyl peroxide. This required benzoyl peroxide labeling is based on labeling that we previously proposed for the ingredient (discussed in section IV.A of this document). In addition, the required labeling reflects our safety assessment of benzoyl peroxide discussed in the previous sections of this document. We believe that the labeling required in this document is necessary for the safe and effective use of OTC topical acne drug products containing benzoyl peroxide.

In addition to the labeling specific to benzoyl peroxide, we are revising labeling for all OTC acne drug products. We revised the warnings and directions for these products such that they meet the content and format requirements in § 201.66. When the final rule for these products was established in 1991, we had not yet established § 201.66.

A. Past FDA Requirements for Labeling

In the 1985 proposed rule, we proposed warnings required for OTC acne drug products containing benzoyl peroxide:

- Do not use benzoyl peroxide on very sensitive skin.
- Keep benzoyl peroxide products away from the eyes, lips, and mouth.
- Benzoyl peroxide may bleach hair or dye fabric.

These warnings were specific to benzoyl peroxide and were not proposed for OTC acne drug products containing other active ingredients. These warnings come from recommendations made by the Panel in the 1982 ANPR.

In the 1995 proposed rule, we proposed the following warning and direction appear on prescription and OTC drug products containing benzoyl peroxide:

- Warning: "When using this product, avoid unnecessary sun exposure and use a sunscreen."
- Direction: "If going outside, use a sunscreen. (sentence in boldface type) Allow [insert name of benzoyl peroxide product] to dry, then follow directions in the sunscreen labeling. If irritation or sensitivity develops, discontinue use of both products and consult a doctor."

For OTC products, the 1995 proposed rule proposed that this labeling be required on the outer carton. For prescription products, the 1995 proposed rule proposed that this labeling appear in the patient package insert.

In the 1995 proposed rule, we also proposed a series of questions and answers that would appear in a package insert and would explain the tumor promotion potential and sensitizing nature of benzoyl peroxide (60 FR 6554 at 6555 to 6556). The questions answered in the 1995 proposed rule included the following:

- What is in (insert brand name of benzoyl peroxide product)?
- Does benzoyl peroxide cause tumors to grow in humans?
- What should I do?

This information essentially summarized the data from animal studies that led to the earlier proposed classification of benzoyl peroxide as category III. We suggested that it appear as a package insert for prescription and OTC products. This labeling in the 1995 proposed rule stems from and agrees with the recommendations of the Committee, which met in 1992 to discuss benzoyl peroxide in acne drug products.

B. Carton Labeling

We are requiring the warnings proposed in the 1985 proposed rule as well as the warning and direction proposed in the 1995 proposed rule (see section V.A of this document). Although we are revising the warnings and direction slightly, the overall meaning remains the same.

This action relates to three submissions that we received in response to the 1995 proposed rule. These submissions argue that we should not require the proposed warning concerning sun exposure. Two of the submissions argue that there is no scientific evidence demonstrating a risk of photosensitivity in humans when using benzoyl peroxide (Refs. 16 and 17). They acknowledge the studies showing that benzoyl peroxide is a skin tumor promoter in rodents. However, they do not believe the results from rodent studies support a finding of significant human health risk. The third submission suggests that cleansers and soaps containing benzoyl peroxide be excluded from the required label warning "use a sunscreen" (Ref. 18). The submission concurs with the recommended label warning to "use a sunscreen" for benzoyl peroxide products. We proposed this warning be included on all OTC benzoyl peroxide products. However, the submission argues that the warning should only be required on products that are left on the skin because it would confuse consumers using products that are washed off after use.

Since receiving these submissions, we have reviewed new data regarding the potential phototoxicity of benzoyl peroxide. The data shows that benzoyl peroxide is not a photocarcinogen in animals. Studies have also shown that 5 and 10 percent benzoyl peroxide preparations can decrease the skin's tolerance to UV radiation (i.e., increase sunburn) after repeated applications (Refs. 19 and 20). In addition, benzoyl peroxide can cause skin irritation, which may worsen with sun exposure. These adverse effects of benzoyl peroxide are important because drug products containing benzoyl peroxide are often used daily on sun-exposed areas of the body (e.g., face). The best ways to protect sun-exposed areas of the body are to cover them up, stay out of the sun, and to use a sunscreen. Therefore, we believe it is important to include information warning consumers to avoid unnecessary sun exposure and to use a sunscreen when using any drug products containing benzoyl peroxide.

For the same reason, we are not exempting cleansers and soaps containing benzoyl peroxide from the "use a sunscreen" warning, as argued by the third comment. This warning is required for all OTC topical acne drug products containing benzoyl peroxide. We do not believe this warning (and the accompanying directions about sunscreen use) will confuse consumers. The warning is clear, simple, and applies to all OTC topical acne drug products containing benzoyl peroxide whether they are washed off or left on. We are moving this direction from the beginning of the directions section to the end. Whether a product is washed off or left on, the directions should instruct consumers to use the product and then apply a sunscreen. We believe this revision will prevent confusion about sunscreen use and adequately address the concern raised by the third submission.

Accordingly, we are adding the following benzoyl peroxide warnings in this document (§ 333.350(c)(4)):

- Do not use if you [bullet] have very sensitive skin [bullet] are sensitive to benzoyl peroxide.
- When using this product [bullet] avoid unnecessary sun exposure and use a sunscreen [bullet] avoid contact with the eyes, lips, and mouth [bullet] avoid contact with hair and dyed fabrics, which may be bleached by this product [bullet] skin irritation may occur, characterized by redness, burning, itching, peeling, or possibly swelling. Irritation may be reduced by using the product less frequently or in a lower concentration.
- Stop use and ask a doctor if [bullet] irritation becomes severe.

In addition, we are adding a new direction for products containing benzoyl peroxide (§ 333.350(d)(2)) (21 CFR 333.350(d)(2))):

- [bullet] if going outside, apply sunscreen after using this product. If irritation or sensitivity develops, stop use of both products and ask a doctor.

We are also revising carton labeling to reflect OTC drug labeling format and content requirements (i.e., "Drug Facts") implemented after the 1995 proposed rule (§ 201.66).

C. Consumer Package Insert

We received three submissions from healthcare organizations arguing that we should not require the patient and consumer package insert labeling proposed for OTC and prescription

benzoyl peroxide drug products in the 1995 proposed rule. One submission argues that the purpose of OTC labeling has never been to tell consumers everything that scientists have discovered, or might still be investigating, about a drug product and its ingredients (Ref. 17). The second submission argues that information related to possible carcinogenicity should not be disseminated until the completion of valid epidemiologic studies (Ref. 16). The submission believes it is not helpful to imply a connection between benzoyl peroxide and sunlight in the absence of supporting epidemiological data. The third submission is concerned that the proposal to include patient package inserts with all topical acne drug products containing benzoyl peroxide will increase costs to the healthcare distribution system (Ref. 21). The submission argues that in order for written materials to accompany each package of a prescription drug product, manufacturers must switch from automated to manual packaging, which would be costly. In addition, the submission argues that the costs of applying the same requirement to OTC products would be even higher because OTC products are more numerous and are distributed in much greater volume.

We agree with the submissions' request to not require a consumer package insert accompanying OTC topical acne drug products containing benzoyl peroxide. The purpose of including a consumer package insert is to disseminate as much information pertaining to the potential risks of using benzoyl peroxide containing drug products. We believe that the proposed carton labeling sufficiently informs the consumer of the potential risks of using these products. After reviewing the newly submitted data, we no longer see the need for a consumer package insert.

We are not creating regulations requiring a patient package insert to accompany prescription topical acne drug products containing benzoyl peroxide because all prescription topical acne drug products are marketed under new drug applications (NDAs). The decision to include patient package inserts for prescription products should be done on a case-by-case basis. Prescription products containing benzoyl peroxide cannot be marketed until we review information submitted for a specific product and determine that the product is safe and effective. As part of this review, we determine labeling that is specific to the product. We have and will continue to require appropriate safety information about benzoyl peroxide in each prescription product as part of the NDA review and approval. Therefore, we do not believe that the proposed labeling needs to be included in monograph regulations.

D. Overall Conclusion

In this document, we are requiring labeling specific to benzoyl peroxide containing drug products. Warnings for drug products containing benzoyl peroxide include the following: (§ 333.350(c)(4)):

- Avoiding unnecessary sun exposure
- Not using on very sensitive skin
- Keeping away from the eyes, lips, and mouth
- Cautioning that benzoyl peroxide may bleach hair or dye fabric

These warnings are not required for other acne active ingredients. However, warnings required for other acne active ingredients, such as "for external use only," are required for benzoyl peroxide. We are also requiring a direction for drug products containing benzoyl peroxide to use a sunscreen when going outside.

We are not requiring a consumer package insert for drug products containing benzoyl peroxide. After reviewing the newly submitted data, we no longer see the need for a consumer package insert. We believe that the proposed carton labeling sufficiently informs the consumer of the potential risks of using these products. We are also not requiring a patient package insert to accompany prescription topical acne drug products containing benzoyl peroxide with this final rule. All prescription topical acne drug products are marketed under NDAs, which already require appropriate safety information about benzoyl peroxide in the labeling of each prescription product as part of the NDA review and approval. We do not believe that the proposed labeling needs to be included in monograph regulations.

VI. Analysis of Impacts

We have examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, we have prepared a final regulatory impact analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. We do not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Need for and Objectives of the Rule

The purpose of this document is to revise the conditions for marketing OTC acne drug products. This final rule establishes that OTC acne drug products containing benzoyl peroxide are GRASE and establishes required labeling for these products. This final rule requires manufacturers of OTC acne products containing benzoyl peroxide to relabel their products and add new warnings and directions within 12 months from the date of publication.

This final rule also requires that the warnings and directions for OTC acne drug products containing resorcinol, resorcinol monoacetate, salicylic acid, and/or sulfur be revised to meet the content and format requirements in § 201.66. We are allowing manufacturers up to 5 years to comply with this provision. Frequent label redesigns are typical for OTC topical acne drug products, with redesigns generally implemented at least every 5 years for a product. Therefore, the regulatory-mandated relabeling will fall within this time period, minimizing the impact on the manufacturer of these products. There are no reformulation costs required by this rule.

B. Number of Products Affected

Estimating the number of manufacturers and affected products is difficult because we lack data on products currently marketed. Our Drug Listing System currently does not have accurate information on the number of

marketed OTC acne drug manufacturers and products containing benzoyl peroxide. We used data from A. C. Nielsen to estimate the dollar sales and the number of stock keeping units (SKUs) that would be affected by this rule. Based on 2006 retail sales data, the total sales for approximately 330 affected SKUs were $263.0 million, or converting to 2009 dollars, $278 million. However, there are likely some affected OTC acne products that we were unable to identify.

Of the 330 affected SKUs, about 25 percent contain benzoyl peroxide and 75 percent contain other ingredients cited in this final rule (i.e., resorcinol, resorcinol monoacetate, salicylic acid, or sulfur). Most manufacturers of products containing benzoyl peroxide will need to relabel and add new warnings and directions within 1 year from the date of publication. Small entities with annual product sales of less than $25,000 will have up to 2 years to comply. Manufacturers of all other OTC acne drug products (containing resorcinol, resorcinol monoacetate, salicylic acid and sulfur) will have up to 5 years to relabel and conform to the OTC format and contents requirements in § 201.66.

C. Cost to Relabel

Estimates of relabeling costs for the types of changes required by this document vary depending on the following: (1) Whether the products are nationally branded or private label, (2) the printing method, and (3) the number of colors used. The costs of product relabeling are also dependent on the timing of the required labeling change. Most OTC manufacturers routinely schedule revisions of product labels every few years. To the extent that the timing of regulatory changes corresponds with routine labeling revisions by the company, the regulatory cost of relabeling is significantly reduced.

We used a labeling cost model developed for FDA by the consulting firm RTI International (RTI) to derive an estimate of the cost to relabel OTC acne drug products (Ref. 22). The model was developed to estimate the cost of revising food and dietary supplement labels. The RTI model assumes that all manufacturers voluntarily revise their labeling every 3 years. We believe that the graphic and design estimates from the RTI model are an appropriate proxy for the costs that would be incurred by OTC acne drug product manufacturers. However, we are unable to use this model to forecast reductions in relabeling costs for year four and five of the implementation period.

The RTI model estimates that the costs to revise labeling ranges from $2,700 to $6,600 for a 1-year implementation period. Assuming an average relabeling cost of $4,650 per SKU, the total one-time cost for 80 SKUs containing benzoyl peroxide would be about $372,000 (80 SKUs x $4,650). To minimize the impact on small entities with annual sales less than $25,000, we are allowing up to 24 months for products containing benzoyl peroxide to be relabeled.

All other manufacturers of acne treatment products containing resorcinol, resorcinol monoacetate, salicylic acid, and sulfur would need to revise their product labels to conform to the OTC format and contents requirements in § 201.66. Based on the labeling cost model, the average incremental costs of conforming to the OTC format and content requirements are estimated to be $3,750 per SKU, assuming a maximum period of 3 years to comply. The total one-time costs to manufacturers to relabel the estimated 250 affected OTC SKUs is about $937,500 (250 SKUs x $3,750). Because the labeling cost model stops at a 3-year implementation period and these manufacturers would have up to 5 years to incorporate these changes with routinely scheduled labeling changes, these relabeling costs would be reduced. However, we lack sufficient information to estimate the reduction.

The present value of total one-time costs for relabeling all of the 330 affected OTC acne treatment products is $1.1 million using a 7 percent discount rate and $1.2 million using a 3 percent discount rate. The annualized total costs of compliance of this rule are $0.4 million using 7 percent and 3 percent discount rates over 3 years.

Using the 2009 dollar value of annual retail sales for OTC acne products of $278 million, the annualized costs of compliance account for less than 0.2 percent of total annual OTC acne retail sales for all entities, for both a 7 percent and 3 percent discount rate over 3 years. Because the period selected for annualization is typically much longer than 3 years, using a 3-year period maximizes annualized compliance costs for this analysis.

D. Benefits of this Rule

The primary benefit of this final rule is that consumers will have standardized and consistent labeling information that is necessary for the safe use of OTC acne products affected by this rule. This final rule finds that OTC acne drug products containing benzoyl peroxide are GRASE and allows these products to remain on the market. This final rule will provide consumers with warnings and directions information that is needed for the safe use of OTC acne products containing benzoyl peroxide. This final rule also will require that the current monograph labeling information for OTC topical acne drug products containing resorcinol, resorcinol monoacetate, salicylic acid, and sulfur be consistently presented according to the OTC Drug Facts labeling requirements in 21 CFR part 201.

With this final rule, there are now five GRASE active ingredients for OTC acne drug products. Consumers will continue to have a range of choices for OTC acne products with safety and use information uniformly presented. A uniform presentation of labeling information should help consumers compare similar products to make informed choices.

E. Alternatives and Steps Taken to Minimize Impacts on Small Entities

For products containing benzoyl peroxide, we considered a longer implementation period, such as 2 years for all of the 80 SKUs, rather than only for those entities with annual sales less than $25,000. However, we believe it is important to provide the new warning statements and directions to consumers as soon as possible. We considered and rejected a shorter implementation period for all other OTC acne products to conform to the OTC format and content requirements. To provide maximum flexibility and to minimize burdens, we are allowing up to 5 years for firms to coordinate required labeling changes with planned revisions. We believe any longer implementation period is impractical and would unnecessarily delay the benefit of providing uniform format and content labeling to consumers who use OTC drug products for the treatment of acne.

F. Impact on Small Businesses

The Small Business Administration defines an entity as small in the pharmaceutical manufacturing industry if the business has fewer than 750 employees. Over 90 percent of manufacturers in the OTC pharmaceutical industry are classified as small. The average annual value of shipments for small entities in Pharmaceutical Manufacturing Preparation NAICS 325412 was $34.9 million in 2002[1]. Converting to 2009 dollars, the average value of shipments

[1] U.S. Department of Commerce, 2002 Economic Census of Manufacturers, "Pharmaceutical Preparation Manufacturing: 2002," Industry Series, NAICS 325412, Table 4. Industry Statistics by Employment Size, December 2004.

per small entity is $39.0 million. However, the Census data do not allow us to estimate the average value of shipments for OTC manufacturers.

To estimate possible impacts on small entities, we used A. C. Nielsen total retail sales for all OTC acne products affected by this rule to calculate the annualized total cost of compliance as a percentage of annual sales. The annualized total costs of compliance of this rule are $0.4 million using 7 percent and 3 percent discount rates over 3 years.

Table 2 of this document presents the annualized costs of compliance as a percent of total annual retail sales for OTC acne products by size of the affected entities. Although we have sales data for each SKU, we were unable to determine the firm size for certain private label SKUs because A. C. Nielsen does not reveal ownership information for certain store brands. These store brands are typically large chain stores. In addition, we combined the category for small entities with 11 other entities whose size information could not be found in financial listings.

TABLE 2.—ANNUALIZED COMPLIANCE COST AS A PERCENT OF OTC ACNE SALES BY SIZE OF ENTITY[1]

Size	2009 Sales (dollars in millions)	Number of SKUs	Annualized Compliance Cost (dollars in millions)		Compliance Cost (Percent of Sales)	
			7% discount rate	3% discount rate	7 % discount rate	3% discount rate
Large	$254.0	233	$0.3	$0.3	0.1%	0.1%
Small	$18.1	49	$0.1	$0.1	0.3%	0.3%
Private Label[2]	$6.1	48	$0.1	$0.1	1.0%	1.0%
Total[3]	$278.1	330	$0.4	$0.4	0.2%	0.2%

[1] The use of a 3-year period for annualizing maximizes the value of compliance costs for this analysis.
[2] Private label represents store brand and unknown brand names.
[3] Total sales and annualized compliance cost may not sum due to rounding.

The annualized costs of compliance are less than 0.2 percent of total annual OTC acne retail sales for all entities. Private label entities compliance costs as a percent of OTC acne sales are about 1 percent over 3 years. For small entities, the annualized costs over 3 years are 0.3 percent annual sales for OTC acne products. These estimates represent maximum values because of the relatively short period used to annualize costs.

These estimates do not account for the additional time granted to small entities to minimize the cost impacts. Industry routinely changes their OTC product labeling, and we have allowed for extended implementation periods to comply with this final rule. Therefore, we believe that it is unlikely that this final rule will have a significant economic impact on a substantial number of small entities. This final rule does not require any new reporting or recordkeeping activities.

G. Summary of Analysis

This analysis shows that this final rule is not economically significant under Executive Order 12866. We have allowed flexible implementation periods to minimize the regulatory costs of revising labeling. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, this analysis, together with other relevant sections of this document, serves as our Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

VII. Paperwork Reduction Act of 1995

We conclude that the labeling requirements required in this rule are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VIII. Environmental Impact

We have determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." The sole statutory provision giving preemptive effect to the final rule is section 751 of the act (21 U.S.C. 379r). We believe that we have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effects of this rule are consistent with Executive Order 13132.

X. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.

1. Iverson, O. H., "Carcinogenesis Studies with Benzoyl Peroxide (Panoxyl Gel 5%)," *Journal of Investigative Dermatology*, 86:442–448, 1986.

2. Iverson, O. H., "Skin Tumorigenesis and Carcinogenesis Studies with 7,12-dimethylbenz [a] anthracene, Ultraviolet Light, Benzoyl Peroxide (Panoxyl Gel 5%) and Ointment Gel," *Carcinogenesis*, 9:803–809, 1988.

3. Comment No. C4, 1981N–114A.

4. Hogan, D. J. et al., "A Study of Acne Treatments as Risk Factors for Skin Cancer of the Head and Neck," *British Journal of Dermatology*, 125:343–348, 1991.

5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Genotoxicity Testing and Data Interpretaion on Pharmaceuticals Intended for Human Use (S2(R1)), February 23, 2010. *http://www.ich.org/lob/media/media4477.pdf.*

6. Giri, U., M. Iqbal, and M. Athar, "Porphyrin-Mediated Photosensitization Has a Weak Tumor Promoting Activity in Mouse Skin: Possible Role of In Situ-Generated Reactive Oxygen Species," *Carcinogenesis*, 17:2023–2028, 1996.

7. Kawanishi, S. et al., "Site-Specific Oxidation at GG and GGG Sequences in Double-Stranded DNA by Benzoyl Peroxide as a Tumor Promoter," *Biochemistry*, 38:16733–16739, 1999.

8. Kensler, T. et al., "Role of Reactive Intermediates in Tumor Promotion and Progression," *Progress in Clinical and Biological Research*, 391:103–116, 1995.

9. Matsumura, Y. and H. N. Ananthaswamy, "Toxic Effects of Ultraviolet Radiation on the Skin," *Toxicology and Applied Pharmacology*, 195:298–308, 2004.

10. Comment No. RPT3, 1981N–0114.

11. Comment No. LET19, 1981N–0114.

12. Comment No. LET20, 1981N–0114.

13. Comment No. LET21, 1981N–0114.

14. Comment No. LET22, 1981N–0114.

15. Comment No. RPT4, 1981N–0114.

16. Comment No. C3, 1992N–0311.

17. Comment No. C4, 1992N–0311.

18. Comment No. C1, 1992N–0311.

19. Jeanmougin, M. and J. Civatte, "Prediction of Benzoyl Peroxide Phototoxicity by Photoepidermotests After Repeated Applications. Preventative Value of a UVB Filter," *Archives of Dermatological Research*, 280 (Suppl): S90–S93, 1988.

20. Jeanmougin, M. et al., "Phototoxic Activity of 5% Benzoyl Peroxide in Man. Use of a New Methodology," *Dermatologica*, 167:19–23, 1983.

21. Comment No. C2, 1992N–0311.

22. "FDA Labeling Cost Model, Final Report" prepared by Mary Muth, Erica Glendhill, and Shawn Karns, RTI International, Prepared for Amber Jessup, FDA Center for Food Safety and Applied Nutrition, RTI International, January 2003.

List of Subjects in 21 CFR Part 333

Labeling, Over-the-counter drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 333 is amended as follows:

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

■ 1. The authority citation for 21 CFR part 333 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

■ 2. Section 333.310 is revised to read as follows:

§ 333.310 Acne active ingredients.

The active ingredient of the product consists of any of the following:

(a) Benzoyl peroxide, 2.5 to 10 percent.

(b) Resorcinol, 2 percent, when combined with sulfur in accordance with § 333.320(a).

(c) Resorcinol monoacetate, 3 percent, when combined with sulfur in accordance with § 333.320(b).

(d) Salicylic acid, 0.5 to 2 percent.

(e) Sulfur, 3 to 10 percent.

(f) Sulfur, 3 to 8 percent, when combined with resorcinol or resorcinol monoacetate in accordance with § 333.320.

■ 3. Section 333.320 is revised to read as follows:

§ 333.320 Permitted combinations of active ingredients.

(a) Resorcinol identified in § 333.310(b) may be combined with sulfur identified in § 333.310(f).

(b) Resorcinol monoacetate identified in § 333.310(c) may be combined with sulfur identified in § 333.310(f).

■ 4. Section 333.350 is amended by revising paragraphs (c) and (d) and removing paragraph (e) to read as follows:

§ 333.350 Labeling of acne drug products.

* * * * *

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredients identified in § 330.310.*

(i) The labeling states "For external use only."

(ii) The labeling states "When using this product [bullet] skin irritation and dryness is more likely to occur if you use another topical acne medication at the same time. If irritation occurs, only use one topical acne medication at a time."

(2) *For products containing sulfur identified in § 333.310(e) and (f).*

(i) The labeling states "Do not use on [bullet] broken skin [bullet] large areas of the skin."

(ii) The labeling states "When using this product [bullet] apply only to areas with acne."

(3) *For products containing any combination identified in § 333.320.* (i) The labeling states "When using this product [bullet] rinse right away with water if it gets in eyes."

(ii) The labeling states "Stop use and ask a doctor [bullet] if skin irritation occurs or gets worse."

(4) *For products containing benzoyl peroxide identified in § 333.310(a).*

(i) The labeling states "Do not use if you [bullet] have very sensitive skin [bullet] are sensitive to benzoyl peroxide."

(ii) The labeling states "When using this product [bullet] avoid unnecessary sun exposure and use a sunscreen [bullet] avoid contact with the eyes, lips, and mouth [bullet] avoid contact with hair and dyed fabrics, which may be bleached by this product [bullet] skin irritation may occur, characterized by redness, burning, itching, peeling, or possibly swelling. Irritation may be reduced by using the product less frequently or in a lower concentration."

(iii) The labeling states "Stop use and ask a doctor if [bullet] irritation becomes severe."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products applied containing any ingredient identified in § 333.310.* The labeling states "[bullet] clean the skin thoroughly before applying this product [bullet] cover the entire affected area with a thin layer one to three times daily [bullet] because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor [bullet] if bothersome dryness or peeling occurs, reduce application to once a day or every other day."

(2) *For products applied and left on the skin containing benzoyl peroxide identified in § 333.310(a).*

(i) The labeling states the directions in paragraph (d)(1) of this section.

(ii) The labeling states "[bullet] if going outside, apply sunscreen after using this product. If irritation or sensitivity develops, stop use of both products and ask a doctor."

(3) *For products applied and removed from the skin containing any ingredient identified in § 333.310.* Products, such as soaps and masks, may be applied and removed and should include appropriate directions. All products containing benzoyl peroxide should include the directions in paragraph (d)(2)(ii) of this section.

(4) *Optional directions.* In addition to the required directions in paragraphs (d)(1) and (d)(2) of this section, the product may contain the following optional labeling: "*Sensitivity Test for a New User.* Apply product sparingly to one or two small affected areas during the first 3 days. If no discomfort occurs, follow the directions stated (select one of the following: 'elsewhere on this label,' 'above,' or 'below')."

Dated: February 25, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–4424 Filed 3–3–10; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF EDUCATION

34 CFR Part 280

RIN 1855–AA07

[Docket ID ED–2010–OII–0003]

Magnet Schools Assistance Program

AGENCY: Office of Innovation and Improvement, Department of Education.

ACTION: Interim final rule; request for comments.

SUMMARY: The Secretary amends the regulations governing the Magnet Schools Assistance Program (MSAP) to provide greater flexibility to school districts designing MSAP programs for the Fiscal Year (FY) 2010 grant competition announced in a notice inviting applications for new awards published elsewhere in this issue of the **Federal Register**. These changes remove provisions in the regulations that require districts to use binary racial classifications and prohibit the creation of magnet schools that result in minority group enrollments in magnet and feeder schools exceeding the district-wide average of minority group students. This new flexibility is necessary to permit school districts interested in receiving funds under this program to determine how best to meet program requirements while also taking into account intervening Supreme Court case law, including the Court's decision in *Parents Involved in Community Schools* v. *Seattle School District No 1 et al.,* 551 U.S. 701 (2007) (*Parents Involved*).

DATES: These regulations are effective March 4, 2010. We must receive your comments by April 5, 2010.

ADDRESSES: Submit your comments through the Federal eRulemaking Portal or via postal mail, commercial delivery, or hand delivery. We will not accept comments by fax or by e-mail. Please submit your comments only one time, in order to ensure that we do not receive duplicate copies. In addition, please include the Docket ID at the top of your comments.

- *Federal eRulemaking Portal:* Go to *http://www.regulations.gov* to submit your comments electronically. Information on using Regulations.gov, including instructions for accessing agency documents, submitting comments, and viewing the docket is available on the site under "How To Use This Site."
- *Postal Mail, Commercial Delivery, or Hand Delivery:* If you mail or deliver your comments about these interim final regulations, address them to Anna Hinton, U.S. Department of Education, 400 Maryland Avenue, SW., room 4W229, Washington, DC 20202.

Privacy Note: The Department's policy for comments received from members of the public (including those comments submitted by mail, commercial delivery, or hand delivery) is to make these submissions available for public viewing in their entirety on the Federal eRulemaking Portal at *http://www.regulations.gov.* Therefore, commenters should be careful to include in their comments only information that they wish to make publicly available on the Internet.

FOR FURTHER INFORMATION CONTACT: Anna Hinton, U.S. Department of Education, 400 Maryland Avenue, SW., room 4W229, Washington, DC 20202. Telephone: (202) 260–1816 or by e-mail: *FY10MSAPCOMP@ed.gov.*

If you use a telecommunications device for the deaf (TDD), call the Federal Relay Service (FRS), toll free at 1–800–877–8339.

Individuals with disabilities may obtain this document in an accessible format (*e.g.,* braille, large print, audiotape, or computer diskette) on request to the contact person listed under **FOR FURTHER INFORMATION CONTACT**.

SUPPLEMENTARY INFORMATION:

Invitation To Comment

We invite you to submit comments regarding the removal of the regulatory provisions in these interim final regulations. The MSAP regulations in 34 CFR part 280, as amended by these interim final regulations, will govern the FY 2010 MSAP competition. Any changes made to these interim final regulations in light of comments would govern the next MSAP competition in FY 2013. To ensure that your comments have maximum effect in developing the final regulations, we urge you to identify clearly the specific section or sections of the interim final regulations that each of your comments addresses and to arrange your comments in the same order as the interim final regulations. We also are considering issuing a notice of proposed rulemaking (NPRM) that would propose provisions to replace those that are removed by these interim final regulations, although we are not soliciting comments on an NPRM at this time. Again, any changes subsequent to these interim final regulations would apply to the next MSAP competition, which the Department anticipates conducting in FY 2013.

We invite you to assist us in complying with the specific requirements of Executive Order 12866 and its overall requirement of reducing regulatory burden that might result from these interim final regulations. Please let us know of any further opportunities we should take to reduce potential costs or increase potential benefits while preserving the effective and efficient administration of the program.

During and after the comment period you may inspect all public comments about these interim final regulations by accessing Regulations.gov. You may also inspect the comments, in person, in room 4W229, 400 Maryland Avenue, SW., Washington, DC 20202, between the hours of 8:30 a.m. and 4 p.m., Eastern time, Monday through Friday of each week except Federal holidays.

Assistance to Individuals With Disabilities in Reviewing the Rulemaking Record

On request, we will supply an appropriate aid, such as a reader or print magnifier, to an individual with a disability who needs assistance to review the comments or other documents in the public rulemaking record for these interim final regulations. If you want to schedule an appointment for this type of aid, please contact Anna Hinton, U.S. Department of Education, 400 Maryland Avenue, SW., room 4W229, Washington, DC 20202. Telephone: (202) 260–1816 or by e-mail: *FY10MSAPCOMP@ed.gov.*

Background

The MSAP is a discretionary grant program that provides funds to local educational agencies (LEAs) for "the elimination, reduction, or prevention of minority group isolation in elementary and secondary schools" with substantial proportions of minority students, and "the development and design of innovative educational methods and practices that promote diversity." 20 U.S.C. 7231; 34 CFR 280.1. The Department awards grants to LEAs for magnet schools that are "part of an approved desegregation plan" and "designed to bring students from different social, economic, ethnic, and racial backgrounds together." 20 U.S.C. 7231b; 34 CFR 280. There are two types of MSAP desegregation plans: (1) Required desegregation plans ordered by a Federal or State court or agency of competent jurisdiction;[1] and (2)

[1] The revisions in these interim final regulations do not affect how the Department treats required desegregation plans under the MSAP.