



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket Nos. FDA-2003-N-0196 (formerly 2003N-0233), FDA-1978-N-0018 (formerly 1978N-0038 and 78N-0038), and FDA-1996-N-0006 (formerly 96N-0277)]

Over-the-Counter Sunscreen Drug Products--Regulatory Status of Enzacamene

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a proposed sunscreen order (proposed order) under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Sunscreen Innovation Act (SIA). The proposed order announces FDA's tentative determination that enzacamene is not generally recognized as safe and effective (GRASE) and is misbranded when used in over-the-counter (OTC) sunscreen products because the currently available data are insufficient to classify it as GRASE and not misbranded, and additional information is needed to allow us to determine otherwise.

DATES: Submit either electronic or written comments on this proposed order by [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

Sponsors may submit written requests for a meeting with FDA to discuss this proposed order by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section VI for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments by any of the following methods:

### Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

### Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must clearly identify the specific active ingredient (enzacamene) and the Docket Nos. FDA-2003-N-0196, FDA-1978-N-0018, and FDA-1996-N-0006 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket numbers, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Submit requests for a meeting with FDA to discuss this proposed order to Kristen Hardin (see FOR FURTHER INFORMATION CONTACT).

FOR FURTHER INFORMATION CONTACT: Kristen Hardin, Division of Nonprescription Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5491, Silver Spring, MD 20993-0002, 240-402-4246.

SUPPLEMENTARY INFORMATION:

## I. Regulatory Background

### A. Regulatory and Statutory Framework

The data and information addressed in this proposed order were originally submitted for review under FDA's Time and Extent Application (TEA) regulation, § 330.14 (21 CFR 330.14), a process that has since been supplemented with new statutory procedures established in the SIA (Public Law 113-195), enacted November 26, 2014. The discussion that follows briefly describes and compares the pre- and post-SIA processes as they apply to the regulatory status of enzacamene.

The TEA regulation established a process through which a sponsor could request that an active ingredient or other OTC condition,<sup>1</sup> particularly one not previously marketed in the United States, be added to an OTC drug monograph to enable compliant OTC drug products containing the condition to be marketed in the United States without an approved new drug application (NDA) or abbreviated new drug application (ANDA). Because this proposed order specifically addresses an OTC sunscreen active ingredient (enzacamene), the remainder of this discussion will refer only to "active ingredients."

Critical steps in a proceeding under the TEA regulation include the following: (1) FDA's determination that an active ingredient had been marketed for the proposed OTC use for a

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<sup>1</sup> For purposes of OTC drug regulation, a "condition" is defined as an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration marketed for a specific OTC use, with specific exclusions (see § 330.14(a)(2)). This document will refer simply to new "active ingredients," since that is the condition under consideration.

material time and to a material extent (eligibility determination), and public call for submission of safety and efficacy data, followed by; (2) review of safety and efficacy data submitted by the sponsor or other interested parties; and (3) FDA's initial determination that the data show the active ingredient to be either GRASE or not GRASE for OTC use under the applicable monograph conditions (including any new conditions arising from FDA's review) (GRASE determination). Under the TEA regulation, FDA's GRASE determinations are effectuated through notice and comment rulemaking to amend or establish the appropriate monograph.

The TEA process in FDA regulations was supplemented by Congress's enactment of the SIA. Among other amendments it makes to the FD&C Act, the SIA creates new procedures specifically for reviewing the safety and effectiveness of nonprescription sunscreen active ingredients, including those, such as enzacamene, that were the subject of pending TEA proceedings at the time the SIA was enacted. Like the TEA regulation, the SIA calls for an initial eligibility determination phase for nonprescription sunscreen active ingredients, followed by submissions of safety and efficacy data and a GRASE determination phase. However, the SIA requires FDA to make proposed and final GRASE determinations for nonprescription sunscreen active ingredients in the form of administrative orders rather than the multistep public rulemaking required by the TEA regulation, and establishes strict timelines for the necessary administrative actions.

Among other requirements, no later than 90 days after the SIA was enacted (i.e., no later than February 24, 2015), FDA must publish a proposed sunscreen order in the Federal Register for any nonprescription sunscreen active ingredient, including enzacamene, for which, on the date of enactment, an eligibility determination had been issued under the TEA regulation and submissions of safety and efficacy data received, and for which a TEA feedback letter had not

yet been issued (section 586C(b)(4) of the FD&C Act (21 U.S.C. 360fff-3(b)(4)), as amended by the SIA). Other provisions of the SIA that are not discussed in this proposed order address procedures applicable to other pending and future sunscreen active ingredient GRASE determinations, pending and future GRASE determinations for OTC products other than sunscreens, issuance of specified guidances and reports, and completion of pending sunscreen rulemakings, among others.

A proposed sunscreen order under the SIA is an order containing FDA's tentative determination proposing that a nonprescription sunscreen active ingredient or combination of ingredients: (1) Is GRASE and is not misbranded when marketed in accordance with the proposed order; (2) is not GRASE and is misbranded; or (3) is not GRASE and is misbranded because the data are insufficient to classify the active ingredient or combination of ingredients as GRASE and not misbranded, and additional information is necessary to allow FDA to determine otherwise (section 586(7) of the FD&C Act, as amended by the SIA). Publication of a proposed sunscreen order triggers several timelines under the SIA, including a 45-day public comment period, and a 30-day period in which a sponsor may request a meeting with FDA to discuss the proposed order.

#### B. FDA's Review of Enzacamene

Buchanan Ingersoll submitted a TEA in 2002 on behalf of Merck KGaA under § 330.14(c) seeking OTC monograph status for the sunscreen active ingredient enzacamene (also known as 4-Methylbenzylidene Camphor (4-MBC) or Eusolex 6300) at concentrations up to 4 percent for use in OTC sunscreen products (enzacamene TEA) (Note 1). FDA issued a TEA notice of eligibility for enzacamene on July 11, 2003 (68 FR 41386), stating that enzacamene at concentrations of up to 4 percent is eligible to be considered for inclusion in the OTC sunscreen

monograph (21 CFR part 352, currently stayed) and calling for submission of safety and effectiveness data for enzacamene. In response, a submission of data dated October 9, 2003, was made to the docket on behalf of Merck KGaA (enzacamene data submission) (Note 2), which referred to materials previously submitted to other dockets.<sup>2</sup> At the time the SIA was enacted, FDA had not issued a TEA feedback letter or otherwise responded to that submission.

In accordance with new section 586C(b)(4) of the FD&C Act as amended by the SIA, we are issuing this notice as a proposed order for enzacamene. Based on our review of the available safety and efficacy data, we have made a tentative determination that enzacamene is not GRASE and is misbranded because the data are insufficient to classify it as GRASE and not misbranded for use in OTC sunscreens, and additional information is necessary to allow us to determine otherwise. The remainder of this proposed sunscreen order describes our review of the available safety and efficacy data, identifies additional data needed to demonstrate that enzacamene is GRASE for the requested use, and explains our rationale for specific conclusions and data requirements.

This proposed order will be open for public comment (see DATES). The sponsor may request a meeting with FDA to discuss this proposed order (see DATES). We also invite the sponsor to submit additional safety and/or efficacy data to inform our further consideration, as publication of a final sunscreen order under the SIA for enzacamene will be contingent on receipt of such information. (See section 586C(b)(9)(ii) of the FD&C Act.) We specifically encourage the sponsor to discuss any proposed study protocols with us before performing the studies.

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<sup>2</sup> These include FDA-1978-N-0018-0744-0756 (Sup 24, 25, 26, 27 and 28), Request to Reopen Rulemaking Record Respect Sunscreen Drug Products for OTC, submitted on April 12, 1999 (1999 enzacamene submission); FDA-1978-N-0018-0766, Citizen Petition (CP1), submitted on December 17, 1980; and Tracking number: 805596eb Legacy Doc. ID, SUP 5, "Supplement from Rona Pearle" SUP5, submitted on August 15, 1985.

## II. Safety Data Considerations for OTC Sunscreen Products Containing Enzacamene

In evaluating the safety of a proposed monograph active ingredient, FDA applies the following regulatory standard: Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (§ 330.10(a)(4)(i) (21 CFR 330.10(a)(4)(i))).

FDA's OTC drug regulations generally identify the types of information that may be submitted as evidence that an active ingredient or other OTC drug condition is safe, as part of the consideration of whether an active ingredient or other condition is GRASE (§ 330.10(a)(2)). For convenience, this order uses the term "generally recognized as safe (GRAS)" to refer to that aspect of the GRASE determination. To apply the general OTC safety standard to each potential new condition, FDA uses its scientific expertise to determine what constitutes "adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use." In assessing what specific testing or other data are needed to adequately demonstrate the safety of enzacamene for use in sunscreen, FDA considers the circumstances under which OTC sunscreen products that could contain enzacamene would be used by consumers.

When used as directed with other sun protection measures, broad spectrum OTC sunscreen products with a sun protection factor (SPF) value of 15 or higher strongly benefit the

public health by decreasing the risk of skin cancer and premature skin aging associated with solar ultraviolet (UV) radiation, as well as by helping to prevent sunburn. (Sunscreens with lower SPF values, or without broad spectrum protection, also help prevent sunburn.) When used as directed by the required labeling, all OTC sunscreen products are applied liberally to the skin and reapplied frequently throughout the day (§ 201.327(e) (21 CFR 201.327(e))). Because the effects of UV exposure are cumulative, to obtain the maximum benefit, users of broad spectrum sunscreens with an SPF value of 15 or higher are directed to use such products regularly--on a routine basis (*id.*). Given these conditions of use, our safety evaluation of an OTC sunscreen active ingredient such as enzacamene must consider both short-term safety concerns (such as skin sensitization/irritation and photosafety) and potential concerns related to long-term sunscreen use, including potential systemic exposure via dermal absorption.

The purpose of the safety testing described in this section II is to establish whether an OTC sunscreen product containing enzacamene and otherwise marketed under the conditions described in a final sunscreen order and in accordance with all requirements applicable to nonprescription drugs would be GRAS for use as labeled. To demonstrate that these requirements are met for enzacamene, initial safety testing should be performed using enzacamene as the sole active ingredient up to the highest concentration for which marketing status is sought and eligibility has been established: 4 percent. If initial testing suggests a particular safety concern associated with enzacamene (e.g., a hormonal activity), FDA may request additional studies to address that concern.

#### A. Human Safety Data

##### 1. Human Irritation, Sensitization, and Photosafety Studies

Studies of skin irritation, sensitization, and photosafety are standard elements in the safety evaluation of topical drug products that, like enzacamene-containing sunscreens, are applied to the skin repeatedly over long periods of time. FDA recommends separate studies for skin irritation and sensitization. Skin irritation studies should generally include at least 30 evaluable subjects and should evaluate the test formulation (i.e., enzacamene in an appropriate test vehicle), the vehicle alone, and both negative and positive controls. Skin sensitization studies generally should include at least 200 subjects and should evaluate the test formulation containing enzacamene, the vehicle, and a negative control. For both irritation and sensitization studies, test site applications should be randomized and the test observer blinded to the identities of the test formulations.

FDA recommends that photosafety evaluation generally involve studies of skin photoirritation (phototoxicity) and skin photosensitization (photoallergenicity). General principles for designing and conducting photosafety studies are described in FDA guidance (Ref. 1). Photosafety studies, like sensitization and irritation studies, should be conducted using enzacamene 4 percent in an appropriate test vehicle, the vehicle alone, and a negative control. In addition, phototoxicity studies should include at least 30 evaluable subjects and photoallergenicity studies should include at least 45 evaluable subjects.

#### Data Available for Enzacamene: Human Irritation, Sensitization, and Photosafety Studies

We reviewed the submitted study reports for human safety studies, including a skin irritation and sensitization study of enzacamene 5 percent in 30 subjects (Note 3); skin irritation and sensitization study of enzacamene 5 percent in 10 subjects (Note 4); a photoirritation study of 4 percent enzacamene in 5 subjects (Note 5); and two photosensitization studies, one using 4

percent enzacamene in 5 subjects and the other using an unknown concentration in 25 subjects (Notes 6 and 7). Although these studies suggest that enzacamene may not be a primary irritant, sensitizer, photosensitizer, or photoirritant, each of the submitted studies has limitations, such as inadequate sample size, lack of blinding, and lack of positive and negative controls, that prevent us from making definitive conclusions. In addition, protocol information, such as the inclusion and exclusion criteria used in subject selection, was not consistently provided.

FDA concludes that the data submitted are not sufficient to assess the dermal safety of enzacamene and specifically its potential to cause irritation, sensitization, photoirritation, or photoallergenicity. We recommend submission of additional data from human irritation, sensitization, and photosafety studies to demonstrate that an OTC sunscreen containing up to 4 percent enzacamene is not an irritant, sensitizer, photosensitizer, or photoirritant.

## 2. Human Dermal Pharmacokinetic (Bioavailability) Studies

Because sunscreens are topically applied, another important safety consideration for enzacamene for use in sunscreens is whether dermal application may result in skin penetration and systemic exposure to enzacamene, and if so, to what extent. A well-designed and -conducted human dermal pharmacokinetic study can be expected to detect and quantify the presence of enzacamene and/or any metabolites in blood or other bodily fluids that may have a bearing on safety, using recognized parameters such as bioavailability percentage, maximum plasma concentration (C<sub>max</sub>), time to maximum plasma concentration (T<sub>max</sub>), total area under the plasma concentration versus time curve (AUC), half-life, clearance, and volume of distribution. This information can help identify potential safety concerns and help determine whether an adequate safety margin for sunscreens containing enzacamene exists. FDA recommends that the pharmacokinetic studies performed on enzacamene also collect additional

safety-related data from regularly scheduled physical examinations, collection of vital signs, and other measures, which may help capture adverse skin events or other potential safety signals. To ensure that maximum penetration of enzacamene has taken place and chances of it being detected are optimal, studies should continue until steady state is reached.

General information and recommendations on the design and conduct of human pharmacokinetic studies can be found in FDA guidance (Ref. 2). To support a GRAS determination for enzacamene (up to 4 percent), such a study should be conducted under maximal use conditions using enzacamene 4 percent in various vehicles, including vehicles that would be expected to enhance absorption. We encourage study sponsors to consult with us before conducting pharmacokinetic studies, because the properties of enzacamene bear on the optimal design.

Data Available for Enzacamene: Human Dermal Pharmacokinetic (Bioavailability) and Clinical Pharmacology Studies

We reviewed three submitted reports of dermal absorption studies in humans in which percutaneous absorption was estimated using radiolabeled ( $^{14}\text{C}$ ) formulations of enzacamene. In one study (Note 8) a  $^{14}\text{C}$ -labeled 5 percent formulation of enzacamene was applied to the lower arms of six volunteers for 6 hours, followed by a 3-day collection of urine and feces. Investigators reported that approximately 54.6 percent of the  $^{14}\text{C}$ -activity applied to the skin was recovered. An average of 0.76 percent enzacamene was recovered in urine and 0.14 percent in the feces. In a second study (Note 9), investigators reported a total recovery of 98.2 percent and 90.7 percent overall recovery of the  $^{14}\text{C}$ -activity applied to the skin from two volunteers, respectively. The third study report (Note 10) was similar to the previous two studies in terms of the general design. Following the analysis of the data from the planned six volunteers, two more

volunteers were enrolled to evaluate the low observed recovery (54 to 69 percent) of the radiolabeled enzacamene. A different recovery schema was applied to these last two patients with satisfactory results in line with the previous studies. As to the utility of the aggregate data, we cannot draw definitive conclusions regarding the dermal absorption of enzacamene based on these studies. The overall number of subjects was low, the studies were single-dose studies, a limited surface area was exposed to the formulation, the recovery of radioactivity was variable, and finally no blood or other body fluids were sampled to provide direct information about systemic exposure. We also note that these studies were conducted in the 1980s and the limit of analytical detection for enzacamene was much higher than it is today.

A review of the published literature identified more recent studies related to the extent of absorption of enzacamene in humans after dermal application. A 2004 article from Janjua et al. (Ref. 3) reports on the absorption from a formulation containing 10 percent enzacamene and 2 other active sunscreen ingredients after whole body application for 4 days in 15 healthy males and 17 postmenopausal females. The article provides only summary bioavailability information but claims that the maximum plasma concentrations were 20 milligrams (mg)/ milliliter (mL) in both men and women and that increasing plasma levels of enzacamene and metabolites were seen, suggesting the presence of accumulation. It is noted that thyroid function was also assessed during this study, but results are confounded by the simultaneous application of three active sunscreen ingredients. A 2006 article from Shauer et al. (Ref. 4) includes in vivo pharmacokinetic data from six healthy volunteers exposed to 4 percent enzacamene applied over 90 percent body surface area for a 12-hour period. The data are limited by the small number of subjects included; however, there was gender-related difference observed in those males who had blood levels that were approximately twice that of females. A 2008 article by Janjua et al.

contains a more complete analysis of in vivo absorption for enzacamene in a 10 percent enzacamene formulation (Ref. 5). The levels of absorption were generally low but accumulation was observed. However, the age of the females enrolled in the study was 2 to 3 times that of the males, confounding the interpretation of age or gender effects.

Overall, the data available are incomplete for the assessment of human bioavailability (dermal absorption) of enzacamene. Accordingly, we request data from human pharmacokinetic studies to assess potential for and extent of systemic absorption. These studies should be performed under expected maximal-use conditions with the proposed maximum concentration as discussed previously.

In addition to the bioavailability data described previously, three reports of clinical pharmacology studies were submitted that evaluate the potential effect of enzacamene on thyroid function. The first was a pilot study in which a 5 percent enzacamene formulation was applied twice, at 3-hour intervals, to the abdomen and back of four adult subjects (two males and two females) (Note 11). Subsequent increases in the thyroid analytes thyroid-stimulating hormone (TSH), T3, and T4 were observed in some subjects. Blood and urine levels of enzacamene were reported to have been measured but no data were reported. We consider the number of subjects in this study too small to draw conclusions about the safety of enzacamene. In addition, there were missing data and the report lacked information about whether subjects' thyroid analyte levels exceeded normal levels.

A second study evaluated the effect on thyroid function of topical application of 5 percent enzacamene (6 grams (g) applied twice, at 3-hour intervals) in nine healthy volunteers (Note 12). This was a double-blind, placebo-controlled, crossover design study, and investigators reported that there was a statistically significant lowering of mean T3 and T4 values in the active

treatment group at 24 hours after application. Although larger than the pilot study, this is a small single-dose study and the changes reported were small relative to placebo and were of questionable clinical significance. Interpretation of the results is also hampered by the fact that some analytes (TSH and free T4) were below normal levels at baseline.

A third study was a parallel-group, placebo-controlled design in which 48 subjects received treatment with either enzacamene (5 g of a 6 percent enzacamene formulation per dose) or placebo twice daily for 14 days (Note 13). According to the investigators, the results of the study did not reveal any significant differences in thyroid function tests between enzacamene and placebo, although there was a small between-group difference in thyroid volume gland decrease (a 1.7 percent reduction in the enzacamene arm and an increase of 3.1 percent in the placebo group). The quality of the study report submitted is inadequate to be used to verify the analyses, but no adverse events of hypothyroidism or hyperthyroidism or abnormal thyroid function tests were reported.

The three clinical pharmacology studies submitted are insufficient either to substantiate or dismiss clinical concerns related to potential thyroid effects from enzacamene. We request submission of any additional clinical thyroid function data or analyses that have not yet been submitted to us, including any provided to the European Scientific Committee on Cosmetic Products and Nonfood Products (SCCNFP) to support its 2008 conclusion that enzacamene at a concentration up to 4 percent is safe for use in finished cosmetic products for whole body application (Ref. 6). If, after full review of nonclinical toxicology data (discussed in section I.B of this proposed order) and any additional clinical data, concerns exist regarding enzacamene's thyroid safety, we will recommend that additional clinical study be carried out. It is

recommended that we be consulted regarding the study protocols prior to commencement of such investigations.

### 3. Human Safety Data to Establish Adverse Event Profile

An evaluation of safety information from adverse event reports and other safety-related information derived from commercial marketing experience of sunscreen products containing enzacamene, as well as from other sources, is a critical aspect of FDA's safety review for enzacamene. The TEA regulation under which the original request for enzacamene was submitted specifically calls for submission of information on all serious adverse drug experiences, as defined in 21 CFR 310.305(a) and 314.80(a), from each country where the active ingredient or other condition has been or is currently marketed as either a prescription or OTC drug; in addition, it calls for submission of all data generally specified in § 330.10(a)(2), which includes documented case reports and identification of expected or frequently reported side effects (§ 330.14(f)(1) and (f)(2)). To evaluate enzacamene, FDA continues to seek individual adverse drug experience reports, a summary of all serious adverse drug experiences, and expected or frequently reported side effects of the condition (*id.*). To assist in the Agency's safety evaluation of enzacamene, FDA emphasizes our need for the following data:

- A summary of all available reported adverse events potentially associated with enzacamene;
- All available documented case reports of serious side effects
- Any available safety information from studies of the safety and effectiveness of enzacamene in humans; and
- Relevant medical literature describing adverse events associated with enzacamene.

Submissions of adverse event data should also include a description of how each country's system identifies and collects adverse events, unless this information has been previously submitted as part of enzacamene's TEA package.

Although we recognize that adverse event data from foreign marketing experience may reflect patterns of use and regulatory reporting requirements that differ from those in the United States, we nonetheless consider such information to be strongly relevant both to our overall GRASE assessment of enzacamene for use in sunscreens and to our consideration of potential product labeling. FDA recognizes that such information may not be available from all countries; where that is the case, please provide a written explanation for the lack of data. Overall, we seek sufficient data to characterize enzacamene's adverse event profile.<sup>3</sup>

Data Available for Enzacamene: Human Safety Data to Establish Adverse Event Profile

The 1999 enzacamene submission states that no complaints from customers concerning tolerance or adverse reactions had been reported for enzacamene by the cosmetic industry during the prior 10 years (Note 14). This information was referred to in the 2002 TEA submission and the 2003 enzacamene data submission. The 1999 enzacamene submission also included a literature search for adverse reactions to enzacamene from the following databases: Medline (1966-1998), Derwent Drug File (1983-1998), and CCSearch (week 3 1998-week 48 1998) (Note 15). There were 17 articles reviewed which had been published or translated into English. Of these, 10 articles describe contact dermatitis and resultant positive photopatch testing in one or two patients. The 7 other articles are literature or case series reviews of up to 400 patients, describing dermatologic adverse reactions to sunscreen use and subsequent photopatch testing.

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<sup>3</sup> See 67 FR 3060 at 3069 (January 23, 2002) (agreeing that the absence of an adverse experience reporting system in a foreign country for drugs or cosmetics does not necessarily mean that a condition cannot be GRAS/E. The GRAS/E determination will be based on the overall quality of the data and information presented to substantiate safety and effectiveness).

On the whole, these reports suggest that enzacamene has the potential to cause contact allergy and photocontact allergy. However, data from this literature have limitations. In some cases, the testing methodology used to determine that enzacamene is an allergen is not described. Also, some of the test formulations used are not described. It is conceivable that the observed reactions may have been specific to particular test formulations, including formulations containing other active ingredients.

The submitted information and literature do not fulfill the criteria described previously. To support the evaluation of safety of enzacamene for use in OTC sunscreens, we request that the sponsor either supplement the data already submitted, including more recent adverse drug experience data, or explain why such data cannot be provided.

#### B. Nonclinical (Animal) Studies

Another important element of FDA's GRAS review of enzacamene for use in sunscreens is an assessment of data from nonclinical (animal) studies that characterize the potential long-term dermal and systemic effects of exposure to enzacamene. Even if the bioavailability data discussed in section II.A.2 suggest that dermal application is unlikely to result in skin penetration and systemic exposure to enzacamene, FDA still considers data on the effects of systemic exposure to be an important aspect of our safety evaluation of enzacamene. A determination that enzacamene up to 4 percent is GRASE for use in sunscreens would permit its use in as-yet-unknown product formulations, which might in turn alter the skin penetration of the active ingredient. Therefore, an understanding of the effects of enzacamene, were systemic exposure to occur, is critical to determine whether and how regulatory parameters can be defined to assure that all conforming enzacamene-containing sunscreens would be GRASE as labeled.

FDA recommends animal testing of the potential long-term dermal and systemic effects of exposure to enzacamene because these effects cannot be easily assessed from previous human use. Taken together, the carcinogenicity studies, developmental and reproductive toxicity studies, and toxicokinetic studies described in sections II.B.1 through II.B.3 should provide the information needed to characterize both the potential dermal and systemic toxic effects and the levels of exposure at which they occur. These data, when viewed in the context of human exposure data, can be used to determine a margin of safety for use of enzacamene in OTC sunscreens.

#### Data Available for Enzacamene: Nonclinical (Animal) Studies Generally

The enzacamene submissions included data from the following types of nonclinical safety studies:

- Acute-dose toxicity studies
  - Oral toxicity (rats, dogs) (Note 16)
  - Dermal toxicity (rats) (Note 17)
  - Intraperitoneal toxicity (rats) (Note 18)
  - Mucosal irritation (rabbits) (Note 19)
  - Skin irritation and sensitization (guinea pigs) (Note 20)
  - Phototoxicity potential (mice) (Note 21)
  - Photosensitization (guinea pig) (Note 22)
- Repeat-dose toxicity studies
  - 17 days oral (rat) (Note 23)
  - 4 weeks oral (rat) (Note 24)
  - 13 weeks oral (rat) (Note 25)

- Liver enzyme induction study (rat) (Note 26)
- Genotoxicity and mutagenicity assays
  - Chromosome aberration assay (Chinese hamster V79 cells) (Note 27)
  - Mutagenicity (Salmonella typhimurium) (Note 28)
  - Photomutagenicity (S. typhimurium, Escherichia coli) (Note 29)
- Reproductive and developmental toxicity studies
  - Orienting tests for embryotoxicity (rabbit) (Note 30)
  - Toxicological investigation (incubated hen's egg) (Note 31)
  - Teratogenicity (rat) (Note 32)

Based on the submitted studies, acute toxicity was low. However, the standard battery of tests detected findings that we will consider further as additional data become available to inform our GRAS assessment. Studies submitted by the sponsor showed an increase in thyroid weight and changes in thyroid function that included an increase in T3 and TSH, along with a decrease in T4. Other thyroid findings included follicular epithelium hypertrophy and hyperplasia. A decrease in adrenal and prostate weights, and alterations in ovarian weights (an increase was seen in some studies while decreased weight was noted in others), was documented with a no observed adverse effect level (NOAEL) of 25-30 mg/kilograms (kg)/day (Note 33).

To followup on these findings, we identified published literature that describes related enzacamene activity. A number of these articles indicate that exposure to enzacamene at high doses has been associated with hormonal changes. Among the in vitro findings (Refs. 7 through 16), a number of articles described the in vitro binding activity of enzacamene to estrogen (ER) and androgen (AR) receptors where it was able to bind to ER $\beta$  but showed inconsistent binding

activity at ER $\alpha$  receptors. No androgenic activity and mixed results for antiandrogenic activity were also documented.

Other effects of enzacamene included in vivo alterations of reproductive tissues and behavior in rats (Refs. 17 through 25). Findings include decreased testis weight; increased prostate volume and altered duct development; delayed preputial separation; decreased prostate weight in males; and increased uterine weight, decreased ovarian weight, and altered sexual behavior in females. Overall, we cannot arrive at a final determination about the findings described in the literature until we receive a complete nonclinical assessment as described in sections II.B.1 through II.B.3.

We did not receive data from toxicokinetic or dermal or systemic carcinogenicity studies. Upon assessment of all available information for enzacamene and based on the nonclinical studies currently recommended to support sunscreen development, the following nonclinical studies are recommended to support the safety of enzacamene:

- Dermal and systemic carcinogenicity
- Fertility
- Prenatal/postnatal toxicity
- Toxicokinetics

Additional discussion of study findings and data gaps are provided in the following subsections.

#### 1. Carcinogenicity Studies: Dermal and Systemic

FDA guidance recommends that carcinogenicity studies be performed for any pharmaceutical that is expected to be clinically used continuously for at least 6 months or “repeatedly in an intermittent manner” (Refs. 26, 27, and 28). Because the proposed use of

enzacamene in OTC sunscreens falls within this category, these studies should be conducted to help establish that enzacamene is GRAS for its proposed use. Carcinogenicity studies assist in characterizing potential dermal and systemic risks by identifying the type of toxicity observed, the level of exposure at which toxicity occurs, and the highest level of exposure at which no adverse effects occur (i.e., NOAEL). The NOAEL would then be used in determining the safety margin for human exposure to sunscreens containing enzacamene.

Systemic carcinogenicity studies can also help to identify other systemic or organ toxicities that may be associated with enzacamene, such as hormonal effects. For example, the effect of persistent disruption of particular endocrine gland systems (e.g., hypothalamic-pituitary-adrenal axis), if any, can be captured by these assays.

#### Data Available for Enzacamene: Genotoxicity Studies

Enzacamene showed no evidence of DNA mutations in one standard Ames test. A chromosomal aberration assay using a Chinese hamster V79 cell line and a photomutagenicity assay were negative. Although these studies somewhat ease concerns about potential genotoxicity and mutagenicity, they were not definitive evaluations of potential toxic effects from long-term systemic or dermal exposure.

#### Data Available for Enzacamene: Carcinogenicity Studies

We did not receive dermal or systemic carcinogenicity studies. Assessments of both dermal and systemic carcinogenicity are recommended because sunscreen products containing enzacamene are expected to be applied over large portions of the body with multiple daily applications. In addition, as discussed previously, marketing of this product according to a final sunscreen order might permit its formulation in a variety of as-yet-unknown vehicles that might

have an impact on systemic absorption. Consequently, FDA seeks information on dermal and system carcinogenicity, in case of the possibility that systemic absorption could occur.

## 2. Developmental and Reproductive Toxicity (DART) Studies (Ref. 29)

FDA recommends conducting DART studies to evaluate the potential effects that exposure to enzacamene may have on developing offspring throughout gestation and postnatally until sexual maturation, as well as on the reproductive competence of sexually mature male and female animals. Gestational and neonatal stages of development may also be particularly sensitive to active ingredients with hormonal activity. For this reason, we recommend that these studies include assessments of endpoints such as vaginal patency, preputial separation, anogenital distance, and nipple retention, which can be incorporated into traditional DART study designs to assess potential hormonal effects of enzacamene on the developing offspring. We also recommend conducting behavioral assessments (e.g., mating behavior) of offspring, which may also detect neuroendocrine effects.

### Data Available for Enzacamene: DART Studies

Potential reproductive and developmental effects from enzacamene were evaluated in two embryotoxicity studies and one teratogenicity study. Enzacamene did not show evidence of embryotoxicity in a pilot rabbit test and hen's egg assay. In a teratogenicity study in rats with oral administration of single daily doses of 10, 30, and 100 mg/kg of enzacamene administered on days 6 to 15 after conception, enzacamene was not found to be teratogenic in any of the treated groups. Additional DART testing is recommended to assess fertility and prenatal and postnatal development in a rodent model.

## 3. Toxicokinetics (Ref. 30)

We recommend conducting animal toxicokinetic studies because they provide an important bridge between toxic levels seen in animal studies and potential human exposure. Data from these studies can be correlated to potential human exposure via clinical dermal pharmacokinetic study findings. Toxicokinetic data could be collected as part of animal studies being conducted to assess one or more of the safety parameters described previously.

#### Data Available for Enzacamene: Toxicokinetics

No toxicokinetic data were submitted as part of any of the nonclinical studies, thus it is difficult to bridge from animal findings to potential human exposure. Toxicokinetic data should be collected as part of the animal studies to allow exposure comparisons between animals and humans.

Toxicokinetic data are particularly important to the evaluation of enzacamene's safety for use in sunscreens because enzacamene appears to have the potential to affect some endocrine-responsive endpoints. We need toxicokinetic data to develop more information about exposure parameters, in order to understand whether a margin of safety exists between the exposures that cause the effects in animals and estimated human exposures. Should we find, after review of a more complete nonclinical program, that additional clinical studies are warranted, we will provide additional recommendations regarding the design of the studies.

### III. Effectiveness Data Considerations for OTC Sunscreen Products Containing Enzacamene

FDA's evaluation of the effectiveness of active ingredients under consideration for inclusion in an OTC drug monograph is governed by the following regulatory standard: Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed.

Proof of efficacy shall consist of controlled clinical investigations as defined in 21 CFR 314.126(b). Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details that permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (§ 330.10 (a)(4)(ii)). For convenience, this order uses the term “generally recognized as effective” (GRAE) when referring to this aspect of the GRASE determination.

To evaluate the efficacy of enzacamene for use in OTC sunscreen products, FDA requests evidence from at least two adequate and well-controlled SPF studies showing that enzacamene effectively prevents sunburn. To determine that enzacamene is GRAE for use in OTC sunscreens at concentrations in a range with the proposed maximum strength of 4 percent as requested, two adequate and well-controlled SPF studies of enzacamene at a lower concentration should be conducted according to established standards.<sup>4</sup> These SPF studies should demonstrate that the selected concentration (below 4 percent) provides an SPF of 2 or more.

The current standard procedure for SPF testing is described in FDA’s regulations in § 201.327(i).<sup>5</sup> Further SPF tests for enzacamene should be performed as described in these regulations, using a test formulation containing enzacamene as the only active ingredient to identify its contribution to the overall SPF test results. (See the following subsection Data

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<sup>4</sup> The upper bound of any concentration of enzacamene ultimately established in the OTC sunscreen monograph will be governed by the safety data, as well as by efficacy.

<sup>5</sup> Although the SPF testing procedure is used primarily for final formulation testing of finished products marketed without approved NDAs, under the sunscreen monograph, it is equally applicable for determining whether or not a sunscreen active ingredient is GRAE.

Available for Enzacamene: Effectiveness for further discussion of submitted SPF tests.) The study should also include a vehicle control arm in order to rule out any contribution the vehicle may have on the SPF test results. Finally, as described in § 201.327(i), an SPF standard formulation comparator arm should be another component of the study design.

Although current sunscreen testing and labeling regulations also specify a “broad spectrum” testing procedure to support related labeling claims for certain OTC sunscreen products marketed without approved new drug applications that contain specified active ingredients included in the stayed sunscreen monograph, those additional claims are permitted, but not required (§ 201.327(c)(2) and (j)). Under current regulations, sunscreen active ingredients need only be effective for the labeled indication of sunburn prevention, for which the SPF test can provide sufficient evidence. Consistent with this approach, we here do not request broad spectrum testing data for enzacamene. Broad spectrum protection is often, although not always, the result of the combined contribution of multiple active ingredients in a final sunscreen formulation. Thus, under the current regulations applicable to other sunscreens, the determination of whether an individual sunscreen product may be labeled as broad spectrum and bear the related additional claims is made on a product-specific basis, applying standard testing methods set forth in those regulations. If enzacamene is established to be GRASE for use in nonprescription sunscreens (based in part on the efficacy data requested here), the final order can likewise address broad-spectrum testing and related labeling conditions for final sunscreen formulations containing enzacamene.

Data Available for Enzacamene: Effectiveness

A total of 11 efficacy studies were submitted. Two studies, an in vitro assessment and a field study, both dated from the 1970s, did not use study designs that we consider valid for SPF

assessment for a GRASE determination (Docket No. 78N-0038, OTC Volume 060083, submitted December 18, 1973; Docket No. 78N-0038, OTC Volume 060130, submitted November 1974). The other nine studies all tested enzacamene as the only active ingredient. These included two studies of 1.25 percent enzacamene and three studies of 2.5 percent enzacamene, concentrations within the range found eligible for consideration of GRASE status in the Agency's 2003 eligibility determination, and three studies of 5 percent enzacamene and one study of 10 percent enzacamene, concentrations above the maximum established to be eligible for consideration, which studies we do not further address in this proposed order. (FDA-1978-N-0018-0766, Citizen Petition (CP1), submitted December 17, 1980.) In each of the five studies addressing enzacamene at concentrations of 1.25 percent and 2.5 percent, enzacamene achieved a mean SPF of 2, but there is substantial variability in the data and it cannot be confirmed that that efficacy was established at any of the concentrations tested. In addition, none of these study reports specified the use of appropriate standard controls to validate the test results. Currently, there are insufficient data to support a finding that enzacamene is GRAE at concentrations up to 4 percent

To support a finding that enzacamene is GRAE at concentrations up to 4 percent, we request data from two adequate and well-controlled SPF studies conducted according to established standards to demonstrate that the lowest selected concentration provides an SPF of 2 or more. Because no study has been identified that establishes that enzacamene is effective at a concentration of 4 percent, we also recommend that such a study be conducted and submitted.

#### IV. Summary of Current Data Gaps for Enzacamene

Based on our review of the available safety and efficacy data as discussed previously, we request the types of data listed in this section of the proposed order, at minimum, for us to

reverse our tentative determination that enzacamene is not GRASE and is misbranded because the data are insufficient to classify enzacamene as GRASE and not misbranded, and additional data are necessary to allow us to determine otherwise. For additional information about the purpose and design of studies recommended to address these data gaps, please refer to the earlier sections of this proposed order referenced in parentheses. We welcome discussions on design of any of the studies prior to their commencement. We request the following types of data:

- Safety Data (see section II)

- A. Human Clinical Studies

1. Skin irritation/sensitization and photosafety (see section II.A.1)
2. Human dermal pharmacokinetic (bioavailability) studies (see section II.A.2)

The need for additional human safety studies (e.g., for evaluation of hormonal disruption) will be based on review of the completed nonclinical studies, as recommended in section IV.C.

- B. Human Safety Data to Establish Adverse Event Profile (II.A.3)

1. A summary of all available reported adverse events potentially associated with enzacamene
2. All available documented case reports of serious side effects
3. Any available safety information from studies of the safety and effectiveness of sunscreen products containing enzacamene in humans
4. Relevant medical literature describing adverse events associated with enzacamene.

Alternatively, the results of a literature search that found no reports of adverse events may be provided. In that case, detailed information on how the search was conducted should be provided.

- C. Nonclinical (Animal) Studies

1. Dermal and systemic carcinogenicity (see section II.B.1)
  2. Fertility (see section II.B.2)
  3. Prenatal/postnatal development (see section II.B.2)
  4. Toxicokinetics (see section II.B.3)
- Effectiveness Data (see section III)

In order for concentrations of enzacamene up to 4 percent to be found to be GRASE for use in nonprescription sunscreen products as requested, at least two SPF studies showing effectiveness of a selected concentration lower than 4 percent should be conducted. An efficacy study of enzacamene at 4 percent is also recommended.

#### V. Administrative Procedures

A copy of this proposed order will be filed in the Division of Dockets Management in Docket Numbers FDA-2003-N-0196, FDA-1978-N-0018, and FDA-1996-N-0006. To inform FDA's evaluation of whether this ingredient is GRASE and not misbranded for use in sunscreen products, we encourage the sponsor and other interested parties to submit additional data regarding the safety and effectiveness of this ingredient for use as an OTC sunscreen product. We also encourage the sponsor and other interested parties to notify us in writing of their intent to submit additional data. However, as noted previously, because the data submitted to date are not sufficient to support a determination that enzacamene is GRASE for use as an active ingredient in OTC sunscreen drug products, at present, OTC sunscreen products containing enzacamene may not be marketed without approval of an NDA (see section 586C(e)(1)(A) of the FD&C Act, as amended by the SIA). Data submissions relating to this proposed order should be submitted to Docket Numbers FDA-2003-N-0196, FDA-1978-N-0018, and FDA-1996-N-0006 at the Division of Dockets Management (see ADDRESSES). In addition, you can submit the

data through the Federal eRulemaking Portal at: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Section 586C(b)(7) of the FD&C Act, as amended by the SIA, provides that the sponsor may, within 30 days of publication of a proposed order (see DATES), submit a request to FDA for a meeting to discuss the proposed order. Submit meeting requests electronically to <http://www.regulations.gov> or in writing to the Division of Dockets Management (see ADDRESSES), identified with the active ingredient name enzacamene, the docket numbers found in brackets in the heading of this proposed order, and the heading “Sponsor Meeting Request.” To facilitate your request, please also send a copy to Kristen Hardin (see FOR FURTHER INFORMATION CONTACT).

#### VI. Proposed Effective Date

FDA proposes that any final administrative order based on this proposal become effective on the date of publication of the final order in the Federal Register.

#### VII. Comments

Similarly, section 586C(b)(6) of the FD&C Act, as amended by the SIA, establishes that a proposed sunscreen order shall provide 45 days for public comment. Interested persons wishing to comment on this proposed order may submit either electronic comments to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the active ingredient name (enzacamene) and the docket numbers found in brackets in the heading of this proposed order. Received comments on this proposed order may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

## VIII. Notes

1. FDA-2003-N-0196-0056, Time and Extent Application (TEA) Request to Reopen the Rulemaking Record; submitted August 21, 2002.
2. FDA-2003-N-0196-0028, C1, dated October 9, 2003.
3. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 10, dated November 27, 1972.
4. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 20, dated September 8, 1982.
5. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 11, dated February 20, 1980.
6. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 12, dated February 20, 1980.
7. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 21, dated June 5, 1985.
8. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 14, dated November 29, 1982.
9. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 15, dated July 17, 1984.
10. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 16, dated July 8, 1984.
11. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 19, dated August 1, 1981.
12. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 18, dated July 2, 1982.
13. FDA-1978-N-0018-0762 (Sup 28), Volume 5, Report 29, Study no. 43/20792, dated October 18, 1995.
14. FDA-1978-N-0018-0754 (Sup 24), dated April 12, 1999.
15. FDA-1978-N-0018-0755 (Sup 24), Attachment 1, dated April 12, 1999.
16. FDA-1978-N-0018-0758 (Sup 24), Volume 1, Reports 1, 2, 3 and 4, Study no. 4/83/71, 4/130/73, 4/131/73, 4/52/80.
17. FDA-1978-N-0018-0758 (Sup 24), Volume 1, Reports 2 and 3, Study no. 4/130/73 and 4/131/73.
18. Id.

19. Id.
20. Id.
21. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 8, dated October 16, 1978.
22. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 9, dated October 16, 1978.
23. FDA-1978-N-0018-0758 (Sup 24), Volume 1, Report 5, dated May 5, 1983.
24. Id.
25. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 7, dated April 26, 1984.
26. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 17, dated May 1, 1984.
27. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 22, Study no. LMP166, dated April 25, 1986.
28. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 13, Study no. 4/56/80, dated June 2, 1980.
29. FDA-1978-N-0018-0761 (Sup 27), Volume 4, Report 28, Study no. 40/13/93, dated April 14, 1993.
30. FDA-1978-N-0018-0760 (Sup 26), Volume 3, Report 23, Study no. 4/20/84, Experiment No. T9207.
31. FDA-1978-N-0018-0761 (Sup 27), Volume 4, Report 24 and 25, dated October 23, 1987, and October 26, 1987.
32. FDA-1978-N-0018-0761 (Sup 27), Volume 4, Report 26, Study no. 4/43/88, Experiment No. T9305, dated September 14, 1983.
33. FDA-1978-N-0018-0759 (Sup 25), Volume 2, Report 7, dated April 26, 1984.

#### IX. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. FDA, Guidance for industry, "Photosafety Testing," May 2003 (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079252.pdf>).

2. FDA, Guidance for Industry, "Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application," February 1987 (available at <http://www.fda.gov/downloads/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072112.pdf>).

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[http://ec.europa.eu/health/ph\\_risk/committees/04\\_sccp/docs/sccp\\_o\\_141.pdf](http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_141.pdf)).

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12. Schmutzler, C., et al., "Endocrine Disruptors and the Thyroid Gland--A Combined In Vitro and In Vivo Analysis of Potential New Biomarkers." Environmental Health Perspectives, vol. 115 (Supplement 1), pp. 77-83, 2007.

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074916.pdf>).

28. ICH, “S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals SIC(R2)” (Revision 1), September 2008 (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074919.pdf>).

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Dated: February 20, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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