U.S. FOOD & DRUG ADMINISTRATION

FEB 0 2 2017

Emil A. Tanghetti, M.D.
Center for Dermatology and Laser Surgery
5601 J Street
Sacramento, CA 95819

Re: Docket Nos. FDA-2006-P-0267 and FDA-2007-P-0064

Dear Dr. Tanghetti:

This letter responds to the two citizen petitions cited above (Petitions) that you submitted to the Food and Drug Administration (FDA) concerning Ziana Gel (clindamycin phosphate 1.2% and tretinoin 0.025%) (Ziana).[1] Ziana is a lincosamide antibiotic and retinoid combination drug indicated for the topical treatment of acne vulgaris in patients 12 years or older.[2] Your Petitions ask FDA to withdraw approval and recall all available stocks of Ziana to prevent the development of harmful antibiotic resistance. Alternatively, you ask us to require the immediate initiation of long-term safety studies evaluating the incidence and prevalence of antibiotic resistance associated with Ziana usage.

We have carefully considered the information submitted in your Petition as well as other data and evidence available to the Agency. Based on our review of these materials, for the reasons set forth below, both Petitions are denied. However, as with all FDA-approved products, we will continue to monitor and review available safety information related to Ziana and take action as appropriate.

I. BACKGROUND

Antibacterial and other antimicrobial drugs have been used in human and veterinary medicine for more than 70 years, with tremendous benefits to both human and animal health. Many infections that once were fatal, or left individuals with severe disabilities, are now treatable or preventable. However, as your Petitions point out, the proliferation of drug-resistant bacterial and other microbial infections (sometimes called antimicrobial or antibiotic resistance)[3] is a serious and growing health problem in the United States and worldwide.

FDA is responding to the problem of antimicrobial resistance on many fronts. FDA has been a key participant in federal initiatives including the National Strategy to Combat Antibiotic-Resistant Bacteria (National Strategy), which was established in 2015 to slow the emergence of resistant bacteria and to

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[1] This letter responds to two identical citizen petitions that you submitted on different dates. The initial submission was dated December 15, 2006, and was originally assigned docket number 2006P-0524/CP1. The resubmitted petition was received on May 21, 2007, and was originally was assigned docket number 2007P-0205/CPI. Both numbers were subsequently changed because of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] Ziana is marketed under NDA 50-802 that was approved on Nov. 7, 2006. Although not addressed in the Petitions, another product (Veltin) with the same active ingredients was approved on July 16, 2010, under NDA 50-803.

[3] The term *antimicrobial* refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites (such as malaria). The term *antibiotic* commonly describes an *antibacterial* drug, or a drug with activity against bacteria in particular.

prevent the spread of resistant infections, among other goals.[4]

Section 505(e) of the Food, Drug, and Cosmetic Act (FD&C Act) establishes the circumstances under which FDA will, after due notice and opportunity for hearing, withdraw approval of a new drug application (NDA) or abbreviated new drug application (ANDA). With respect to safety concerns, the agency will withdraw approval of a drug if it finds either of the following:

> That clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved

or

> That new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonable applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.[5]

Section 505(o) of the FD&C Act establishes circumstances where the Agency may require postapproval studies or clinical trials. FDA may require a responsible person for a drug to conduct postapproval studies or postapproval clinical trials of the drug for any of the following purposes:

> To assess a known serious risk related to the use of the drug involved.
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> To assess signals of serious risk related to the use of the drug.
>
> To identify an unexpected serious risk when available data indicates the potential for a serious risk.[6]

In the case of a product with an approved NDA the Agency "may require a postapproval study or studies or postapproval clinical trial or trials … only if the Secretary becomes aware of new safety information."[7] The FD&C Act defines "new safety information" as:

> Information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by the Secretary about –
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> (A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary

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[4] For more information on the National Strategy and to access related Federal initiatives, see http://www.cdc.gov/drugresistance/federal-engagement-in-ar/national-strategy/index.html; for more detail on FDA's activities related to antibiotic and antimicrobial resistance, see http://blogs.fda.gov/fdavoice/index.php/2014/09/fdas-take-on-the-executive-order-and-national-strategy-to-combat-antibiotic-resistant-bacteria and http://www.fda.gov/newsevents/publichealthfocus/ucm235649.htm.

[5] Section 505(e)(1) and (2) of the FD&C Act; see also 21 CFR 314.150(a)(2)(i) and (ii).

[6] Section 505(o)(3).

[7] Section 505(o)(3)(C).

has become aware of (that may be based on a new analysis of existing information)since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.[8]

FDA's regulations at 21 CFR 7.45 set out guidelines for FDA-requested recalls. As stated there:

(a) The Commissioner of Food and Drugs or designee may request a firm to initiate a recall when the following determinations have been made:
(1) That a product that has been distributed presents a risk of illness or injury or gross consumer deception.
(2) That the firm has not initiated a recall of the product.
(3) That an agency action is necessary to protect the public health and welfare.

Recall of drug products is a voluntary action that can serve as an alternative to an FDA-initiated court action. Generally, when a drug recall is warranted, the agency works with manufacturers and others on a cooperative basis. See 21 CFR part 7.

II. DISCUSSION

Your Petitions maintain that the topical use of Ziana to treat acne represents a public health risk because it contributes to the development of antibiotic-resistant bacteria, including harmful bacterial species other than the target bacterium for acne, *Propionibacterium acnes* (*P. acnes*). In support of this position, you state that the reported incidence of resistant *P. acnes* has increased by over 50 percent since the mid-1970s.[9] You also cite a study in which topical clindamycin therapy elicited resistant organisms as early as 12 weeks into therapy, with substantial increases in resistant *P. acnes* and coagulase-negative *staphylococci,* while a combination product containing clindamycin and benzoyl peroxide reduced overall and resistant species of these same bacteria.[10] You further contend that "the only way to avoid the development of resistance when prescribing Ziana is to also prescribe a benzoyl peroxide product;"[11] however, you caution that this approach is unlikely to succeed because medication compliance is inversely related to the complexity of the therapy and because "there is no proven method to ensure that patients will comply with this dual therapy."[12] In addition, you state that, in dermatology alone, the incidence of potentially harmful community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) comprises as much as 50 percent of all *Staphylococcus aureus* positive cultures in some regions.[13] Although you recognize that "conclusive evidence identifying the causation of this increase is

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[8] Section 505-1(b)(3).

[9] Petition at 2, note 4 (citing Eady, EA, M Gloor, and JJ Leyden, 2003, *Propionibacterium acnes* Resistance: A Worldwide Problem, Dermatology, 206:54-56 (Eady, et al. (2003)). We note, however, that the cited reference provides prevalence data only for a single year (1997) and location (Leeds, United Kingdom) and does not address the percent change over time.

[10] Petition at 2, note 6 (citing Cunliffe, WJ, KT Holland, R Bojar, and SF Levy, 2002, A Randomized, Double-Blind Comparison of Clindamycin/Benzoyl Peroxide Gel Formulation and a Matching Clindamycin Gel With Respect to Microbiologic Activity and Clinical Efficacy in the Topical Treatment of Acne Vulgaris, Clin Ther, 24(7):1117-1133).

[11] Petition at 3 (citing Tan, HH, 2004, Topical Antibacterial Treatments for Acne Vulgaris: Comparative View and Guide to Selection, Am J Clin Dermatol, 5:79-84).

[12] Petition at 3 (citing Osterberg, L and B Terrence, 2005, Adherence to Medication, N Engl J Med, 353:487-497).

[13] Petition at 3 (citing Cohen, P and K Kurzrock, 2004, Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Skin Infection: An Emerging Clinical Problem, J Am Acad Dermatol, 50:277-280 (Cohen and Kurzrock (2004))). We note that

not yet available," you argue that FDA should take the requested actions against Ziana because "any form of bacterial resistance has the ability to transfer to other species" and therefore "all efforts to prevent the development of antibiotic resistance should be instituted."[14]

We have reviewed your Petitions and available scientific literature, and we find no basis for withdrawing approval of Ziana's NDA. First, your Petitions do not contain evidence raising concerns of a correlation between the use of Ziana specifically and adverse clinical effects associated with the development of antibiotic resistance. You also provide no rationale for withdrawing approval of Ziana alone even though the concerns and arguments you raise could apply generally to the use of both topical and systemic antibiotics to treat acne and many other conditions.

Second, we have reviewed the available medical literature on antibiotic-resistant *P. acnes* and/or the association between antibiotic resistance and the use of clindamycin or other antimicrobial drugs for treating acne. Our review focused on potential public health concerns related to the development of resistant strains of either *P. acnes* or other bacterial species. Resistance to *P. acnes* in antibiotic-treated acne patients may manifest as lack of or loss of therapeutic effect.[15] Since alternative acne treatments are available, including other topical antibacterial drugs, oral antibacterial drugs, and oral isotretinoin, this lack of or loss of therapeutic effect can be ameliorated.

While topical antibacterial drugs are included in first line treatment recommendations in clinical care guidelines for acne,[16] we acknowledge that treatment of acne patients with topical antibiotics is associated with colonization with antibiotic-resistant *P. acne.* There is also a concern that topical treatment with antibiotics over time may lead to the development of resistance in other skin flora such as staphylococcal species or that development of resistance to clindamycin may also lead to cross-resistance to other bacterial drugs.[17,18] However, we are unaware that any signal has emerged over the decades that acne patients (or their close contacts) are more prone to serious infections caused by resistant organisms. Although *P. acnes* can be pathogenic and serious infections have been reported, these infections are infrequent and seem to occur in a different patient population as they are generally associated with neurosurgical procedures and prosthetic implants (e.g. prosthetic joint, prosthetic heart valves).[19] There are antibacterial drug alternatives to clindamycin which may be used to treat serious infections caused by *P. acnes.*

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although CA-MRSA is a clinically significant antibiotic-resistant infection, this article does not correlate the occurrence of CA-MRSA with the use of topical antibiotics, and this article reflects the experience at only one health center.

[14] Petition at 3, notes 8 (citing Cohen and Kurzrock (2004), supra note 12, and 9 (citing Levy, SB, March 1998, The Challenge of Antibiotic Resistance, Sci Am, 46-53 (Levy (1998))), respectively.

[15] Nord, CE and C Oprica, 2006, Antibiotic Resistance in *Propionibacterium acnes*, Microbiological and Clinical Aspects, Anaerobe,12:207-210 (Nord and Orica (2006)) and Eady, EA, 1998, Bacterial Resistance in Acne, Dermatology, 196:59-66 (Eady (1998)).

[16] Zaenglein AL and Pathy AL et al. Guidelines of care for the management of acne vulagaris. J Am Acad Dermatol 2016;74:945-73.

[17] Eady, et al. (2003), supra note 8; Eady (1998), supra note 14.

[18] Simonart, T and M Dramaix, 2005, Treatment of Acne With Topical Antibiotics: Lessons From Clinical Studies, Br J Dermatol, 154:395-403.

[19] Eady, et al. (2003), supra note 8; Eady (1998), supra note 14; Bologna, JL and RL Adelson, 1997, Spread of Antibiotic-Resistant Bacteria From Acne Patients to Personal Contacts – A Problem Beyond the Skin?, J Lancet, 350:972-973. Resistant strains of *P. acnes* may also occur in close contacts of acne patients. Nord and Oprica (2006), supra note 14; Levy (1998), supra note 13.

Third, your request that we withdraw Ziana's approval is not supported by your assertions about the efficacy of benzoyl peroxide in suppressing the development of antibiotic resistance to clindamycin. We acknowledge that the use of benzoyl peroxide together with a topical antibacterial drug is recommended in expert clinical care guidelines.[20] However, this use of Ziana has not been evaluated in adequate and well-controlled trials. As is common in medical practice, physicians could write separate prescriptions for both Ziana and a topical benzoyl peroxide product.

For all the reasons stated above, we do not believe that the evidence and arguments in your Petitions support a conclusion that bacterial resistance associated with the use of Ziana represents a potential safety concern that merits withdrawing the product's NDA or requesting a voluntary recall.[21]

We also are denying your alternative requests that we require long-term safety studies to evaluate the incidence and prevalence of antibiotic resistance associated with Ziana usage and that we initiate a voluntary recall. As discussed above, the available evidence has led us to believe that further study into this risk is not warranted at this time.[22] The available evidence also do not lead us to believe that an FDA requested recall is warranted at this time.[23] We note that the prevalence of antibiotic resistance continues to be studied, with findings being published in the scientific literature.

While we do not agree with the requests in your Citizen Petition, FDA shares your concerns regarding the growing public health risks posed by antimicrobial resistance in humans. We will continue to work to emphasize the prudent use of antibiotics in drug labeling, join with U.S government partners to promote public awareness about preventing antibiotic-resistant infections, and facilitate the development of new antibacterial drugs to treat serious bacterial diseases in patients with unmet medical need due to antimicrobial resistance.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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[20] Zaenglein AL and Pathy AL et al (2016)

[21] For the same reason we also disagree with your assertion that potential antibiotic resistance associated with the use of Ziana may cause the product to violate 21 CFR 300.50. The potential antibiotic resistance issue that you raise is unrelated to the specific requirements for a fixed combination prescription drug identified in that section.

[22] The *Microbiology* subsection of the Ziana label includes the following statement: "Resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin."

[23] *See* 21 CFR 7.45