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August 27, 2003

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 75N - 183H

To Whom It May Concern:

Aplicare, Inc., is submitting the following comment to the above-referenced docket in response to the Agency's May 29, 2003 *Federal Register* Notice ("Notice" or "May 2003 Notice"). The Notice reopened the administrative record for the rulemaking for over-the-counter ("OTC") topical antimicrobial drugs to accept comments and data regarding OTC health care antiseptic drug products filed since the administrative record officially closed, and to request public comment on such submissions.

Our comments are in response to submissions regarding the ingredients povidone-iodine ("PVP-I") and isopropyl alcohol ("IPA"), which are listed as Category I ingredients for patient preoperative skin preparation uses in the amended Tentative Final Monograph for health care antiseptics, 59 Fed. Reg. 31402 (June 17, 1994) ("TFM"). We are writing to support comments that agree with the Category I designation of the ingredients and to provide further information supporting use of PVP-I and IPA in combination for preoperative skin preparation, including pre-catheterization and pre-injection.[1]

Introduction

The Agency published the TFM on June 17, 1994. The administrative record was closed on August 17, 1995. Subsequent to closure of the record, submissions were made to the docket by a number of companies and organizations to provide data and information on the use of the ingredients PVP-I and IPA and for pre-operative skin preparation

[1] To the extent the agency determines that the rulemaking requires reopening to consider the combination, we believe that reopening the record is in the best interest of the public health. In that case, we request that the agency treat this comment as a petition to reopen the rulemaking and find that good cause exists to consider the information presented herein in developing the final monograph for these products, *see* 21 CFR § 330.10(a)(7)(v). Information before the agency in the June 15, 1995 Citizen Petition from 3M Health Care regarding Docket No. 75N-183H (listed as CP2 in the docket) ("3M petition"), and in other submissions from 3M referenced on page 3 of its petition, is stated by 3M to support finding that the combination of PVP-I and IPA has been marketed in the U.S. for a material time and to a material extent. *See* 3M petition at 3, 30. Thus, the combination is properly the subject of the rulemaking.

indications and to support their designation as Category I in the TFM.[2] The Agency's May 2003 Notice stated the reason for the reopening of the record was the Agency's determination that the late-submitted data and information are significant and relevant to developing the final monograph for health-care antiseptic drug products. Aplicare agrees and is commenting to support the inclusion of additional information regarding the merits of PVP-I and IPA. We further agree with the Agency and prior submissions to the docket that the individual ingredients PVP-I and IPA are properly classified as Category I for the preoperative skin preparation uses listed in the TFM. However, Aplicare also believes that it is equally important that the recently accepted submissions and the rest of the administrative record be supplemented by information provided herein on products combining PVP-I and IPA, including Aplicare's newly developed formulation, described below.

As demonstrated by our attached literature review, the PVP-I/IPA combination has demonstrated improved immediate kill of microorganisms compared with PVP-I formulations and improved antimicrobial persistence compared with IPA formulations. Thus, it is important that this combination be recognized because it provides benefits over the individual Category I ingredients that are important to the public health. Further, products containing a combination of PVP-I and IPA (*e.g.*, 3M's DuraPrep™)[3] as active ingredients have been on the market for many years and are widely distributed and used. Therefore, sound public health policy demands that the combination be considered before the TFM is finalized.

Aplicare was in the beginning stages of doing safety and efficacy testing on its combination formulation when the May 2003 Notice was published. Aplicare's preliminary data demonstrates its formulation to be safe and effective for the preoperative skin preparation uses discussed in the comments and listed in the TFM, as well as for pre-catheterization.[4] Aplicare expects to supplement this comment with its data for consideration in the rulemaking within a month. In the interim, Aplicare will appreciate the Agency considering (1) its support for the data and information submitted by other companies demonstrating the safety and efficacy of PVP-I and IPA, and (2) the attached comprehensive literature review on health care antiseptic products that demonstrates the scientific merits of combinations of PVP-I and IPA. The review also includes articles on PVP-I and ethyl alcohol (EtOH) combinations, which we believe are

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[2] Such submissions include:
- December 12, 1995 and March 7, 1996 letters from the Cosmetic, Toiletry, Fragrance Association/ Soap Detergent Association Industry Coalition submitting in vitro and in vivo efficacy data, including published literature and unpublished industry data, to support the Category I classification of PVP-I and IPA.
- February 14, 1996, July 8, 1996, and October 2, 1996 letters from ConvaTec submitting additional data compiled from published literature studies and protocols and final reports of in vivo and in vitro studies conducted by ConvaTec to support Category I status for IPA 70-91.3% as a health care personnel handwash and a preoperative skin preparation, and a final report on the evaluation of CalStat 70% IPA and Iodine solutions for preoperative skin preparation.

[3] 3M's DuraPrep™ product is made up of an acrylate/PVP-I copolymer and IPA. The 3M petition provides information to demonstrate that the acrylate/PVP-I copolymer in DuraPrep™ is equivalent to PVP-I with regard to safety and efficacy and does not enhance or degrade the antimicrobial efficacy of the product for its intended use. *See* 3M petition at 8-13.

[4] Aplicare has preliminary data demonstrating its formulation to be effective for preparation of the skin prior to catheterization and during catheter dressing change procedures on dry sites such as the abdomen.

relevant because the mechanism of action of ingredients and indications for use are practically the same as PVP-I and IPA; further, a number of PVP-I and EtOH combinations have been on the market since the mid to late 1990's.

In sum, substantial scientific evidence, and the time and extent to which these combined ingredients have been marketed, establishes the PVP-I and IPA combination as safe and effective and demonstrates the synergistic effect of the combination of active ingredients. As demonstrated herein, the combination meets the Agency's requirements for combining safe and effective OTC ingredients, as well as Agency guidelines for combining ingredients from the same therapeutic category.

Below we describe Aplicare's formulation and the scientific and public health rationale for combining the ingredients. The attached literature review provides an overview of findings and a summary table of studies, products tested, procedures, and important results for the key articles.

Aplicare's formulation and rationale for the combination of ingredients

Aplicare is developing two products that will consist of a) single (1) or b) triple (3) swabsticks impregnated with a formulation combining 7.5% PVP-I (w/w) and 72% IPA (v/v) (the "X-07-AB formulation"). The single swabstick product configuration is currently intended to be marketed for preparation of the skin prior to injection. The triple swabstick is currently intended to be marketed for preparation of the skin prior to surgery of "dry" (*e.g.*, abdominal) surgical sites, including those where maintenance of indwelling vascular access devices is required.

Description of formulation

Aplicare's X-07-AB formulation is similar to 3M's currently marketed combination of PVP-I and IPA for preoperative skin preparation, DuraPrep™, in that it contains the same active ingredients at concentrations within the ranges designated as Category I in the TFM (PVP-I, 5 to 10%, and IPA, 70 to 91.3 %). The mechanism of antimicrobial action of Aplicare's X-07-AB formulation is twofold. The antimicrobial effect is produced by both IPA's rapid bactericidal effect via dehydration and protein denaturation and PVP-I's prolonged bactericidal effect via oxidation. Acrylate is also included in the formulation as an inactive thickening agent, which provides two additional benefits. First, by increasing the viscosity of the formulation, it facilitates application of the solution onto the skin and helps decrease the chance of solution "runoff" and pooling underneath the patient being prepped. If not blotted away from the skin, it is not uncommon for pooled iodine-based formulations to cause burns. Second, as the formulation dries, the acrylate serves to enhance the film-forming characteristics of PVP-I formulations. This film helps prevent the active ingredients from being inadvertently rinsed off prepared sites by either water or bodily fluids.[5]

[5] Although in Aplicare's formulation, the acrylate is not incorporated into the PVP molecule, the viscosity enhancing and film forming effects are similar to those produced by the acrylate/PVP-I copolymer in 3M's DuraPrep™. Acrylate is also found in other products currently on the market that combine PVP-I and EtOH for preoperative skin preparation uses.

Rationale for ingredient combination

In the TFM, the Agency recognized PVP-I (5 to 10%) and IPA (70 to 91.3 %) as Category I ingredients for patient preoperative skin preparation uses. As demonstrated by the information provided herein, the combination of PVP-I and IPA provides a rational therapy that satisfies the OTC combination regulations[6] and the Agency's 1978 policy on combining ingredients from the same therapeutic category.[7] In Aplicare's formulation, each ingredient has a different mode of activity (IPA, dehydration and protein denaturation; PVP-I, oxidation) and resulting effectiveness against microorganisms. IPA is relatively more fast acting than PVP-I, while PVP-I demonstrates more persistence in activity over time. When combined, the resulting formulation is both faster acting than PVP-I alone and more persistent than IPA alone. As a result, the combination is more advantageous than either ingredient alone.

The public health benefits of this combination are clear and logical. Indeed, the antimicrobial activity provided by each active ingredient individually as well as by the combination is well understood by healthcare professionals familiar with patient preoperative prepping.[8] In addition to their well-established efficacy, formulations containing the combination of PVP-I and IPA provide a number of additional advantages, specifically:

- Faster and easier to apply compared with the common practice of preparing the skin prior to surgery using first a PVP-I based detergent "scrub", followed by an additional PVP-I "topical solution" or "paint". The addition of IPA to PVP-I allows the formulations to dry more rapidly than individual PVP-I products, thus saving valuable time of healthcare professionals.
    - Simpler prepping procedures lead to their being carried out more consistently, potentially resulting in reduced infection rates.
    - In situations where time is critical, rapid drying and effect are especially important.

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[6] Agency regulations provide that safe and effective active ingredients may be combined to yield a generally safe and effective combination drug product when 1) each active ingredient contributes to the claimed effects of the combination, 2) the combination does not decrease the safety and effectiveness of the active components, and 3) the combination as properly labeled as to indications, directions for use, and warnings provides a rational concurrent therapy for its intended use in a significant proportion of the target population. *See* 21 CFR § 330.10(a)(4)(iv). As discussed above and in the attached literature review, the PVP-I/IPA combination provides complementary modes of action that both contribute to the therapeutic effect, and has equivalent or better safety and effectiveness than the individual ingredients.

[7] The agency's 1978 guidelines state that Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the above regulatory standard in all respects and the combination is "on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose." *See* FDA's September 1978 *General Guidelines for OTC Drug Combination Products.*. Such combinations "may utilize each active ingredient in full therapeutic dosage or sub-therapeutic dosage, as appropriate." *Id.* As discussed above and in the literature review, the PVP-I/IPA combination meets the regulatory standard and on a benefit/risk basis is equal to or better than its individual ingredients for patient preoperative preparation uses, including uses in pre-catheterization and catheter dressing changes.

[8] *See generally* attached literature review at sections 2.0-5.0 *See also* 3M petition at 3-4, 28-29 (describing, as of June 1995, widespread acceptance of Duraprep™, *i.e.*, 13 million surgical and IV site prep procedures in the U.S. alone, and citing surveys of surgeons and operating room supervisors finding that Duraprep saves time, reduces variations in prepping procedures, and enhances drape adhesion).

- Faster and easier to apply compared with the common practice of preparing the skin prior to central line dressing changes, which typically first use three (3) IPA impregnated swabsticks followed by three (3) PVP-I impregnated swabsticks. Providing both active ingredients in the same formulation negates the possibility of the healthcare professional applying the IPA and PVP-I impregnated swabsticks in the wrong order, potentially resulting in reduced infection rates.
- The staining characteristics of PVP-I allow for easier recognition of areas that have been disinfected compared with formulations containing only IPA.
- In formulations containing acrylate, additional advantages include:
    - improved dressing adherence because acrylate forms a film typically adherent to both skin and dressing tape.
    - improved resistance to inadvertent removal by water or bodily fluids because acrylate forms a film resistant to removal by these liquids.
    - the flow and distribution of solution is easier to control when compared with typically less viscous PVP-I "scrub" and "topical" solutions.

All of these additional attributes are important to healthcare workers responsible for carrying out the above procedures and ultimately to patients. Both groups benefit from an antimicrobial formulation that is at least as efficacious as each ingredient alone and that has improved efficiency and usability, resulting in potentially lower infection rates.

These benefits explain the general acceptance of PVP-I/IPA products currently on the market. Indeed, 3M's DuraPrep™ has been on the market since 1988, and the company reported an excellent safety record in its 1995 petition to the agency.[9]

Conclusion

We believe this comment provides important information in support of and supplementary to comments recently accepted into the administrative record that endorse the designation of PVP-I and IPA as Category I ingredients for preoperative skin preparation uses. Effective skin disinfection is critical in preventing surgical and indwelling catheter site infection. Formulations containing a combination of PVP-I and IPA provide important advantages over formulations containing only one of these active ingredients, including more rapid kill combined with enhanced persistence, as well as speed and ease of use. As a result, the combination is an improvement for both healthcare workers and patients over formulations containing either ingredient alone. Further, because products combining PVP-I and IPA have been widely marketed OTC in the U.S. for a significant period of time for preoperative skin preparation uses, we believe a final monograph would be incomplete and the public health would not be well served without the inclusion of the PVP-I/IPA combination in the rulemaking.[10]

In sum, there is a compelling public health interest in including the combination of these active ingredients in the Final Monograph for products intended for use in preoperative

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[9] *See* 3M petition at 30-32; note 8, *supra*.

[10] Because there are also preoperative skin preparation products on the market combining PVP-I and EtOH, which is also a Category I ingredient, Aplicare would support amending the TFM to consider more generally allowing combinations of the individual Category I preoperative skin preparation active ingredients listed in proposed section 333.412, where a combination can be supported by sufficient data and information to demonstrate that the combination is GRAS/E and not misbranded for preoperative skin preparation uses.

skin preparation, including pre-injection and pre-catheterization. Specifically, proposed Subpart E of the TFM should be amended to include a combination of the active ingredients PVP-I, 5 to 10%, and IPA, 70 to 91.3% as follows: (1) by adding the combination to currently reserved 21 CFR § 333.420 (Permitted combinations of active ingredients); (2) by amending 21 CFR § 333.460 to allow each of the permissible indications listed in paragraph 333.460(b) to be included in labeling for the combination; and (3) to add the claim of pre-catheterization to paragraph 333.460(b) as a permissible indication for the combination. We believe the safety and effectiveness data summarized in the attached literature review are sufficient to place the combination in Category I in the Final Monograph for Health-Care Antiseptic Drug Products for use in patient preoperative skin preparation, including pre-injection and pre-catheterization uses. As stated above, Aplicare continues to develop data on its formulation, and expects to provide such data to the agency for consideration in the rulemaking within a month.

Yours truly,

Greg Art

Greg Art
Director of Product Development

Attachment