

Appendix 3

June 20, 2003

VIA FEDERAL EXPRESS

USAN Review Board
c/o Joseph G. Valentino, Esq.
Secretary, USAN Review Board
12601 Twinbrook Parkway
Rockville, MD 20852
Phone: (301) 816-8256

REPLY TO USAN COUNCIL LETTER DATED MAY 23, 2003

Winston Laboratories ("Winston") sends this letter pursuant to the Rules of Procedure (the "Rules") of the USAN Review Board (the "Board"). We respond to the letter from the USAN Council (the "Council") dated May 23, 2003, which stated the Council's basis for its decision to retain "zucapsaicin" as the official USAN for cis-8-methyl-N-vanillyl-6-nonenamide 9 (the "Compound").

Below we dispute specific claims made by the Council. For convenience, we have used as headings either the titles from our original petition or allegations taken from the Council's letter. Following our response to each of the Council's specific contentions, we conclude by highlighting several key issues that the Council's response sidesteps or ignores entirely.

"Zucapsaicin" Violates Several Key Guiding Principles for Nonproprietary Drug Names

1. *The name "zucapsaicin" violates General Rule #4: "A name should be free from conflict with other nonproprietary names and with established trademarks; it should be neither confusing nor chemically misleading."*

The Council's letter repeatedly discounts any possibility of confusion between "zucapsaicin" and similar sounding nonproprietary and trade names such as capsaicin, capsaicin oleoresin, capsicum, and Capzasin®. The Council believes that the "zu" prefix is sufficiently differentiating. As a company whose subsidiary markets a capsaicin-containing product, our experience seems to indicate otherwise. To cite one piece of anecdotal evidence, our receptionist recently became confused when a caller inquired about "zucapsaicin"; thinking that the caller must have been asking about capsaicin, she incorrectly referred him to the subsidiary.

At a minimum, the name "zucapsaicin" would exacerbate already preexisting confusion that surrounds "capsaicin." Here, the Council's response completely misses the point of the GenDerm v. Biozone Labs. case when it simply makes the factual observation, "The compound identified as 'nonivamide' is structurally and chemically different than capsaicin and zucapsaicin." In their structures, there is clearly no equivalence between the Compound and nonivamide. What this example demonstrates is the considerable confusion as to what constitutes "capsaicin," to the point where litigation was needed to enjoin the defendant from labeling nonivamide as "synthetic capsaicin," as it was sometimes mistakenly called in the trade.

The Council itself has acknowledged this confusion, admitting in its letter dated March 24, 1993: "The literature indicates confusion in the nomenclature of capsaicin."

Not only is there confusion surrounding "capsaicin"; there is also confusion surrounding the "zu" prefix. The Council completely discounts the possibility that any confusion might be caused by the dual use of "zu" as both the prefix for "zucapsaicin" and as an identifier for the animal source of monoclonal antibodies, because in the latter role "zu" is used only "as an infix in monoclonal antibody nomenclature and would never appear without the 'mab' suffix and a unique prefix." It should be noted, however, that the Council is the entity that formulated the "very detailed, complicated" nomenclature scheme for monoclonal antibodies. Most health care professionals, let alone laypeople, are unlikely to recognize this distinction. We recognize that this type of confusion is far less likely to occur than is confusion between "zucapsaicin" and "capsaicin"; however, an important function of nomenclature is to avoid even a remote chance of confusion, if it can be easily prevented. In this case, it certainly can.

The Council cites precedence in the form of two other Z-isomers which are denoted by the prefix "zu": zuclophene and zuclopenthixol. However, these names appear to be extremely old, zuclophene having been adopted as a USAN in 1967 and zuclopenthixol not appearing to be an official USAN. (Clopenthixol was apparently adopted as a USAN in 1965). Notable, too, is the fact that zuclophene was apparently coined first, and the name designated for the E-isomer was not "clophene" but "enclomiphene," which provides somewhat more differentiation between the two entities.

Much has changed since the 1960s, though, so these precedents may no longer have particular relevance. For one thing, "zu" was undoubtedly not in use as an identifier for the animal source of monoclonal antibodies at the time that zuclophene and zuclopenthixol were coined. Second, it is unlikely that there was the same degree of confusion surrounding any of these names as there has been involving capsaicin. Third, and most important, the past few years have witnessed a dramatic increase in the health-care profession's understanding of the prevalence of medication errors caused by drug name confusion. A name that might have been considered appropriate in 1967, or even in 1993, may no longer be suitable, given what the health-care profession has learned about the scope of medication errors caused by drug name confusion.

2. *The name "zucapsaicin" violates General Rule #5: "Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks."*

The Council makes several incorrect assertions in their response to the evidence we presented on this point. For instance, the Council erroneously contends, "no such usage [of civamide in the medical and scientific literature] was claimed at the time the Council adopted the USAN in 1993." This allegation is belied by the December 23, 1992 letter from Gary Knappenberger of GenDerm which the Council attached to its response, in which Mr. Knappenberger wrote, "We are aware of at least two articles in print which use the name civamide for this isomer."

The Council also claims, "Only Winston (and previously GenDerm), and not the regulatory agencies, has [sic] repeatedly used the name civamide." This assertion is simply not true. It is an empirical fact that the name used predominantly by the medical and scientific communities for the Compound is "civamide," not "zucapsaicin" or "cis-capsaicin." For instance, a simple query using the Internet search engine Google finds 100 web pages mentioning "civamide," as

opposed to 24 for "zucapsaicin" and 12 for "cis-capsaicin." Most of these web pages have absolutely no connection to Winston (or to GenDerm, for that matter). This evidence, in conjunction with the list of more than twenty references presented with our petition of March 17, 2003, shows that "civamide," not "zucapsaicin," is the *de facto* name of established usage.

U.S. Food and Drug Administration ("FDA") communications concerning the Compound often refer to the Compound as "civamide" and not as "zucapsaicin." In fact, in a recent example of drug-name confusion that we discovered in drafting this response, the FDA Orange Book (23rd Edition, 2003) contained an orphan drug designation listing for the Compound that gave "civamide" as the nonproprietary name and mistakenly listed "zucapsaicin" as the trade name!

3. *The name "zucapsaicin" violates Specific Rule #14: "A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the non-proprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula..."*

The Council's letter alleges, erroneously, that the Compound is "not a new [chemical] entity." If that were the case, then why was there a need for the Council to coin a new nonproprietary name for the Compound? The Compound is indeed a new chemical entity. It is not found in nature and must be chemically synthesized. It is not yet even listed in the Merck Index (13th Edition, 2001). The FDA is treating the Compound as a new chemical entity in its evaluation of drug products containing the Compound.

As such, the first two sentences of Specific Rule #14 would appear to be applicable. As quoted above, they clearly state that it is not routine for the stereoisomeric form of a new chemical entity such as the Compound to be identified in the nonproprietary name. Instead, the stereochemical configuration should be presented in the chemical name and in the structural formula, as it is for the Compound.

The Council completely ignores the essence of Specific Rule #14 as quoted above. Instead, it relies on a highly selective excerpt from Specific Rule #14 as support for its position: "Subsequently, if a name is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing name:..." Tellingly, the Council does not enumerate the prefixes named in points a) through e) that immediately follow this quoted excerpt. This omission is no doubt intentional, as "zu" is not one of the prefixes named therein. Indeed, it is very clear from the context—in particular, the focus on the racemate, the levo rotatory form, and the dextro rotatory form, and the lack of any mention of Z, cis-, E-, or trans-isomers—that the prefixes mentioned in points a) through e) are applicable to enantiomers, i.e., optical isomers. The same goes for the list of enantiomers given by the Council (e.g., omeprazole and esomeprazole, etc.) whose prefixes do conform to the prefixes given in points a) through e). These compounds are not diastereoisomers, i.e., geometric isomers such as capsaicin and the Compound, and this distinction between diastereoisomers and enantiomers is crucial: "Diastereoisomers are chemically distinct and often pharmaceutically different compounds. . . Enantiomers have identical physical and chemical properties except that they rotate the plane of polarized light in opposite directions and behave differently in a chiral environment." (Health Canada, "Stereochemical Issues in Chiral Drug Development, February 14, 2000")

In fact, capsaicin and the Compound manifest several noteworthy differences in their pharmacological and toxicological properties, as we stated in our petition. For example:

- The Compound has been shown to be ten times more potent as a neuropeptide depletor than capsaicin.
- The Compound is not neurotoxic, even at high doses, while capsaicin is neurotoxic at high doses.
- The Compound is has greater oral absorption than capsaicin.

In short, our contention—that the name of a geometric stereoisomer is not routinely specified in the nonproprietary name for a new chemical entity but is designated in the chemical name and structural formula—appears consistent with Specific Rule #14 as written. The Council's selective reading of Specific Rule #14 ignores the essence of the rule and inappropriately lumps geometric isomers with optical isomers, when the two are usually treated quite differently in practice (cf. the FDA's Policy Statement for the Development of New Stereoisomeric Drugs).

Selecting a Name Without Reference to Capsaicin would be Misleading to Health-Care Practitioners

As noted immediately preceding, this assertion by the Council is contrary to Specific Rule #14. Moreover, as also discussed earlier, "civamide" rather than "zucapsaicin" is the term that health-care and scientific professionals routinely use for the Compound, so it is the latter name that appears to be misleading.

Quite in contrast to the Council's claim that "zucapsaicin" is consistent with General Rule #1, we believe that "zucapsaicin" fails several important criteria specified in this rule. In particular, its potential to be confused with other drugs (e.g., capsaicin, capsaicin oleoresin, Capzasin®) renders it unsafe for "use in the routine processes of prescribing, ordering, dispensing and administering drugs" (General Rule #1.a.) and also makes it less than suitable "for use in educational programs for students in medically oriented professions and for use in scientific and lay publications." (General Rule #1.b.)

The Council Has No Reason to Conclude that Having the Names "Capsaicin" and "Zucapsaicin" Will Result in Harm to Patients

Since no products containing the Compound have been approved for commercial use, it is understandable why there are no reported medication errors attributable to the name "zucapsaicin." However, non-trivial *a priori* evidence of potential drug-name confusion is demonstrated by the pre-existing confusion surrounding "capsaicin," the undeniable similarity between "capsaicin" and "zucapsaicin," and our own experience in both developing the Compound and marketing a capsaicin-containing product, as noted earlier. Parenthetically, we find it interesting that the Council argues that there is no basis for expecting confusion between "zucapsaicin" and "capsaicin," but makes the uncorroborated assertion that our preferred candidate, civamide, "conflicts with the nonproprietary designations rifamide, cisapride, cinitrapide, cinflumide, and cintramide." We contend that, in fact, "capsaicin" and "zucapsaicin" are far more likely to be confused than would "civamide" with any of the nonproprietary names listed by the Council.

Changing the Name in the United States Only Would Engender More Name Confusion

The Council points out that the International Nonproprietary Name ("INN") Committee has no procedure in place to change a recommended INN, so even if the Compound's nonproprietary name were changed in the United States, it would likely remain zucapsaicin in the other member states of the WHO. This situation would, the Council alleges, be more confusing than the current one. We beg to differ. The Council's main concern should be the suitability of the nonproprietary name in the United States. If a change is warranted to forestall drug-name confusion in the United States, common sense and past practice seem to dictate that such a change be made, even if it would cause a discrepancy between the nonproprietary name in the United States and that in the rest of the world. The Council admits that this is what happened in the change from amrinone to inamrinone, it is probably what occurred in the change from tomoxetine hydrochloride to atomoxetine hydrochloride, as well.

Conclusion

Having provided point-by-point responses to the Council's letter, we conclude by considering the big picture. Viewed from this perspective, the Council's letter appears to neglect several important points that should be central to the Board's consideration of our petition:

1. First is recognition of the enormity of the problem of medical errors due to drug-name confusion. Much of the growing recognition of this problem has come in the last few years. To cite just two examples, the landmark 1999 Institute of Medicine Report attributed some 7,000 deaths per year to medication errors, and between 1996 and 2001, drug name confusion accounted for 15 percent of all errors reported to the United States Pharmacopeia Medication Errors Reporting Program. The growing recognition of the scope of problem of look-alike and sound-alike drug names has caused regulatory agencies and health-care institutions to change their procedures, rules, and guidelines. Practices that might have been appropriate even five years ago are no longer considered acceptable. For instance, the FDA has been more aggressively screening and testing proprietary drug names prior to approval and has proposed a rule change requiring bar coding of all prescription drugs, in order to reduce medication errors from confusing drug names. Next week, in fact, the FDA is holding a public meeting on "how best to minimize the potential for medication errors due to similarities in drug names."

By contrast, in its responses to our request for a reconsideration of the "zucapsaicin" name, the Council has repeatedly dismissed our reasonable concerns about the potential for drug-name confusion. Instead of evaluating the appropriateness of the name "zucapsaicin" based on present conditions, the Council has repeatedly focused on the past, in particular on the process by which the name "zucapsaicin" was adopted. The Council maintains that correct operating procedure was followed in negotiations with GenDerm, so there is no need to revisit the nonproprietary name of the Compound. Although we dispute certain aspects of the Council's description of its negotiations with GenDerm, we want to re-emphasize that we are not asking the Board to review the adoption process. Instead, we are seeking the Board's judgment on the suitability of the name. In particular: is the name "zucapsaicin" consistent with the stated Guiding Principles for U.S. Adopted Names, and even more important, does the name have potential to sow confusion among patients, pharmacists, physicians, and others in the health-care field?

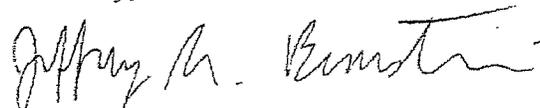
2. Although the Council still has not explicitly addressed the relative costs and benefits of the requested action, its letter implicitly suggests that there is no benefit (except an unspecified "marketing benefit" to Winston) but also relatively little cost to changing the nonproprietary name of the Compound. We agree that a name change would benefit Winston, but any such gain would derive solely from a reduced probability of drug-name confusion, a benefit that would redound to many parties—not just Winston as the Council alleges, but also patients, health-care professionals, and the medical and scientific community. Hence, the best available information supports a rather different conclusion: a name change would benefit many parties, with essentially no cost to doing so.

The Council's implicit stance seems to favor waiting until after there is actual harm caused by drug-name confusion (i.e., after any products incorporating the Compound are approved and marketed and after problems materialize) to give any consideration to changing the name. We believe that this "wait-and-see" attitude is similarly based on an inappropriate assessment of relative costs and benefits, and it is out of step with the prevailing sentiment of taking pro-active measures to reduce medication errors. It would be far preferable to change the name from "zucapsaicin" while the Compound is still in the investigational stage, rather than after products incorporating the Compound have been marketed. By taking the requested action now, the Board can forestall the prospect of medication errors that would foreseeably occur were any products incorporating the Compound introduced commercially under the name "zucapsaicin." It is also cheaper and less disruptive, not just for Winston but for all affected parties, to make a name change now rather than later.

3. Entirely neglected by the Council is the fact that Winston is not insisting that the name of the Compound necessarily be changed to civamide. Civamide would be our preferred name for the Compound, as it is the *de facto* name of established usage among the medical and scientific community and seems far more in accordance with the Guiding Principles of the USAN Council than does "zucapsaicin." However, we are open to other alternatives, and we have repeatedly expressed to the Council our willingness to negotiate the adoption of some other non-confusing name not containing "capsaicin." The Council has never entertained this notion. Coming from an organization that has frequently invoked the importance of a mutually negotiated outcome, this refusal seems particularly incongruous.

In summary, nothing in the Council's response changes our position as stated in the petition. We respectfully request that the Board rule favorably on our request.

Sincerely,



Jeffrey R. Bernstein, Ph.D.
Vice President, Chief Financial Officer