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JJH: JCL: TGG: RF

XF: ~~FDA Muriatic Acid~~ 376

TO: Distribution

FROM: Tom Grumbles
DATE: September 20, 1984

teroffice
mmunication

SUBJ: COMMENTS TO FDA: MURIATIC ACID GRAS STATUS

VISTA

Enclosed is a copy of the comments sent to FDA regarding the proposed GRAS revocation for byproduct hydrochloric acid. FDA is under no statutory time frame for decision making on this issue and it's anybody's guess when a decision will be made. We will keep in touch with FDA to monitor progress.

Thomas G. Grumbles

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TGG004

Enclosure

Distribution: Tom Huffman, Jim Gibson, Kyle Resh, Carl Kerfoot, Betsy Meyer, Wayne Hilgers, Bob Klein, Bill McClain, W.J.B. Vogel, R.D. Gamblin, Mike Fortier

LAW OFFICES

KELLER AND HECKMAN

1150 17TH STREET, N.W.

SUITE 1000

WASHINGTON, D.C. 20036

(202) 956-5600

June 9, 1989

VIA TELECOPIER

Mr. Thomas G. Grumbles
Vista Chemical Company
15990 North Barker's Landing Road
Houston, Texas 77224

Re: Options for Obtaining Appropriate FDA Status for Byproduct HCl

Dear Tom:

Following up on the telephone conversation that Holly Foley and I had with you today, the purpose of this letter is to provide you with a brief summary of the alternatives available for establishing appropriate Food and Drug Administration (FDA) status for Vista's hydrochloric acid (HCl) produced as a byproduct of linear alkyl benzene production. As we understand it, chlorine is used as a catalyst in this process with HCl being produced as a byproduct. You have already generated a large amount of information on residual benzene levels in the HCl but do not yet have a complete impurity profile on the acid.

As we discussed, it is difficult to predict at this stage what the best alternative will ultimately be for establishing to FDA's satisfaction the safety of Vista's byproduct HCl for use in direct food additive applications. The existing alternatives, however, may be broken down into the following: (1) a data submission to FDA demonstrating, if possible, that the byproduct HCl is essentially equivalent, in terms of the nature and levels of impurities, to the acids which the Agency is currently willing to consider generally recognized as safe (GRAS); (2) submission of a GRAS Affirmation Petition specifically for HCl produced as a byproduct of the Vista process; and (3) submission of a Food Additive Petition (FAP) for the acid.

The first two options would both have the objective of ensuring explicit inclusion of byproduct HCl from the Vista process in the final GRAS Affirmation Regulation for hydrochloric acid which the Agency has been working on for the past five years. The third option would request promulgation of a separate Food Additive Regulation specifically clearing the use of the Vista acid in food additive applications.

The best approach to take in submitting data to FDA on Vista's byproduct HCl will depend largely on the outcome of your additional analytical work on possible impurities present in the acid. If the analytical data demonstrate that the HCl is at least as pure as the acid that is currently considered by FDA to be GRAS--an unlikely outcome at this point--it may not be necessary to prepare more than an informal, informational submission of the data to the Agency. If the impurities found in Vista's acid differ from those found in direct process HCl but are clearly innocuous at the levels found, a GRAS Affirmation Petition may be indicated. Finally, if relatively high levels of impurities are detected, or if any carcinogens are present in measurable quantities, it probably will be necessary to submit the data in the form of a Food Additive Petition.

To provide you with some indication of the types of information needed and the necessary format to follow depending upon the type of submission chosen, we are enclosing herewith copies of §§ 170.35 and 171.1 of the Food Additive Regulations, which set forth, section-by-section, the information requirements established by FDA for GRAS Affirmation Petitions and Food Additive Petitions, respectively. With specific regard to the byproduct HCl, whether a GRAS Affirmation or Food Additive Petition is ultimately determined to be the most appropriate option, the following types of information will be needed:

- A description of the manufacturing process leading to the formation of byproduct HCl, including any steps taken to purify the acid;
- Specifications applied by Vista to HCl that will be sold into the food processing industry, copies of analytical methods used to ensure compliance with the specifications, and data from several (3 to 5) production lots demonstrating compliance of the acid with your internal specifications.
- Specifications for the raw materials used in the process and methods for ensuring compliance with the same;

- The identities of possible impurities in the HCl based upon the manufacturing process and purity of the starting materials;

- Results of analyses on a number of production lots encompassing at least a several week manufacturing period showing the measured levels of detectable impurities in the acid and the lower detection limit for any anticipated impurities that are not detected;

- Data validating the reliability of the analytical procedure for impurities and demonstrating the claimed lower detection limits;

- All available toxicological data on the impurities (with the exception of compounds, such as benzene, the safety of which FDA has already evaluated);

- A description of the food processing applications in which Vista's byproduct HCl is used, and a rough breakdown of the percentages of the total quantity of HCl produced by Vista that are used in the various applications;

- If possible, data demonstrating the fraction of HCl used in ion exchange resin regeneration that may remain in the resin and, in turn, may be added to corn syrup that is processed through the ion exchange column. (The latter information will be used to determine how much of the measured quantities of impurities in the HCl may ultimately become a component of food when the HCl is used in this "secondary" direct additive application.)

In addition to this information specific to the production and use of the byproduct HCl, a GRAS Affirmation Petition or Food Additive Petition will need to include an Environmental Assessment (EA) discussing the possible environmental impact of the use of byproduct HCl produced specifically by the Vista process. A description of the general types of information needed to complete an EA for either a Food Additive or GRAS Affirmation Petition is set forth in 21 C.F.R. § 25.31a, "Environmental assessment for proposed approvals of FDA-regulated products-Format 1" (copy enclosed). We can provide you with more specific details of the EA requirements when and if you decide to file a petition for the acid.

While it is premature to predict the type of submission to FDA that will best fit the circumstances once additional analytical data are developed, it appears likely that either a Food Additive Petition or GRAS Affirmation Petition will prove to be the best route for establishing appropriate status for Vista's byproduct HCl. However, in the event that the additional analytical data demonstrate that the acid is essentially identical to HCl produced by the fused silica or burner acid procedures, both of which are considered by FDA to be GRAS, or if the analytical data are equivocal and do not clearly indicate that a petition is called for, it may prove wise to prepare an informal submission of data to the Agency and meet with the appropriate FDA officials to discuss the significance of the data and the appropriate course to take from that point. Such a submission should contain most of the information outlined above for inclusion in a petition but may be compiled in a more informal way and contain less detail on subjects other than the identities and levels of impurities in the acid. Regardless of the form taken by the submission, it will be essential to document with as much specificity as possible the composition of the acid and the procedures utilized to identify and quantify the impurities.

As we discussed, while the information requirements for a GRAS Affirmation or Food Additive Petition and the FDA review process are well defined, it is difficult to predict with any confidence the duration of the review process and timing of publication of a responsive regulation. The uncertainty of the timing that is typical when dealing with FDA is exacerbated here by the fact that the Agency is in the process of preparing a rulemaking affirming as GRAS direct-process HCl. For this reason, if the data permit, it will probably be preferable to submit a GRAS Affirmation Petition for Vista's HCl rather than filing a Food Additive Petition since the acceptance for filing a GRAS Affirmation Petition will permit the immediate marketing of the byproduct HCl during the pendency of the GRAS petition review.

In other words, the short-term goal of submitting a GRAS Affirmation Petition is simply to obtain acceptance of the Petition for filing; if FDA's initial review of the data lead to this acceptance, your marketing efforts need not be disrupted while awaiting completion of the petition review process. On the other hand, if a Food Additive Petition proves to be the only realistic alternative for submitting data on byproduct HCl to FDA, it will be necessary to await completion of the review and promulgation of a responsive Food Additive Regulation before marketing the acid for direct food additive

use. In this case, considering the rate at which the FDA staff typically operates, a responsive regulation for the acid is unlikely to issue before 12 months from the date of submission, and may well take 18 to 24 months.

Once you have had a chance to review the information provided above, we will be happy to discuss with you in more detail the available options for moving forward to establish appropriate FDA status for the acid and, in particular, the analytical data that will be needed regardless of the specific alternative chosen. At that time, we will be pleased to discuss with you and your technical associates details of the analytical procedures that are most likely to yield the types of data needed as well as suitable analytical sensitivities for the various prospective impurities based on their relative toxicities. We look forward to hearing from you and stand ready to assist in any way possible.

Cordially yours,

Peter L. de la Cruz

Enclosures

cc: William L. McClain, Esq.

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MEMORANDUM

FROM: Jerome H. Heckman

RE: GRAS Affirmation Petition; Marketing During Review

This memorandum discusses the propriety of marketing a food ingredient or indirect additive while a GRAS Affirmation Petition (GAP) is being reviewed by the Food and Drug Administration (FDA). The research reported below as well as direct xperience with FDA demonstrate that substances for which a GRAS Affirmation Petition has been accepted for filing by the Agency may be marketed during the review process without any reasonable concern about adverse FDA action.

A. Background

Section 201(s) of the Federal Food, Drug and Cosmetic Act (Act) defines a "food additive" in relevant part as:

> [A]ny substance the intended use of which results or may reasonably be expected to result, . . . in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized among experts qualified by scientific training and experience to evaluate its safety as having been adequately shown . . . to be safe under the conditions of its intended use.

The exclusion of substances which are generally recognized as safe (GRAS) by qualified experts from the definition of the term, food additive, means that such substances do not require pre-clearance by FDA under § 409 of the Act, which governs food additives. Thus, substances which are GRAS may be marketed subject only to the general good manufacturing practices requirements such as compliance with the specifications set forth in the Food Chemicals Codex or other applicable guidelines.

The Act is silent on the question of procedures for determining whether a substance should be classified as GRAS. The Food Additives Regulations acknowledge at § 170.30(d):

> The food ingredients listed as GRAS in Part 182 of this chapter or affirmed as GRAS in Part 184 or § 186.1 of this chapter do not include all substances that are generally recognized as safe for their intended use in food. Because of the large number of substances . . ., it is impractical to list all such substances that are GRAS.

Consequently, it is the responsibility of the manufacturer, in the first instance, to determine whether a substance he manufactures is GRAS for any specific intended use. If he determines that it is GRAS, he is free to market the substance without notification to, or approval by, FDA. Obviously, if FDA should consider the manufacturer's determination of status to be erroneous, the Agency can take appropriate regulatory action; but in this case, the burden of proof will fall upon FDA to demonstrate that the substance is not GRAS.

In connection with the need to articulate standards whereby FDA could determine whether a substance is eligible for classification as GRAS, it proposed (35 Fed. Reg. 18623, Dec. 8, 1970) and then promulgated (36 Fed. Reg. 12093, June 25, 1971) a new Section 121.3 (recodified as § 170.30) in which detailed requirements for eligibility for GRAS classification were presented. Subsequently, on March 25, 1972 (37 Fed. Reg. 6207), the Commissioner of Food and Drugs proposed "a mechanism under which an interested person may petition him . . . to review the GRAS status of . . . substances not being considered with the present GRAS list review."

B. Marketing During Review Is Contemplated

1. Preamble to GRAS Regulations

The preamble to FDA's 1972 proposed GRAS regulations casts light upon the question under discussion. Thus, at 37 Fed. Reg. 6207, the following statement is made:

> A food ingredient which is found not to meet the GRAS criteria may be eliminated from the food supply completely or may be permitted to remain in the food subject to a food additive regulation or may be permitted to remain in food pursuant to an interim food additive regu-

> lation pending further study to resolve whatever questions may exist with respect to the ingredient. [Emphasis supplied.]

The important point to note here is the clear implication that the food ingredient whose status is being reviewed is present in the food supply while the review is proceeding. Otherwise, the statement that it may be eliminated or may be permitted to remain would have no meaning.

2. Recent FDA Action

In a June 25, 1985 letter, Richard J. Ronk, Deputy Director of FDA's Center for Food Safety and Applied Nutrition, indicated that FDA would not take regulatory action against a direct food additive which was the subject of a pending GRAS petition (copy enclosed). Mr. Ronk's response reaffirmed that substances being reviewed for GRAS affirmation are marketable during the pendency of the review.

Mr. Ronk's letter was written in response to an action by the State of Michigan Department of Agriculture. The state had asked a manufacturer of food products to discontinue its distribution of products containing certain alledgedly unapproved food ingredients. Michigan erroneously believed that the distribution of the product was in violation of the Federal Food, Drug and Cosmetic Act because one of the ingredients in the product was not subject to an FDA food additive regulation. The product involved was the subject of a pending GAP.

In an effort to resolve this dilemma, we wrote Mr. Ronk at FDA asking him to clarify the status of a direct food additive which is subject to a pending GRAS affirmation petition. Our letter to Mr. Ronk contended that the filing of a GRAS affirmation petition permits the marketing of a substance to continue during an FDA review and that acceptance of a petition amounts to at least a prima facia finding that GRAS status was probable and no market interruption is warranted. Thus, while a GRAS petition is outstanding, FDA was precluded from taking any negative action or supporting the discontinued marketing proposed by the State of Michigan.

In his June 1985 response, Mr. Ronk noted that FDA will not take action against products which contain ingredients that are the subject of a pending GRAS affirmation petition. Therefore, Mr. Ronk concluded that a company can market a food ingredient during the review of a GRAS application.

3. Other FDA Statements

At a FDA conference attended by attorneys (including Mr. Heckman) and others from this office, as well as counsel from another firm, Mr. Damon Larry of the GRAS Review Branch of the Division of Food and Color Additives explicitly noted his understanding that one of the major reasons for filing GRAS Affirmation Petitions in lieu of food additive petitions was the recognition that filing a GAP permits marketing of the substance in question, whereas filing a food additive petition does not.

At a meeting of the Food and Drug Law Institute in Washington, D.C., on December 8-10, 1980, Mr. Ronk, in response to a question from the floor, re-affirmed his more privately stated interpretation that marketing a substance during review of a GAP is legal and that FDA would take no enforcement action under these circumstances. The proposition that an ingredient can be marketed during the pendency of a GRAS affirmation proceeding is supported by the nature of the proceeding itself. Its purpose is to affirm, or at least determine, the GRAS status of a substance. If the substance were known to be not GRAS, there would be no purpose for the proceeding and, indeed, under this circumstance the substance could not be marketed in the absence of a regulation. But until a decision has been made, FDA would be hard pressed to act against a substance for which it had publicly solicited comments concerning GRAS status.

4. FDA Enforcement Policy

Finally, it should be noted that FDA has not, to the best of our knowledge, seized or otherwise taken adverse regulatory action against any substance for which a GAP had been accepted for filing. Indeed, § 170.35(c)(5) provides that if the Commissioner concludes that there is a lack of convincing evidence that a substance is GRAS, he may conclude that it should be considered a food additive and publish a notice in the Federal Register in accordance with § 170.38. Section 170.38 provides a procedure whereby the Commissioner issues a notice proposing to determine that a substance is not GRAS and is a food additive subject to § 409 of the Act. This proposal is then open for public comment. Subsequently, as a result of comments sent in response to the proposal, the Commissioner may determine that the substance is GRAS. If he concludes that

there is a lack of convincing evidence that the substance is GRAS, he must publish a notice in the Federal Register as follows:

1. He may promulgate a food additive regulation governing the use of the additive.

2. He may promulgate an interim food additive regulation governing the use of the additive.

3. He may require discontinuation of use of the additive [emphasis supplied].

4. Finally, he may adopt any combination of the above three approaches for different uses or levels of use of the additive.

It is apparent, therefore, that the acceptance of a GAP for filing implies a recognition by FDA that the product is being marketed during the review; if the substance is not affirmed as GRAS but is deemed safe for the intended use, it will be cleared by a food additive regulation or an interim food additive regulation as appropriate. Only in the event that the evidence does not show that the substance is safe will FDA require discontinuation of the use of the additive.

C. Conclusion

Summarizing, the relevant regulations support the proposition that a substance being reviewed for GRAS affirmation is being marketed during the review, and Agency spokesmen have repeatedly taken the position that such marketing is permitted. There has never been adverse Agency action against the marketing of a substance which was the subject of an accepted GAP. This collectively supports the conclusion that marketing a food ingredient during the review of a GAP presents no cause for real concern about any adverse FDA action.